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Research Article

STUDY OF THEOPHYLLINE AGAINST EXPERIMENTALLY INDUCED HYPERLIPIDEMIA

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ABSTRACT
The present study was planned to evaluate the anti-hyperlipidemic activity of theophyllin, a bronchodilator for its effect on lipid levels, HMG-CoA reductase activity and lipid peroxidation in Poloxamer 407 and high-cholesterol diet-induced hyperlipidemia in rats. The animals were divided into four groups, viz. normal, high cholesterol diet (control), Atorvastatin and theophylline treated groups. In Poloxamer-407 induced acute hyperlipidemia model, blood samples were collected at 15 and 24 hour period, and there after lipid parameters and HMG-CoA reductase activity were estimated and compared with atorvastatin reference standard treated animals. In high fat diet-induced model, animals were given respective treatment for a period of twenty one days. Lipid parameters and antioxidant parameters were measured and compared with atorvastatin treated animals at the end of study period. High cholesterol diet and Poloxamer 407 caused a significant increase in serum total cholesterol (TC), LDL-C, VLDL-C, TG and atherogenic index (AI) along with significant decrease in HDL-C and HDL/LDL ratio. In poloxamer model, Theophylline pre-treatment showed a significant decrease in total cholesterol, LDL-C, VLDL-C, and atherogenic index, with no marked change in HDL-C, TG and HDL/LDL ratio. It also showed significant inhibition of HMG-CoA reductase activity as compared to poloxamer control group. Similarly, in high fat diet model, theophylline demonstrated significant reduction in serum cholesterol, TG, VLDL and AI. In addition this, antioxidant parameters were measured in terms of Malondealdehyde levels, superoxide dismutase, catalase and reduced glutathione. Theophylline did not show any remarkable change in this parameter suggesting lack of antioxidant mechanisms. Based on our data, it is suggested that theophylline possesses hypolipidemic activity. The mechanism of action of this could be attributed to reduction ($p < 0.05$) in an AI and inhibition of HMG-CoA reductase activity.
Keywords: Theophylline, Poloxamer 407, High-cholesterol diet, Hyperlipidemic, Rats

INTRODUCTION

Hypercholesterolemia is one of the major risk factor of atherosclerosis as endothelial cell bind Low density lipid. When activated (e.g. by injury), these cells get attached to monocytes/macrophages and generates free radicals that oxidize low density lipid, resulting in lipid peroxidation and destruction of receptor needed for normal receptor – mediated clearance of low density lipid[1]. Theophylline, a methylxanthine derivative, is a weak and non-selective inhibitor of phoshodiastrases (PDES) of cyclic nucleotides, leading to an increase in intracellular concentration of cyclic AMP and cyclic GMP[2]. The other well-describe pharmacologic action of the drug is its potent antagonistic activity at adenosine receptors. Theophylline has also been shown to increase release of interleukin-10 (presumably by mechanism involving inhibition of PDE), antagonize tumors necrosis factor alpha, inhibit the pro-inflammatory effects of prostaglandin, decrease release of intracellular calcium ion, prevent the translocation of nuclear factor-kβ into nucleus and thus potentially reduce the expression of inflammatory genes and increase the apoptosis and histone deacetylase activity[3]. In the light of these mechanisms of theophylline, it will be attracting to study its action and mechanism against experimentally – induced hyperlipidemia.

MATERIALS AND METHODS

Chemicals

Poloxamer 407, coconut oil, cholic acid, and cholesterol were purchased from S. d. Fine chem. Ltd (Mumbai, India). Theophylline was provided by Cipla Ltd (Mumbai, India). Atorvastatin was provided by Cadila Pharma (Ahmedabad, India). Total Cholesterol (TC) (CHOD-PAP method), Triglycerides (TG) (GPO-PAP method), and HDL-C (PEG-CHOD-PAP-LCF method) assay kits were purchased from Span Diagnostic Ltd. (Surat) India.

Animals

In these experiments (LMCP/09/05) we followed the guidelines for care and use of laboratory animals as approved by Institutional Animal Ethic Committee (IAEC) constituted as per CPCSEA, Ministry of Social Justice and Empowerment (Registration No. 228) Government of India. Male Sprague-Dawley (SD) rats weighing approximately 250 g were obtained from Cadila Research Centre (Ahmedabad, India). The animals were housed in a temperature-controlled room (22 ± 2oC), humidity with a 12:12 h light: dark cycle and allowed free access to water throughout the duration of the experiment. In addition, the animals were provided with a diet pellets for 10~14 days to allow them to acclimate.

Experimental Hyperlipidemic Diet

A Method of Blank et al., 1965 (II) for high-cholesterol diet was prepared by mixing the normal basal diet [22.9 % (wt/wt) crude protein, 5.9 % crude oil, 7.10 % crude ash and 3.11 % crude fiber (Surat Agro Industries)], cholic acid, cholesterol and Coconut oil in a ratio of 92:1:2:5, and then pelleting the mixture.

Experimental Procedures

Poloxamer 407-induced Hyperlipidemic Model

To render the animals hyperlipidemic, the rats were subjected to a 6 h-fast. Next, the rats were administered an intra peritoneal injection (i.p.) of 1 ml of 30 % w/v of solution of poloxamer-407 (p-407). Dose of Poloxamer 407 that had been prepared by combining the agent with saline for injection and then refrigerated overnight to facilitate dissolution of Poloxamer 407[4]; starting in first hour after the administration of the Poloxamer 407, the rats were treated with theophylline for 24 hour by oral gavage.

High-cholesterol Diet-induced Hyperlipidemic Model

The animals were fed a high-cholesterol diet for 21 days. The rats were then divided into 4 groups of 6 animals; briefly normal group received Standard chaw diet and all other groups received high cholesterol diet. Rest all other groups received treatment for 21 days. The result of theophylline treated group was compared with that of standard and control group of animals.

Blood Sampling

At the end of 21st days food was withdrawn and after overnight fasting, blood samples were collected in the morning by retro-orbital puncture technique in a coagulant free vessel and kept at room temperature for 1 h. The blood Samples were centrifuged at 3000 g and 4ºC for 10 minutes after which the serum was stored at -70ºC for further biochemical tests.

Biochemical Estimations

The levels of Triglycerides (TG), Total cholesterol (TC) and HDL-C in the serum were determined by enzymatic colorimetric methods using commercial kits [Span Diagnostic. Ltd. (Surat, India)]. The concentration of Low Density Lipid-Cholesterol (LDL-C) and the AI were calculated using the following equations (Friedewald equation):

$$LDL\text{-}C = TC - TG/5 - HDL\text{-}C$$
$$AI = VLDL + LDL / HDL\text{-}C$$

Statistics

All results are presented as the mean ± S.E.M. The data were evaluated by one-way ANOVA using the Sigmastat 2.03 software, after which the differences between the mean values were assessed using Tuckey's multiple range test. Statistical significance was considered at $p < 0.05$.

RESULTS AND DISCUSSION

The present study, we evaluated the effects of theophylline on the serum lipid levels of hyperlipidemic rats induced by Poloxamer 407 and the administration of a high cholesterol diet. It is known that one of the major risk factors of atherosclerosis is hyperlipidemia. Hyperlipidemia and high cholesterol diet increase serum TC and LDL-C levels, resulting in an increased risk for the development of atherosclerosis. Thus regulating the serum cholesterol level is an important aspect in atherosclerosis prevention, as it has been shown that atherosclerosis could be suppressed by controlling the level of serum cholesterol.

Effect of Theophylline on Biochemical Parameters in Poloxamer 407-induced Hyperlipidemic Rats

Rats with hyperlipidemia induced by Poloxamer 407 had remarkably high serum levels of TG, TC, and LDL-C, a significantly increase in AI when compared with the normal rats. In this model, serum samples were collected at two time points i.e. after 15 h and at the end of 24 h. As can be seen in Table 1 and 2, theophylline showed significant reduction in TC, TG, VLDL and LDL along with increased HDL/LDL ratio after 24 h period as compared to control group. It is increase in serum HDL levels. It is also noted that atorvastatin showed significant reduction in abnormal lipid levels in both study periods; however extent of reduction was more remarkable in 24 h group as compared to 15 h period. Table 3 shows the effect of theophylline and atorvastatin on the ratio of HMG-CoA / Mevalonate of liver tissue homogenates of Poloxamer treated rats. Theophylline significantly raised this ratio (0.98 ± 0.06) as compared to control group (0.55 ± 0.06) in both the standard and treatment groups indicating significant down regulation of HMG-CoA activity. Which seems indicates one of the important mechanisms of theophylline for its lipid lowering action. Poloxamer 407 is a hydrophilic, non-toxic, surface active agent with a low degree of toxicity that is being adapted for more specialized applications such as sealing permeabilized cell membranes and vascular occlusion procedures[5-10]. It has been shown to cause significant elevations in serum cholesterol and triglyceride levels after a single injection in rodent models[11]. In order to determine whether prior inhibition of the activity of HMG-COA reductase using orally administered atorvastatin and theophylline would reduce plasma cholesterol and triglycerides concentration following i.p injection of 30 % (w/w) Poloxamer 407 to rats. In Poloxamer model, theophylline (20 mg/kg) and atorvastatin (50 mg/kg) treatments significantly reduced lipid levels viz. serum cholesterol, LDL, VLDL levels and AI. Besides, theophylline also raised the ratio of HMG-CoA/Mevalonate indicating the reduction of HMG-CoA activity. An indirect increase in cholesterol synthesis with Poloxamer through stimulation of HMG-CoA reductase is reported by Davis[12]. Therefore, it is suggested that antihyperlipidemic activity of theophylline in Poloxamer model could be due to inhibition of HMG-CoA reductase activity.

Effect of the Theophylline on Biochemical Parameters in High Fat Diet-induced Hyperlipidemic Rats

The effects of theophylline and atorvastatin on the serum lipid levels of rats fed a high-cholesterol diet are shown in Table 4. The rats fed a high-cholesterol diet showed remarkably high serum levels of TG, TC, and LDL-C, as well as an increased AI when compared with the rats fed a normal diet. The serum lipid levels in theophylline-administered rats (20 mg/kg of body weight) were significantly reduced when compared with the hyperlipidemic control group. Along with, serum HDL-C levels and HDL/LDL ratio were also raised in presence of theophylline treatment but this rise was not found statistically significant (Table 4). The induction of hyperlipidemia by a high-cholesterol diet in experimental animals has long been used to assess the beneficial effect of hypolipidemic agent on the regulation of cholesterol[13]. Oral administration of theophylline resulted in a decreased concentration of TG, TC and LDL-C as well as increased atherogenic index value, with no significant changes in the HDL-C levels. These results indicate that theophylline could function as a hypolipidemic agent to prevent hyperlipidemic atherosclerosis by lowering the serum lipid levels. Besides, effect of theophylline was also checked on the lipid peroxidation in term of MDA level, SOD, catalase and glutathione levels. As shown in Table 5, there was significant rise in MDA content observed in control group. Atorvastatin significantly reverted rise in lipid peroxidation by lowering MDA ($p < 0.05$) along with significant rise in SOD levels. However, theophylline receiving rats did not show any changes in the measurement of antioxidant parameters. Hence, these results are suggesting that theophylline is devoid of any antioxidant –activity. An extensive range of antioxidant defenses, both the endogenous and exogenous are present to protect cellular components from free radical-

induced damage. These defenses include antioxidant enzymes like superoxide dismutase (SOD), catalase and chain breaking antioxidants Malondealdehyde (MDA) is the end product of lipid peroxidation. Therefore measurement of MDA is an indirect method for assessing the extent of lipid peroxidation. High cholesterol diet induced a significant increase in MDA and SOD level, along with significant decrease in catalase activity when compared with the result of animals receiving standard diet. The increase in SOD may be due to the adaptive mechanisms because of oxidative stress. It has been reported that oxidative stress increase SOD production[14]. Increase in MDA level could be due to increase in lipid peroxidation. Decrease in catalase activity might be due to over production of superoxide anion, which inactivates catalase by converting the resting ferric enzyme to poorly active Ferro-oxy form. As can be seen from our data, there were no remarkable changes noted in the levels of MDA, SOD, catalase and glutathione in theophylline received rats compared to respective control group. Therefore, we rule out the possibility of involvement of antioxidant mechanism in the antihyperlipidemic activity of theophylline. Hence, we suggest hypolipidemic activity of theophylline against experimental hyperlipidemia in rats. The hypolipidemic activity of theophylline in both the above model could be due to significant reduction of atherogenic index and HMG COA reductase activity. Similar type of study has been reported from our lab using Nicorandil[15]. There is also an increasing evidence that theophylline has anti-inflammatory effect in the role of its bronchodilator effects[3]. Further, these authors have also proposed several mechanisms of action of theophylline including phosphodiesterase inhibition, adenoreceptor antagonism, increase interleukin-10 release, inhibition of TNF-α, inhibit the pro-inflammatory effect of prostaglandin, inhibition of intracellular calcium release, inhibition of NF-kβ, increase histone deacetylase activity. Thus based on this report, it can be speculated that the antihyperlipidemic-activity of theophylline could be due to mainly its anti-inflammatory component. Further, based on our findings reduction in AI and inhibition of HMG COA reductase activity could play significant role in its hypolipidemic activity However, there is a need to establish these molecular mechanisms individually against hyperlipidemia disorder.

Table 1: Effect of Theophylline on biochemical parameters in Poloxamer 407-induced hyperlipidemic rats (15 hour)

Treatment	Dose (mg/kg bw)	TC (mg/dl)	TG (mg/dl)	HDL-C (mg/dl)	VLDL-C (mg/dl)	LDL-C (mg/dl)	HDL/ LDL Ratio	A.I
Normal		102.1 ± 5.1	176..5 ± 13.5	40.24 ± 6.1	20.42 ± 1.03	61.86 ± 9.4	0.67 ± 0.13	1.83 ± 0.5
Hyperlipidemic Rats								
Control		301.5 ± 9.4^{e}	328.5 ± 26.8^{e}	23.29 ± 4.6	60.31 ± 1.9^{e}	278.25 ±13.3^{e}	0.08 ± 0.04^{d}	15.58 ± 3.8^{e}
Theophylline	20	271.5 ± 9.5	274.8 ± 21.9	31.39 ± 4.3	55.10 ± 1.9	244.12 ± 10.7	0.12 ± 0.01	8.56 ± 1.2
Atorvastatin	50	152.17 ± 12.7^{c}	217.01 ± 27.3^{b}	44.55 ± 2.8^{b}	30.43 ± 2.5^{c}	107.61 ± 12.3^{c}	0.44 ± 0.10^{c}	2.46 ± 0.3^{b}

TC: total cholesterol, TG: triglyceride, HDL-C: high-density lipoprotein-cholesterol, LDL-C: low-density lipoprotein-cholesterol, A.I.: atherogenic index. Values are the mean ± S.E.M. for 6 rats. $^{b}p < 0.05$,$^{c}p < 0.001$ *vs*. the control value, $^{d}p < 0.05$,$^{e}p < 0.001$ *vs*. the normal value

Table 2: Effect of Theophylline on biochemical parameters in Poloxamer 407-induced hyperlipidemic rats (24 hour)

Treatment	Dose (mg/kg bw)	TC (mg/dl)	TG (mg/dl)	HDL-C (mg/dl)	VLDL-C (mg/dl)	LDL-C (mg/dl)	HDL/ LDL Ratio	A.I
Normal		84.11 ± 5.3	177.24 ± 13.3	45.23 ± 3.9	16.82 ± 1.06	22.06 ± 5.03	1.14 ± 0.6	0.93 ± 0.20
Hyperlipidemic Rats								
Control		358.53 ± 9.4^{e}	328.52 ± 26.8^{e}	23.29 ± 4.7	71.61 ± 2.1^{e}	258.89 ± 7.0^{e}	0.095 ± 0.04^{d}	13.41 ± 1.9^{e}
Theophylline	20	268.20 ± 10.7^{c}	304.38 ± 29.2	42.15 ± 6.4	53.64 ± 2.1^{c}	172.41 ± 8.14^{c}	0.23 ± 0.07^{c}	6.16 ± 1.1^{b}
Atorvastatin	50	225.50 ± 16.3^{c}	201.29 ± 23.5^{c}	63.46 ± 6.12^{c}	45.09 ± 3.26^{c}	116.93 ± 17.23^{c}	0.48 ± 0.11^{c}	2.80 ± 0.6^{c}

TC: total cholesterol, TG: triglyceride, HDL-C: high-density lipoprotein-cholesterol, LDL-C: low-density lipoprotein-cholesterol, A.I.: atherogenic index. Values are the mean ± S.E.M. for 6 rats. $^{b}p < 0.05$,$^{c}p < 0.001$ *vs*. the control value, $^{d}p < 0.05$,$^{e}p < 0.001$ *vs*. the normal value

Table 3: Assessment of HMG Co-A Reductase activity

Treatment	Dose (mg/kg bw)	HMG-CoA/Mevalonate ratio
Normal		0.76 ± 0.04
Hyperlipidemic Rats		
Control		0.55 ± 0.06
Theophylline	20	0.98 ± 0.06^{b}
Atorvastatin	50	1.16 ± 0.11^{c}

$^{b}p < 0.05$,$^{c}p < 0.001$ *vs*. the control value, $^{d}p < 0.05$,$^{e}p < 0.001$ *vs*. the normal value. HMG-CoA REDUCTASE: 3- Hydroxy 3-Methyl Glutaryl-CoA

Table 4: Effect of Theophylline on biochemical parameters in High fat diet-induced hyperlipidemic rats

Treatment	Dose (mg/kg bw)	TC (mg/dl)	TG (mg/dl)	HDL-C (mg/dl)	VLDL-C (mg/dl)	LDL-C (mg/dl)	HDL/ LDL Ratio	A.I
Normal		111.83 ± 8.6	101.90 ± 5.4	49.12 ± 4.67	20.38 ± 1.09	42.39 ± 11.12	1.1 ± 0.06	1.39 ± 0.3
Hyperlipidemic Rats								
Control		324.13 ±15.8^{e}	447.32 ± 14.7^{e}	27 ± 3.2^{d}	89.46 ± 2.9^{e}	207.66 ± 14.7^{e}	0.14 ± 0.01^{e}	11.88 ± 1.6^{e}
Theophylline	20	261.94 ± 15.8^{b}	282.90 ± 10.1^{c}	39.9 ± 5.9	56.58 ± 2^{c}	165.47 ± 18.1	0.22 ± 0.08	6.58 ± 1.4^{b}
Atorvastatin	50	199.78 ± 13.7^{c}	171.15 ± 8.6^{c}	55.12 ± 5.5^{c}	34.23 ± 1.7^{c}	110.43 ± 18^{b}	0.667 ± 0.1^{b}	2.98 ± 0.8^{c}

TC: total cholesterol, TG: triglyceride, HDL-C: high-density lipoprotein-cholesterol, LDL-C: low-density lipoprotein-cholesterol, A.I.: atherogenic index. Values are the mean ± S.E.M. for 6 rats. $^{b}p < 0.05$,$^{c}p < 0.001$ *vs*. the control value, $^{d}p < 0.05$,$^{e}p < 0.001$ *vs*. the normal value.

Table 5: Effect of Theophylline on antioxidant enzyme levels

Treatment	Dose (mg/kg bw)	MDA / mg of protein	Glutathione (µmol/mg of protein)	SOD (units/min/mg of protein)	Catalase (units/min/mg of protein)
Normal		6.57 ± 0.98	7.69 ± 1.09	0.19 ± 0.012	1.833 ± 0.12
Hyperlipidemic Rats					
Control		15.28 ± 2.01[d]	4.59 ± 0.98[d]	0.14 ± 0.015[d]	1.58 ± 0.053[d]
Theophylline	20	11.75 ± 1.89	4.82 ± 0.76	0.14 ± 0.023	1.44 ± 0.14
Atorvastatin	50	7.06 ± 1.15[b]	12.67 ± 1.56[b]	0.31 ± 0.015[b]	1.80 ± 0.14

[b]$p < 0.05$,[c]$p < 0.001$ *vs*. the control value,[d]$p < 0.05$,[e]$p < 0.001$ *vs*. the normal value. GSH: Glutathione, SOD: Superoxide dismutase, MDA: Malondialdehyde

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