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Lipid Lowering Effect of Alpha Adrenoreceptor Blocker and Antidiabetic Drug in Experimental Animals

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Abstract: Lipid Lowering Effect of Alpha Adrenoreceptor Blocker and Antidiabetic Drug in Experimental Animals. **Methods:** Hyperlipidemia was induced by intraperitoneal injection of poloxamer 407 at a dose of 400mg/kg body weight in wistar albino rats. Drugs treatment were done by oral gavage for 3 days. At the end of the study, animals were kept fasted overnight and then blood sample was collected. The serum cholesterol (TC), triglycerides (TC), HDL, LDL, VLDL were calculated. **Results:** From the present investigation, it was observed that pioglitazone and terazosin drug have shown significant reduction in serum cholesterol, triglycerides, LDL, VLDL and increase in HDL level in p-407 induced hyperlipidemia.**Conclusion:** It is concluded that Pioglitazone and terazosin may possess antihyperlipidemic activity in Poloxamer 407 induced Hyperlipidemic Rats.
Keywords : Hyperlipidemia, Poloxamer 407, pioglitazone, Terazosin, Atorvastatin, lipid profile.

INTRODUCTION

Hyperlipidemia, also known as hyperlipoproteinemia, is characterised by unusually high amounts of lipids and lipoproteins in the blood.[1] Any aberrant lipid levels are included in this type of dyslipidaemia, which is the most frequent. Hyperlipidemia is basically divided into two types viz. primary and secondary type. [2,3] Primary hyperlipidemia is caused by genetic factors (for example, a mutation in a receptor protein), whereas secondary hyperlipidemia is caused by extrinsic factors such as diabetes. Because of their influence on atherosclerosis,

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lipid and lipoprotein abnormalities are frequent in the general population and are regarded as an unmodifiable risk factor for cardiovascular disease. Furthermore, some types may put you at risk for acute pancreatitis.[1]

According to the world health organisation (WHO), excessive blood cholesterol is responsible for around 56 percent of all occurrence of cardiovascular disease (CVD) worldwide, resulting in nearly 4.4 million death per year. When compared to 1990, it is estimated that more than 62.4 percent of person in India died from cardiovascular disease. [1,4]

Hyperlipidemia is a secondary metabolic disorder linked to diabetes that also increases the chance of developing the disease. Aside from the cause-effect link with diabetes, high levels of triglycerides, cholesterol, and low density lipoprotein in the blood are risk factors for cardiovascular disorders such as atherosclerosis, hypertension, and coronary heart disease.[1] Hyperlipidemia related to increased oxidative stress causing significant production of oxygen free radicals, which may lead to oxidative modification in LDL ,which present a significant function in the initiation and progression of atherosclerosis and associated cardiovascular diseases.[5,6]

In addition, hyperlipidemia is induced by secondary effect of diabetes therefore by secondary effect of diabetes therefore, the agent having some antidiabetic effect also showed favourable effect to hyperlipidemia. [7,8] Type 2 diabetes is treated with thiazolidinediones (TZD), pioglitazone, and rosiglitazone. Pioglitazone is a less strong agonist of the peroxisome proliferator-activated receptor gamma (PPAR-) than rosiglitazone, but it is also beneficial in lowering fasting blood glucose and HbA1c levels. Pioglitazone, a commonly used antidiabetic, has been proven to improve HDL and decrease LDL and TG in diabetics, in addition to improving glycemic control. All anti-diabetic medicines affect lipid profiles differently, however pioglitazone has a better lipid-lowering effect than other anti-diabetic treatments, including rosiglitazone. In type 2 diabetic individuals, pioglitazone has been proven to have better cardiovascular advantages than rosiglitazone and glimipride. When compared to atorvastatin alone, co-administration of pioglitazone with atorvastatin improved the lipid profile in non-diabetic patients with high cardiovascular risk. Pioglitazone has a minor PPAR alpha (PPAR-) agonist effect in addition to PPAR-, which may be responsible for improved lipid and cardiovascular profiles.[9]

Alpha-blocking drugs are used as first-line treatment for benign prostatic hyperplasia (BPH), one of the most common causes of consultation for obstructive or irritative urological problems in middle-aged and elderly men. They are also used as second-line treatment for uncontrolled arterial hypertension, in monotherapy or in combination.[10]

In vitro investigations have shown that terazosin metabolites have antioxidant characteristics, which could be effective in preventing atherosclerosis in hypertensive patients, especially when other comorbidities like dyslipidaemia and diabetes are present. Then there's evidence of doxazosin's hypocholesterolaemia and antioxidant properties, which haven't been established with other alpha-blockers but suggest a possible benefit against endothelial dysfunction in a variety of situations.[10]

Poloxamer 407(P-407) is a non-ionic surfactant made up of polyoxyethylene and polyoxypropylene units in a block copolymer. It’s known for its biocompatibility and capacity to administer medications for a variety of diseases, and it works as a barrier against post-surgical adhesion. P-407 possesses remarkable thermo-reversible characteristics, in that it is liquid at room temperature but aggregates and forms a gel at body temperature before producing micelles. This temperature-dependent micelle and gel formation ability makes them commercially beneficially in personal care products including mouthwashes, deodorants and skin care products, as well as an inactive substance that can be used as a vehicle or media for a range of medicinal preparations [11]

In the present investigation we determined the lipid lowering effect of the alpha-blocking drugs terazosin and antidiabetic drug i.e. pioglitazone in hyperlipidemia model.

MATERIALS AND METHODS:

Ethics approval: The study was approved by institutional ethics committee of YSPM’s YTC, Satara MH India.

Drug and Chemical: Terazosin tablets (Intas Pharmaceutical Ltd), Pioglitazone tablets (Ontop Pharmaceutical PVT.Ltd), Atorvastatin tablets (Emcure Pharmaceutical Ltd), Poloxamer 407 (Ozone Pharmaceutical Ltd) were used for these research study.

Animals:

Inbred 30 Wistar albino rats (150–220 gm) were selected for present study. The animals were housed at room temperature (22-28 ºC) 12 hr dark and light cycle and given standard laboratory feed and water *ad-libitum*. The study was approved and conducted as per the norms of the Institutional Animal Ethics Committee (25/12/2017/CPCSEA). Animals were maintained as per committee for the purpose of control and supervision of experiments on animals guidelines. [12,13]

Induction of hyperlipidemia:

The inducing agent was poloxamer 407. Before administration, P-407 was completely dissolved in water and refrigerated overnight to aid its complete dissolution. The syringe and needle to be used for the induction was cooled to avoid gelation within the syringe during injection.[11]

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 intraperitoneal injection (i.p.) of a 400 mg/kg dose of poloxamer 407. [14,15] It had been prepared by combining the agent with saline or water for injection and then refrigerated over-night to facilitate dissolution of poloxamer 407. Starting two hours after the administration of the poloxamer 407, the rats were treated with prepared samples once daily for 3 days by oral gavage.[15]

Animals grouping and treatment:

A total of 30 rats were used. The rats were randomly divided into 5 groups. Each group contained 6 rats.

Group I: Normal Control rats fed with normal chow and distilled water (NC)

Group II: Hyperlipidemic Control rats induced without treatment (HC)

Group III: Hyperlipidemic rats treated with the standard drug (Atorvastatin 10mg/kg p.o.)

Group IV: Hyperlipidemic rats treated with the antidiabetic drug (pioglitazone 10mg/kg p.o.)

Group V: Hyperlipidemic rats treated with the alpha blocker drug (terazosin 5mg/kg p.o.)

Biochemical estimations:

Blood was collected by retro-orbital sinus puncture, under mild ether anaesthesia in the experimental models. The collected samples were centrifuged for 15 minutes at 2500rpm. Then serum samples were collected and analysed for serum Total Cholesterol (TC), Triglycerides (TG), High Density Lipoprotein Cholesterol (HDL-C), Low Density Lipoprotein Cholesterol (LDL-C) and Very Low-Density Lipoprotein Cholesterol (VLDL-C).[12]

Statistical analysis:

The data was statistically analysed using one-way ANOVA followed by Tukey's multiple test. The results were expressed as Mean ± SEM (n=6). A value $P < 0.05$ was considered to be significance. [16]

RESULTS AND DISCUSSION

Table 1: Effect of Pioglitazone and Terazosin on lipid profile of P-407 induce hyperlipidemia

Group	Cholesterol (mg/kg)	Triglycerides (mg/kg)	HDL (mg/kg)	LDL (mg/kg)	VLDL (mg/kg)
Normal control	142 ±13.78	99 ±5.80	44 ±3.12	86 ±7.66	26 ±1.66
Toxicant control (Poloxamer 407)	322 ±22.11	198 ±12.33	24.00 ±1.44	185 ±12.86	56 ±4.33
Standard (Atorvastatin)	158 ±14.33	122 ±14.18	41 ±3.22	91 ±8.63	27 ±1.18
Test I(Pioglitazone)	202 ±18.22	143 ±12.44	33 ±2.11	134 ±11.12	41 ±3.33
Test II (Terazosin)	283 ±17.33	167 ±15.33	29 ±2.33	165 ±14.33	51 ±4.12

The values are expressed as a mean ± SEM, n=6, $p<0.05$ when compare to normal control and hyperlipidemic control.

Graphical Representation:

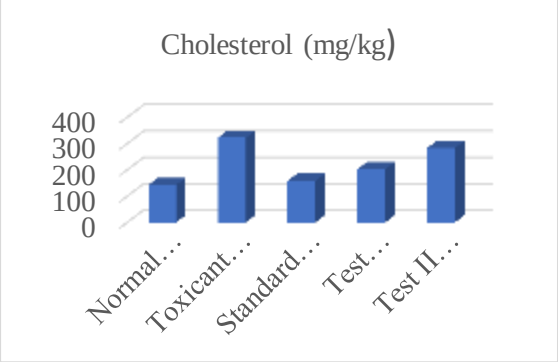


Fig.No.1 Effect of Pioglitazone and Terazosin on Total Cholesterol

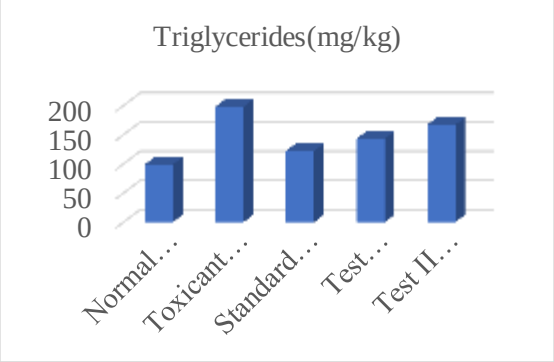


Fig.No.2 Effect of Pioglitazone and Terazosin on Triglycerides

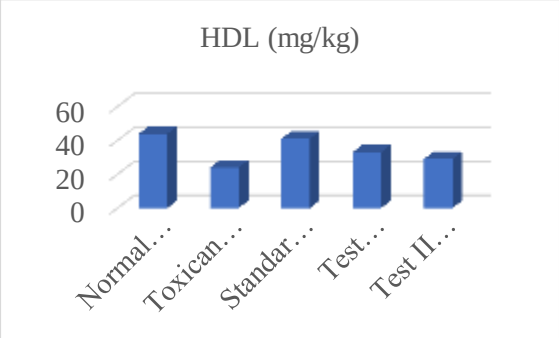


Fig.No.3 Effect of Pioglitazone and Terazosin on HDL

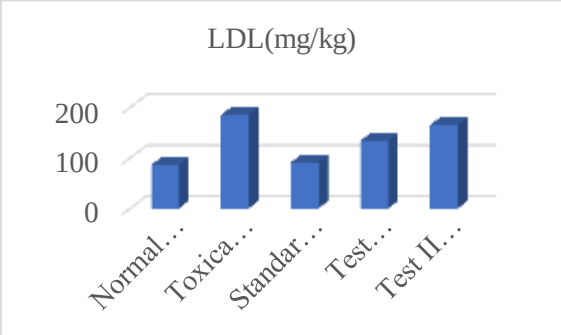
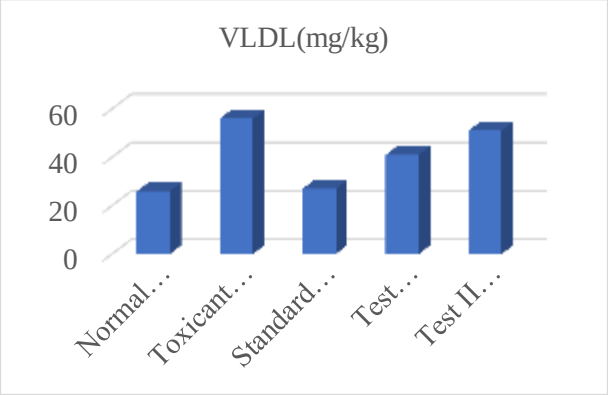


Fig.No.4 Effect of Pioglitazone and Terazosin on LDL



Lipids are water-insoluble organic molecules that are soluble in organic solvents. Lipids provide a variety of tasks, including chemical messengers, energy storage and provision, temperature regulation, and membrane lipid layer development. Hyperlipidemia is defined as an unusually high level of lipids, such as total cholesterol (TC), triglycerides (TG), and lipoproteins (lipoproteins) [17]. Hyperlipidemia-related diseases are substantial risk factors for the development of cardiovascular disease (CVD) [18].

Hyperlipidemia is a risk factor for atherosclerosis beginning and progression [19] as well as a high-risk factor for coronary heart disease development. As a result, the causal hyperlipidemia can be targeted for prevention or therapy of such illness. The abnormal high concentration of serum lipid is mainly due to increase in the mobilization of free fatty acids from the peripheral depots. [20,21]

Poloxamer 407 is non-ionic surfactant and is nontoxic to cellular membrane, was used successfully to induce hyperlipidemia in previous studies it causes effects by activating HMG CoA enzyme A. Poloxamer 407 a block copolymer composed of a hydrophobe that is flanked on each side with hydrophillic polyoxyethylene units. Our previous findings demonstrated that elevation in plasma TG was more sensitive than elevation in total plasma cholesterol following P-407 administration.[22]

Pioglitazone is a glucose-lowering medication that works as an agonist of peroxisome proliferator–activated receptor gamma.[13] All anti-diabetic drugs have varying effect on lipid profile but overall pioglitazone has shown more favourable lipid-lowering effect in comparison to other antidiabetics.[23]

Terazosin, which is structurally similar to prazosin, is a novel selective alpha 1- adrenoceptor antagonist.[24] The association between thyroid hormone imbalance and blood lipids encompasses processes such as beta oxidation at the muscle and liver level, as well as increasing the turnover of LDL, which could explain the decrease in cholesterol levels. Terazosin would cause a change in thyroid hormone levels, allowing us to notice a reduction in cholesterol and triglyceride levels.[10]

Group I administered with saline or water considered as normal control group. Group II administered with poloxamer 407 showed significant increase in lipid profile level except HDL level as compared to normal control group. Group III administered with atorvastatin showed significant decrease lipid profile except HDL level which is good cholesterol as compared toxicant control group. Group IV treated with pioglitazone significantly decreased TC, TG, LDL, VLDL and increased HDL level as compared to hyperlipidemic control group. Group V treated with terazosin significantly decreased TC, TG, VLDL, LDL and increased HDL level as compared to toxicant control group.

Conclusion:

In conclusion the present study has demonstrated that pioglitazone and terazosin are found to be of potential anti-hyperlipidemic activity in poloxamer-407 induced hyperlipidemia in wistar rats and it is observed that significant reduction of cholesterol, triglycerides, LDL, VLDL and increases HDL cholesterol level. According

to above study we can conclude that pioglitazone showed more significant effect as compared to terazosin. So pioglitazone is beneficial in preventing atherosclerotic cardiovascular diseases.

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