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Dyslipidemia Induced by Atenolol in Common Rabbits *Oryctolagus cuniculus*

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Abstract: The study was conducted to find out the effects of atenolol on blood lipid profile of common rabbits (*Oryctolagus cuniculus*). The administration of an oral dose of 0.6 mg atenolol kg^{-1} day^{-1} for 27 days produced a strong dyslipidemia, which was evident by a significant ($p<0.05$) reduction in mean plasma cholesterol and triglycerides levels, a marked alteration in mean HDL-cholesterol concentration and a non-significant elevated level of LDL-cholesterol. These findings suggest that atenolol is an inappropriate antihypertensive monotherapic agent for patients suffering with the abnormalities of lipid metabolism.

Key words: Atenolol, selective β-blockers, lipid profile, dyslipidemia, hypocholesterolemia, antihypertensive

INTRODUCTION

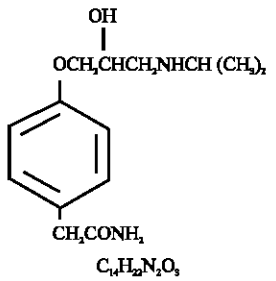
Hypertension occurs in more than two thirds of individuals after the age of 65 years (JNC, 1997). For individuals aged 40 to 70 years, each increment of 20 mm Hg in systolic BP or 10 mm Hg diastolic BP doubles the risk of cardiovascular diseases across the entire BP ranges from 115/75 to 185/115 mm Hg (Lewington *et al*., 2002).

Many patients can be treated satisfactorily with a single antihypertensive drug, the choice of which can be determined by safety, convenience and freedom from side effects. Another group will require a combination of two or three antihypertensive agents to give good control with a low level of side-effects. Antihypertensive therapy has been associated with 35 to 45% mean reductions in stroke incidence: 20 to 25% in myocardial infarction and more than 50% in heart failure (Neal *et al*., 2000).

The principal agents used in a single drug treatment of hypertension are thiazide, diuretics, beta (β) adrenoceptor antagonists and Angiotensin Converting Enzyme (ACE) inhibitors, calcium antagonists and some vasodilators are also effective. β-blockers are the first-line drug therapy for hypertension (Mycek *et al*., 2000 a,b). They reduce blood pressure primarily by decreasing cardiac output, also decrease sympathetic outflow from the central nervous system (CNS) and inhibit the release of renin from the kidneys, thus decreasing the formation of angiotensin II and secretion of aldosterone (Yang and Fayad, 2003).

Atenolol, one of the most frequently used cardio selective β-blockers, is indicated for patients with essential hypertension, angina pectoris and acute myocardial infarction and showed a trend of lower incidence in fatal and nonfatal stroke compared with diuretics in patients with mild to moderate essential hypertension (Wilhelmsen *et al*., 2005).

TENORMIN (atenolol), is a synthetic β-selective (cardio selective) adrenoceptor blocking agent, chemically described as benzeneacetamide, 4 –[2'-hydroxy-3'- [(1-methylethyl)amino]propoxy]. The molecular and structural formulae are:



Atenolol (free base) has a molecular weight of 266. It is a relatively polar hydrophilic compound with water solubility of 26.5 mg mL^{-1} at 37°C. Atenolol blocks the action of the sympathetic nervous system and reduces the heart rate thus treating the abnormally rapid heart rhythms. It also reduces oxygen demand of cardiac muscles by decreasing the force of cardiac muscles contraction and lowers blood pressure (Guyton and Hall, 2000).

Atenolol can be administered orally as tablets, capsules or syrup or by injection. Intravenous dose is largely dissipated by 12 h, whereas β-blocking activity of single oral doses of 50 and 100 mg is still evident beyond 24 h following administration (Benowitz, 1998). The most serious and frequent side effects of the drug are related to its β-receptor inhibition property, that include heart failure, bronchospasm, fatigue (Reith *et al*., 1996), resulting in metabolic changes affecting cholesterol concentration (Fogari *et al*., 1999; Kuster *et al*., 2002). Present study deals to observe the alterations in lipid profile of common rabbit blood following the administration of atenolol.

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MATERIALS AND METHODS

The experiment was conducted at the Department of Physiology, University of Karachi, in June 2005 to July 2005 for 27 days.

Animals: Eight common rabbits (*Oryctolagus cuniculus*) at 12 months of age, weighing from 1480-1570 g, obtained from local supplier were used in the experiment. They were kept in barred cages and placed in a well ventilated environment.

Feed: Three rabbits were kept as control and the remaining five were considered as test animals. They were fed on normal diet containing alfalfa grass, cabbage and carrots during the experiment.

Drug: The selected antihypertensive drug Tenormin (Atenolol by ICI, Pakistan) available in tablet form each containing 25 mg atenolol purchased from local chemist (Batch No. IP-1598-K.N). The recommended oral dose for human is 25 mg daily. The dose calculated for administration to the experimental animal was 0.6 mg kg^{-1} day^{-1}. This dose was administered orally to each test animal for 27 days.

Blood sampling: Blood samples obtained with the help of 3cc disposable syringes from the marginal vein of animal ear. Sampling was done on day 0, 3, 7, 10 and 27, respectively. To obtain plasma heparin was used as anticoagulant and each blood sample was centrifuged (Model YJ 03-043-4000) at 2500 rpm for 5 min; supernatant was transferred to eppendorf tubes and stored at 4°C.

Biochemical analysis: Biochemical analysis included the measurement of plasma total cholesterol, triglycerides, HDL-cholesterol (HDL-C) and LDL-cholesterol (LDL-C) by using biochemical kits (Randox, Cat.No. CH-200; TR-1696; CH-203; CH-1350). Absorbance was read on colorimeter (Model AE-11M, ERMA, INC.). Statistical analysis of data was performed by t-test and two-way ANOVA.

RESULTS

Cholesterol: On day 0, test animals having a mean cholesterol concentration of 49.29±0.64 mg dL^{-1}. A gradual non-significant reduction after the administration of 0.6 mg atenolol daily was observed in comparison to controls (Fig. 1). On day 27 all test rabbits showed a reduction of 13% in cholesterol concentration from its initial mean level i.e., 42.53±0.66 mg dL^{-1}, while control group attained a constant mean cholesterol level.

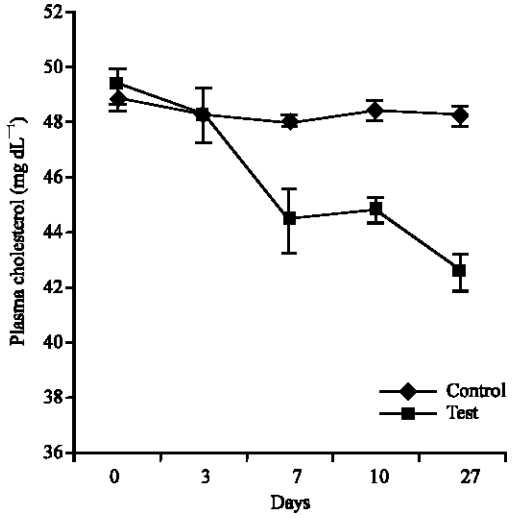

Fig. 1: Comparison of mean plasma cholesterol in control and test rabbits

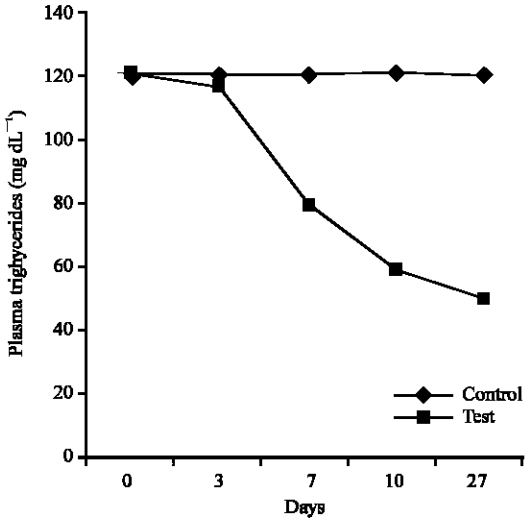

Fig. 2: Comparison of mean plasma triglycerides in control and test rabbits

Triglycerides: From day 3 to 27, a significant reduction ($p<0.05$) of mean triglycerides level is evident in test rabbits, following the administration of drug when compared with untreated controls. At the end of experiment on day 27 mean triglycerides level was 49.31±1.60 mg dL^{-1} in test animals (Fig. 2), indicating a mean fall of 59% of the concentration at the beginning of experiment, i.e., 121.75±0.43 mg dL^{-1}.

HDL-C: Figure 3 shows a significant reduction ($p<0.05$) in mean HDL-C levels on day 7 in test animals when compared with controls, whereas an elevation of mean HDL-C concentration was observed in test animals on

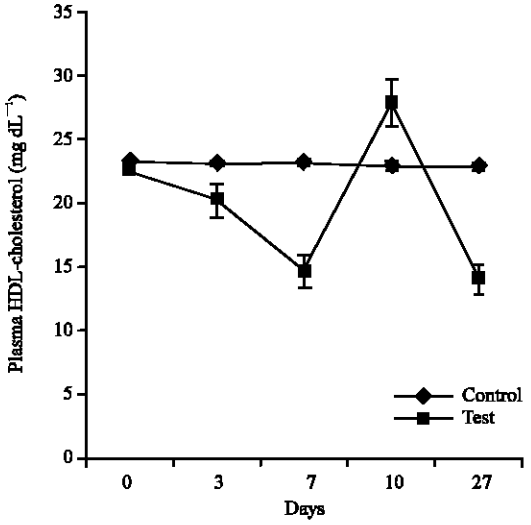

Fig. 3: Comparison of mean plasma HDL-cholesterol in control and test rabbits

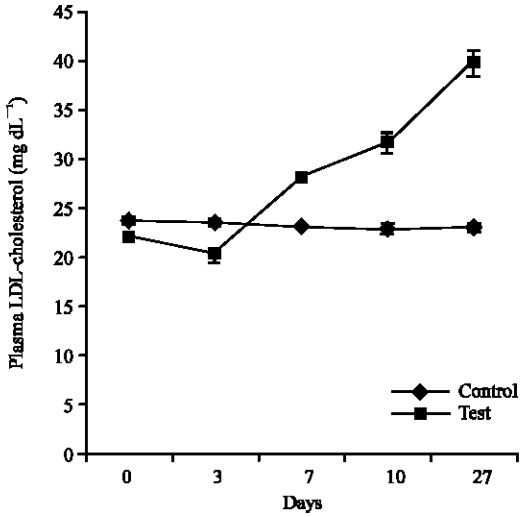

Fig. 4: Comparison of mean plasma LDL-cholesterol in control and test rabbits

day 10 i.e., 27.68±1.82 mg dL^{-1} that was followed by further reduction to 13.86 mg dL^{-1}, which is very close to the mean concentration on day 7.

LDL-C: LDL-C levels of test rabbits from day 0 to day 3, showed initially a mean fall of 1.64 mg dL^{-1} and from day 3 onwards LDL-C continued to increase non-significantly (Fig. 4), reaching a maximum mean level of 39.64±1.19 mg dL^{-1}. On average this rise was 45% of the initial mean concentration of LDL-C i.e., 21.88±0.17 mg dL^{-1}.

DISCUSSION

The β-adrenergic blockers are commonly recommended as first-line antihypertensive drug therapy. These drugs are efficacious but have some contraindications. (Mycek *et al*., 2000 a,b). For the present study atenolol used as selective β-blocker to observe the effects on blood lipid profile, shows a non-significant decrease in blood cholesterol level from day 3 to 10 and maintained at lower levels at the end of the study. This effect may be due to inhibition of β-adrenoceptors that slightly decreases HDL-C levels (Kuster *et al*., 2002).

Plasma triglycerides show a significant gradual reduction from day 3 and continue to decline at the end of experiment. Plasma HDL-C shows reduction from day 0 to day 7, elevated on day 10 and then again decreases back to level near the day 7. This observation got support by the study where atenolol increases HDL-C by 7% after one month, the change being due to rise of HDL3 sub-fraction (Valimaki *et al*., 1986). On the other hand plasma LDL-C levels slightly reduced from the day 0 to day 3 and then a gradual non-significant increase in the LDL-C level on day 27 is observed. The long term treatment with atenolol has an unfavorable effects on HDL-C and the HDL/LDL ratio (Thulin *et al*., 1999; Rabkins *et al*., 1994).

Findings also suggest that β-selective, β-blockers are likely to adversely affect the plasma lipids (Fogari *et al*., 1999) and they show a strong dyslipidemic effect with a prior normal or near normal base line lipid levels (Kuster *et al*., 2002). It is also suggested that β-blockers are less effective in lowering blood pressure in the elderly patients due to pathophysiologic conditions in the arteries, heart, kidneys, brain and on the metabolism of lipids and carbohydrates (Grossman and Messerli, 2002).

Thus atenolol is not appropriate drug as first-line therapy in elderly population. Most patients with hypertension will require two or more antihypertensive medications to achieve the blood pressure goal (Cushman *et al*., 2002; Black *et al*., 2001).

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