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DO PPIs AFFECT SERUM LIPIDS? A PILOT STUDY IN RABBIT MODEL

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Abstract:

Proton pump inhibitors are frequently used drugs among all age groups owing to their complete acid blocking property, a most common health problem of the current age world around. Literature suggests some abnormal effects to be associated with the prolonged use of PPIs like kidney injury and MI. We tried to evaluate the effects of PPIs on serum lipid profile in this Pilot study. Rabbits were selected with normal weigh and healthy look, one was kept as control (No drug given) while others were given PPIs at normal human doses of 40mg/70kg/day orally for 6 wks. Blood sample drawn after sacrifices were evaluated for serum lipid profile in Isra University hospital lab. There was clear difference between serum lipid profile of drug free Rabbit and PPIs treated Rabbits including total lipids, serum cholesterol, serum LDL-C, Triglycerides and Serum HDL-C.

Conclusion: *The prolonged use of PPIs results in increased levels of serum total lipids, cholesterol, LDL-C, Triglycerides and reduced level of serum HDL-C.*

Key Words: *PPIs, Lipid Profile, Pilot Study.*

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INTRODUCTION:

Proton Pump Inhibitors (PPIs) are a group of drugs most frequently used in outpatient departments as well as indoor patients. These agents include omeprazole, esomeprazole, pentaprazole, rabiprazole etc. They completely block the synthesis of HCl in the stomach so have wide spectrum of uses like peptic ulcers, stress ulcers , drug induced ulcers, ulcers caused by H. pylori infections and gastroesophageal reflex disease. These are acid unstable drugs so need enteric coating to reach duodenum for absorption [1]. These drugs are prodrugs so must be activated for effectiveness. These agents are available in oral and parenteral form and inhibit >90% acid secretion at standard doses. Their metabolites are excreted through kidneys and feces. Side effects include achlorhydria, increased risk of fractures, vitamin B12 deficiency, diarrhea, hypomagnesemia and increased incidence of pneumonia [2]. Oral bioavailability of PPIs ranges from 30-90% with high protein binding and metabolized through cytochrome P450 (CYP450) enzyme system via CYP2C19 and CYP3A4 [3]. Omeprazole was the 1st PPI introduced in 1989 that steadily replaced the treatment for acid-related disorders as it was more effective and good safety profile as compared to H2-blockers, prostaglandin analogs etc [4,5]. Later on six PPIs were approved by the FDA (Food and Drug Administration) in 2015 [6] The duration of use for these agents has frequently been extended beyond the recommended guidelines around the world specially over the counter purchase [7]. Previously these agents were supposed to be non-nephrotoxic but few recent international retrospective studies have pointed out that serum urea and creatinine were found elevated in patients on long term therapy with PPIs which increase the risk of chronic kidney disease by 20%-50% [8-10]. Available PPIs have been derived from benzimidazole so they contain heterocyclic structure with a pyridine linked through a methylsulfinyl group with the benzimidazole moiety which probably responsible for their shorter half-lives and a potential target for future modifications [11]. Cardiac events were also reported in literature however there is a lack of knowledge about the proper mechanism responsible for that. This study is directed to evaluate the effects of these agents (Omeprazole, Esomeprazole and Pantoprazole) on the serum lipid profile if any, and to compare the same in different PPIs on the rabbit model. Hopefully current study will ease the path for other researchers to work out these effects in human subjects.

METHODOLOGY:

Animal were purchased under inclusion criteria of healthy ,male rabbits weighing 2-3 kg on average excluding sick and low weight from the Hyderabad city. Animals were kept in separate cages and acclimatized which was followed by oral dose administration which was calculated from the normal human dose (40mg/70Kg). All other diet was normal for all groups. The experiment was carried out for 6 weeks followed by sacrifices of animal, blood samples were collected and sent to Isra Research lab. for lipid analysis using Hitachi analyzer . Total Lipids, cholesterol, HDL,LDL and Triglycerides were measured and presented in tabular form along with graphical presentation.

RESULTS:

It was observed that serum total lipids were 68mg/dl in control group and 98 mg/dl in experimental group B (Omeprazole treated), 94mg/dl in group C(Esomeprazole treated) and 82mg/dl in group D (Pantoprazole treated). Serum cholesterol levels was 19.9mg/dl in control group A while in Omeprazole treated group B it was 25.9mg/dl , 26.2 mg/dl was noted in esomeprazole group C and it was 24.2 mg/dl in pantoprazole group D. Serum LDL-cholesterol was found increased in experimental groups as compared to 3.9mg/dl of control group A, to 6.6mg/dl in group B and 5.4mg/dl in group D while there was slight reduction in group C. Serum triglycerides were also increased in all animals with 26.1mg/dl in omeprazole treated, 31.6mg/dl in esomeprazole treated, and 14.6mg/dl in pantoprazole treated (group D) which was much higher than the 8.1mg/dl of the control one. Serum HDL-Cholesterol was found 13.6mg/dl in control animal which was reduced in experimental animals 7 mg/dl in omeprazole treated , 2.1mg/dl in esomeprazole treated while it was 10.4mg/dl in pantoprazole treated animal.(Table1)and (figure 1).

Table 1. lipid profile parameters in various PPIs treated and control animals

Parameters	Group A(Control)	Group B(Omeprazole)	Group C(Esomeprazole)	Group D(Pantoprazole)
Total Lipids	68 mg/dl	98 mg/dl	94 mg/dl	82 mg/dl
Cholesterol	19.9 mg/dl	25.9 mg/dl	26.2 mg/dl	24.2 mg/dl
HDL-C	13.6 mg/dl	7 mg/dl	2.1 mg/dl	10.4 mg/dl
LDL-C	3.9 mg/dl	6.6 mg/dl	2.9 mg/dl	5.4 mg/dl
Triglycerides	8.1 mg/dl	26.1 mg/dl	31.6 mg/dl	14.6 mg/dl

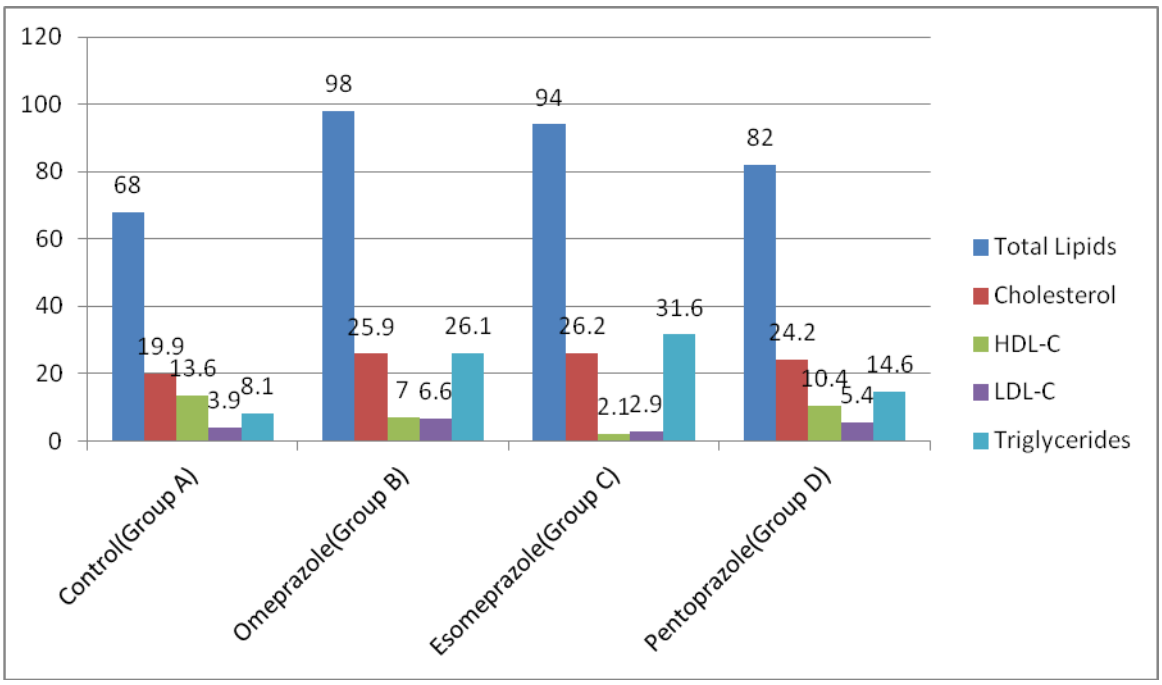

Figure 1: Serum lipid profile in study animals

DISCUSSION:

We could not find any such study on the literature search to compare our findings but it is very clear from the result figures that these agents do affect the lipid profile increasing the total lipids ,cholesterol and triglycerides while the protective cholesterol(HDL) is reduced that seems a possible mechanism behind the cardiac effects associated with PPIs. How these lipids got raised requires more detailed investigations on the complex cholesterol synthesis pathway along with the various enzymes responsible for the same. Several recent studies have also shed light on PPIs and the cardiovascular system. PPI users have been shown to have a significantly greater risk of heart attack than those on other antacid medication (12, 13). PPIs were also reported to reduce the production of NO (nitric oxide), so losing a natural protective agent for the blood vessels (14).PPIs were seen to damage the vascular endothelial cells quickly these agents inhibit the cellular acidic nature compartment (lysosome) rendering its ability to clean up the waste products resulting into the accumulation of the same further inhibiting the lysosomal function (15). The current research was just a pilot study but the observations were quite important from research point of view so large scale study is required in animal model to find the exact picture that these changes in serum lipids were by chance or there exist real impact of PPIs on these biochemical parameters. We assume these changes in lipids induced by PPIs prone the population to cardiovascular events however this needs further exploration in animal as well as human subjects.

CONCLUSION:

Pump Inhibitors (PPIs) do affect the serum lipids as we found.

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