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STUDY OF ALTERATION IN SERUM LIPIDS BY CARDIOSELECTIVE BETA BLOCKERS IN ALBINO RABBITS

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Abstract:

Dyslipidemia is a major cardiovascular risk factor. Several agents mainly beta blockers, which are extensively used for the prevention and treatment of cardiovascular diseases, have been reported to have adverse effects on the lipid profile. In addition, agents belonging even to the same class such as cardioselective beta blockers can also have significantly different actions on lipid levels. These effects should be considered when selecting a specific agent, particularly in high-risk patients. Therefore in the present study, effects of atenolol and bisoprolol on serum lipid were investigated on hypercholesterolemia induced albino rabbits by feeding the animals with normal diet supplemented with 1% cholesterol and 10% ground nut oil for 8 weeks. Rabbits with hypercholesterolemic diets throughout the experiment were used as positive control. There was significant increase in all the parameters of lipid profile after 8 weeks treatment of hypercholesterolemic diet. Administration of atenolol for 3 weeks in hypercholesterolemic rabbits decreased the total cholesterol, LDL, and HDL but increased TG and VLDL. The changes in all these parameters were not significant statistically. In contrast, there was significant decrease in total cholesterol, LDL, TG and VLDL and increase in HDL by the administration of bisoprolol. But changes of only TG, HDL and VLDL were statistically significant. So bisoprolol showed little favorable effect on lipid profile than atenolol. Therefore these effects might have to be considered while prescribing in high risk patients for the benefit of the patients.

Keywords: *Cardioselective beta blockers, atenolol, bisoprolol, serum lipids*

Introduction

Cardiovascular diseases, a major group of non-communicable diseases, have become a major public health problem in many developing countries.[1, 2] In today's world, most of the deaths are attributable to noncommunicable diseases & just over half of these are because of cardiovascular diseases.[3] Cardiovascular diseases (CVDs) comprise of a group of diseases of heart & vascular system & the major CVDs include:

- Coronary (or ischaemic) heart disease
- Cerebrovascular disease (stroke)
- Hypertension (high blood pressure)
- Heart failure
- Rheumatic heart disease

According to World Health Report 2003, an estimated 16.7 million of total global deaths result from the various forms of cardiovascular diseases (CVDs). Out of these, 7.2 million are due to ischaemic (coronary) heart disease.

That's why the WHO has drawn attention to the fact that coronary heart disease is our "***MODERN EPIDEMIC"***.[4] **Coronary heart disease** (CHD), also known as coronary artery disease (CAD), ischaemic heart disease and atherosclerotic heart disease, is the end result of the accumulation of atheromatous plaques within the walls of the arteries that supply the myocardium (the muscle of the heart) with oxygen and nutrients.

The risk factors that contribute to the acceleration of CAD may be modifiable and unmodifiable. Modifiable risk factors are sedentary lifestyle, smoking, obesity, physical inactivity, lipid disorders, hypertension, insulin resistance and the unmodifiable risk factors include age, male, gender, genetics.

The prospective community based ' FRAMINGHAM HEART STUDY' provides support for the concept that HYPERCHOLESTEROLEMIA , HYPERTENSION & other factors are correlated with the cardiovascular risk.[5] Both are the well-established risk factors for '*Atherosclerosis*.[6,7] High plasma concentration of cholesterol, particular those of low-density lipoprotein (LDL) , is one of the principal risk factor for atherosclerosis but decrease in HDL cholesterol or lower HDL:LDL ratio also causes the atherosclerosis and are associated with increased risk of CAD. Atherosclerosis is an inflammatory disease in which arterial wall thickens as a result of the accumulation of lipids into the subendothelial cells of the intima of the arteries. This chronic inflammatory response in the walls of arteries is due to the accumulation of macrophages, white blood cells and promoted by low density lipoproteins(LDL), inadequate removal of fats and cholesterol from the macrophages by functional high density lipoproteins (HDL) .[8]

The lesions of atherosclerosis occur principally in large and medium-sized elastic and muscular arteries. In central nervous system it frequently provokes stroke & transient cerebral ischemia. In the peripheral circulation, it causes intermittent claudication and gangrene and jeopardizes the limb viability.[9] While different cardiac consequences due to atherosclerosis of the coronary arteries are stable angina, unstable angina, myocardial infarction (MI), heart failure, arrhythmias and sudden death.[10] So the goals of treatment include relief of symptoms, inhibition or slowing of disease progression by treatment of lipid disorders and control of hypertension, prevention of future cardiac events such as myocardial infarction (MI), and improved survival. [11]

Beta-adrenergic receptor antagonists (beta-blockers) have received enormous clinical attention because of their efficacy in the treatment of hypertension, ischemic heart disease, congestive heart failure and certain arrhythmias. They probably reduce almost every cardiovascular events of coronary artery disease. That's why the beta-blockers are the first medications considered for the people having coronary artery disease and hypertension. [12] These drugs adversely affect lipoprotein metabolism and increase the associated coronary disease risk and offset the beneficial effects of lowering blood pressure. To overcome these problems cardioselective blockers or $beta_1$-adrenoceptor blocking agents are increasingly used now-a-days, for hypertension and coronary heart diseases .Many studies have shown that they have less deleterious effects on lipid profile and in diabetics . But cardioselective beta blockers are not absolute $beta_1$ blockers. They can exhibit some $beta_2$ receptor blocking activity also, that is why it is pertinent to study the effect of these drugs on serum lipid profile.

The aim of the present work was to study the subacute effects of cardioselective beta blockers on serum lipid profile in albino rabbits. The drugs evaluated were Atenolol and Bisoprolol.

Materials & method

Animals

The present study was conducted on normal adult healthy albino rabbits of either sex , weighing 1.5 - 2.0 kg. They were housed in iron cages & maintained under standard conditions of 12 hours light & dark cycle, room temperature

25 ± 3°C & 35-60% humidity. The animals were maintained on standard pellet diet & water ad libitum two weeks before start of experiment. The study was approved by Institutional Ethical Committee of G.S.V.M. Medical College, Kanpur.

Drugs

Atenolol, 5mg/kg/day and Bisoprolol, 0.5 mg/kg/day

Dose calculations were done according to table from Paget & Barnes(1964).[13]

Experimental design.

After 2-weeks period of adaptation, all the animals were divided into two groups, comprising of 12 rabbits in each and marked to permit individual identification. After that blood samples were taken from all the rabbits of both groups, for the estimation of basal serum lipid profile, which was considered as 'day 0' sample serving as a normal control for their respective groups. This was immediately followed by induction of experimental hypercholesterolemia in all the animals by administering the cholesterol enriched diet (standard diet containing 1% cholesterol and 10% ground nut oil) and water ad libitum for 8weeks (60 days) and the 'day 60' sample (cholesterol fed control) was drawn again. After that animals of group I were continued with the same cholesterol enriched diet along with Atenolol and group II were fed with cholesterol enriched diet along with Bisoprolol for 3 weeks more and at ' day 81' (11 weeks) (test), blood samples were drawn again to observe the effect of drugs on serum lipid profile.

Induction of hypercholesterolemia in rabbits

Rabbits were made hypercholesterolemic by feeding a high cholesterol fat diet. Deoxycholic acid was mixed thoroughly with powdered standard rabbit diet (100g/day/rabbit). Simultaneously 1% cholesterol was dissolved in 10% warmed ground nut oil and this oil solution was added slowly in to powdered mixture to obtain homogeneous soft cake. This cholesterol rich (HFD) preparation was molded in the shape of pellets of about 3g each and fed for 8 weeks by 100g/day/rabbit for the induction of hypercholesterolemia.[14]

Collection of blood samples

For estimation of serum lipid profile, blood samples were taken in the plain vials from the marginal vein of pinna of rabbits at 'day 0' (before induction of hypercholestrolemia), 'day 60' (before administration of drugs) and 'day 81'(after 3 weeks of drugs administration) by using disposable syringes under aseptic conditions, after overnight fasting and then centrifuged at 3000 rpm for 10 minutes. The clear supernatant serum was taken for the estimation of serum lipid profile in each group. Estimations of serum triglyceride, total serum cholesterol & HDL cholesterol were done separately by using their respective reagent kits & by their respective enzymatic methods with the help of UV spectrophotometer while the estimation of serum LDL & VLDL cholesterol were done by the methods noted against them.

Estimation of serum lipid profile

Total Serum Cholesterol & HDL Cholesterol & Serum Triglyceride Estimation : Estimation of total serum cholesterol level was done by using Cholesterol oxidase-phenol-aminophenazone (CHOD-PAP) method & HDL cholesterol by Polyethylene glycol Cholesterol oxidase-phenol-aminophenazone (PEG-CHOD-PAP) method by using a span diagnostic reagent kit (code no. LG 052) and serum triglyceride level was estimated by using glycerol phosphate oxidase-phenol-aminophenazone (GPO-PAP end point assay) method, by using span diagnostic reagent kit (code no. LG 062)

Serum LDL Cholesterol was calculated on the basis of Friedwald's equation.

Serum LDL cholesterol (mg/dl) = Total cholesterol - (HDL+Triglyceride/5)

Serum VLDL Cholesterol :- VLDL(mg/dl) = Total cholesterol - (HDL + LDL)

Statistical analysis.

Data of changes in serum lipid profile were expressed as the mean ± SE (standard error). The values of day '0' were compared statistically with 'day 60' and value of 'day 60' were compared with 'day 81' in both the groups using paired-t test and value of $P<0.05$ was considered to be statistically significant.

Observations & results:-

TABLE:-1 Effect of Atenolol on serum lipids

Treatment	TOTAL CHOLESTEROL(Tc)	TRIGLYCERIDE (TG)	HDLc	LDLc	VLDLc
Normal control ('day 0')	79.5± 3.59	81 ± 6.61	26.33 ± 2.46	36.97 ± 1.42	16.2 ± 1.32
Cholesterol fed Control ('day 60')	182.17±13.55*	139.17±17.38*	40.5±4.72*	113.83±8.67*	27.83±3.47
Cholesterol + Atenolol ('day 81')	170.67±6.47	160.67±29.46	33.67±3.39	105.03±8.10	32.13±5.89

Tc = Total cholesterol, HDLc = HDL - cholesterol, LDLc = LDLcholesterol, VLDLc = VLDLcholesterol, Values are mean ± SEM

Levels of significance *P < 0.05 when compared with normal control rabbits, $^{\neq}$P<0.05 when compared with cholesterol fed control rabbits

TABLE.2:- Effect of Bisoprolol on serum lipids

Treatment	TOTAL CHOLESTEROL(Tc)	TRIGLYCERIDE (TG)	HDLc	LDLc	VLDLc
Normal control ('day 0')	79.67±5.5	76.83±3.72	20.67±0.99	43.63±5.57	15.37±0.74
Cholesterol fed Control ('day 60')	175.17±10.75*	157.17±12.08*	42.67±2.03*	101.07±10.8*	31.43±2.42*
Cholesterol + Bisoprolol ('day 81')	160.83±4.92	138.83±7.18$^{\neq}$	48.5±3.49$^{\neq}$	84.57±4.18	27.77±1.44$^{\neq}$

Tc = Total cholesterol, HDLc = HDL - cholesterol, LDLc = LDLcholesterol, VLDLc = VLDLcholesterol, Values are mean ± SEM

Levels of significance *P < 0.05 when compared with normal control rabbits, $^{\neq}$P<0.05 when compared with cholesterol fed control rabbits

These observations indicated Serum total cholesterol, triglycerides , HDL and LDL-cholesterol, were increased significantly (P<0.05) in both the groups after 60 days of cholesterol feeding except VLDL-cholesterol levels which was not increased significantly in group I but increased significantly (P<0.05) in group II. Administration of ATENOLOL for 3 weeks did not show any significant effect on serum lipid profile but administration of bisoprolol for 3 weeks, decreased serum total cholesterol, serum triglyceride, LDL and VLDL levels which were significant and increased HDL level but the changes in serum total cholesterol and LDL levels were nonsignificant (ns).

Discussion

In the last few years, there have been revolutionary changes in the therapy of cardiac diseases. The beta-blockers have got enormous attention by improving the quality of life of many patients who suffered from heart diseases, but long term use of the beta-blockers may have many adverse side effects such as severe bradycardia, congestive distress especially in patients of bronchial asthma etc. In these circumstances, the search for a harmless and clinically useful indigenous preparation for cardiovascular diseases was warranted which should decrease the LDL cholesterol and increase the HDL-cholesterol because low levels of HDL-cholesterol and high levels of LDL cholesterol have proved important predictors for the development of coronary heart disease.[15] The effects of beta blockers on blood lipids have been studied extensively. Many studies have shown that non-selective beta blockers increase TG levels and lower HDL-C levels without affecting LDL-C levels while $beta_1$-selective or cardioselective beta blockers do not appear to have such adverse effect on the lipid profile [16, 17, 18,19] and in some studies, it has been reported that they increased HDL-C levels and lowered the total cholesterol (TC) and TG levels.[20] There is variability in effects of nonselective and cardioselective beta blockers on lipid profile in different studies as well as among the agents of cardioselective beta blockers also. Therefore the present study was planned to see the effects of two cardioselective beta blockers atenolol and bisoprolol on serum lipid profile in albino rabbits

In this present study, administration of atenolol for 3 weeks, increased the TG and VLDL levels while decreased the total cholesterol, LDL and HDL levels. The results of most of the parameters of lipid profile correspond to many studies but not at the level of significance. Few such studies done by Nandeesha et al, 2009 and Rizos et al, 2003, showed that atenolol increased TG levels significantly.[21, 22] Similarly lower HDL-C levels and increase LDL-C and TG levels were demonstrated by Howes et al, 1996.[23] Another study done by Bur et al, 2002, also showed the decrease in total cholesterol and HDL in which effects of terazosin and atenolol were seen in two different groups of hypertensive patients with hyperlipidemia but there was decrease in TG level. [24] In yet another study of Frick et al, 1987, there was increase in triglyceride level and decrease in HDL level by the administration of atenolol in hypertensive patients. [25] The changes in VLDL level were supported by the study of Notghi et al, 1989.[26]

Similarly administration of bisoprolol decreased total serum cholesterol, serum TG, LDL and VLDL levels while increased the HDL levels. Decrease in serum TG & VLDL and increase in HDL were significant (p< 0.05) while changes in total serum cholesterol and LDL were nonsignificant (ns). The results were supported by the study of Drexel et al, 2001, who concluded that effective antihypertensive doses of bisoprolol do not exert the typical dyslipidaemic effects of beta-blockers but rather tend to induce small but favorable changes in plasma triglycerides, LDL and HDL cholesterol, and especially in the atheroprotective HDL2 cholesterol subfraction.[27]

From the above study it is evident that the cardioselective beta blockers used in the study have little but not absolutely favorable effects on lipid profile. Bisoprolol showed an early, more favorable and significant effects than atenolol which did not show any significant change after 3 weeks of treatment. This may be either because of the short duration of therapy or may be because these are not absolute beta-1 blockers; they also exhibit some beta-2 blocking activity. As beta-2 receptors are involved in different metabolic process like glycogenolysis in liver & muscles and lipolysis in adipose tissues (also beta 1 and beta-3 receptors); blocking of these receptors will inhibit the enzymes glycogen phosphorylase ,triglyceride lipase involved in these process (glycogenolysis and lipolysis) and increase the levels of different lipoproteins like serum TG , LDL , VLDL and ratio of LDL/HDL . Therefore non-β_1-selective agents are thought to affect the plasma lipid profile adversely by blocking both β_1- and β_2-receptors, thereby preventing normal catecholamine-stimulated lipolysis .Inhibition of lipoprotein lipase can also occur as a result of a permissive effect of unopposed α-adrenergic stimulation, when both β_1- and β_2-adrenoceptors are blocked.[28] As a consequence, β1-selective blockers are expected to cause less marked alterations in HDL-C and TG levels. Bisoprolol, which has been reported to be much more β_1 selective (120 fold for β_1 than β_2) than atenolol (20 fold for β_1 than β_2), showed more favorable effect on lipid profile as compared to atenolol.[29] Such findings seem to confirm that greater the β_1 selectivity of β-blocker, the less adverse effect on lipid concentrations.[30] Some genetic factors like polymorphisms of the beta2 and beta3 adrenoreceptor genes may be associated with increased risk for increase in LDL-C and TG levels during treatment with beta blockers.[31,32] In fact, the clinical significance of β1-blocker-induced changes in lipid metabolism are not yet fully elucidated, but the proven risk potentiation between dyslipidemia and cardiovascular risk strongly suggests choosing of drugs with neutral or beneficial effects on serum lipid and these effects might have to be considered when selecting a specific agent, particularly in high-risk patients of cardiovascular disease.

Conclusion

In conclusion, the results of this study show that bisoprolol produced little but more favorable effects on plasma lipids than atenolol. Even though both are cardioselective, atenolol increases the TG regardless of significant change. This favorable effect of bisoprolol could be of clinical relevance in the long-term management of high risk patients of cardiovascular disease. So the agents belonging to even the same class (e.g. cardioselective beta-blockers) can have significantly different actions on lipid levels. Therefore it is advisable to prescribe and use the cardioselective beta blockers carefully in heart diseases keeping in mind their influence on serum lipid profile and their possible outcomes in hypertensive and coronary heart disease patients

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