Alterations in Plasma Electrolytes and Serum Liver Enzymes Induced by Atenolol in Common Rabbits Oryctolagus cuniculus

Ruqaïya Hasan, Aisha Javaid, Habib Fatima and Wajeeha Safdar
Department of Physiology, University of Karachi, Karachi 75270, Pakistan

Abstract: This study is done to find out the effects of atenolol on plasma electrolytes sodium, potassium, calcium and on serum enzymes, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) of common rabbits Oryctolagus cuniculus following the administration of an oral daily dose of 0.6 mg atenolol for 27 days. Observations showed a non-significant rise in sodium concentration, a significant elevation and ultimate fall of potassium concentration and reduction of calcium levels significantly to half of the normal values. These findings suggest the diuretic action of drug; possibly the prolonged use cause the renal dysfunction. Long-term treatment of hypertension by atenolol may impair the hepatic function indicated by significant very low and high levels of serum AST and ALT, respectively.

Key words: Atenolol, antihypertensive, electrolytes, β-blocker

INTRODUCTION

Hypertension results from increased peripheral vascular smooth muscle tone, which leads to increased arteriolar resistance and reduced capacitance of the venous system (Mycek et al., 2000a). More than 90% of patients have essential hypertension, a disorder of unknown origin affecting the blood pressure-regulating mechanism (Williams, 2001).

Family history of hypertension increases the likelihood that an individual will develop hypertensive disease (Mycek et al., 2000a). Environmental factors such as stressful lifestyle, high dietary intake sodium, obesity and smoking further predispose an individual to the occurrence of hypertension. Diabetes mellitus is associated with physiological changes that potentiate dysfunction, including hypertension (Brown and Hu, 2001).

Mild hypertension can often be controlled with a single drug. More severe hypertension may require treatment with several drugs that are selected to minimize adverse effects of the combined regimen (Kaplan, 1998).

Beta-blockers are currently recommended as first-line drug therapy for hypertension (Mycek et al., 2000b). These agents are competitive antagonists. The β-blockers reduce blood pressure primarily by decreasing cardiac output. They may 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).

Drug information: TENORMIN (atenolol), a synthetic, β-selective (cardio selective) adrenergic receptor blocking agent, may be chemically described as benzene acetamide, 4-[2-hydroxy-3-[(1-methyl ethyl) amino] propoxy]. The molecular and structural formulas are:

![Molecular structure of atenolol]

Atenolol is available in 25, 50 and 100 mg tablets for oral administration. Atenolol is a β-adrenergic blocking agent. It inhibits the action of the sympathetic nervous system thus reduces the heart rate and is useful in treating aberrantly rapid heart rhythms. Atenolol also reduces the force of cardiac muscle contraction, lowers blood pressure and decreases the oxygen demand by cardiac muscles (Burns et al., 2004).

The most serious and frequent side effects of atenolol are related to its β-receptor blocking property, which include heart failure, bronchospasm and fatigue (Reith et al., 1996).

In the present study an attempt is made to observe the effects of short-term monotherapy with β-blocker atenolol (Tenormin) on plasma sodium, potassium, calcium and serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in domestic rabbits.
MATERIALS AND METHODS

Animals: Twelve months old male rabbits *Oryctolagus cuniculus*, weighing approximately 1470-1570 g, brought from local animal market and kept in separate cages in open atmosphere.

Feed: Five rabbits were considered as test animals and were fed with normal diet containing cucumber, alfalfa grass, cabbage, carrots, alternatively. The remaining three rabbits kept as control and were also fed with normal diet.

Drug: Antihypertensive drug Tenormin (Atenolol by ICI, Pakistan) available in tablets each containing 25 mg atenolol was purchased from local market (Batch No. IP-1598-K.N.). The recommended oral dose for human is 25 mg day\(^{-1}\) and an oral dose of drug calculated for experimental animals was 0.6 mg kg\(^{-1}\) day\(^{-1}\). Drug was administered to test animals for 27 days.

Blood sampling: Blood samples of animals including controls and tests were obtained on day 0, 3, 7, 10 and 27, respectively. Blood was drawn from marginal vein of rabbit ear using 3 cc disposable syringes.

To obtain plasma, heparinized blood was centrifuged (Model, YJ03-043-4000) at 2500 rpm for 5 min, supernatant was transferred to eppendorf tubes and stored at 4°C in refrigerator to be used next day for biochemical analysis of electrolytes.

To obtain serum, whole blood sample was kept for 1 h at room temperature then centrifuged, clear serum in the form of supernatant was used immediately for biochemical analysis of enzymes AST and ALT.

Biochemical analysis: Biochemical analysis was done by using plasma and serum separately. For the determination of electrolytes (sodium, potassium and calcium) and enzymes (AST and ALT), biochemical kits (Randox Cat. No. NA 7167, PT 1600, CA 590, AS 147, AL 146) were used. Absorbance was read on photoelectric colorimeter (Model AB-11M ERMA INC.). Data was analyzed statistically by t-test and two-way ANOVA.

RESULTS

Sodium: A consideration of Fig. 1a, indicates the mean plasma sodium concentration of test rabbits, which was 148.92±0.30 meq L\(^{-1}\) on day 0, after the daily oral administration of 0.6 mg atenolol, increased up to 249.82±3.25 meq L\(^{-1}\) on day 27. The significant (p<0.05) rise in sodium concentration was predominant from day 10 onwards depending on the duration of drug administered.

Fig. 1: Comparison of mean plasma electrolytes in control and test rabbits following the daily oral administration of 0.6 mg atenolol

However statistical analysis showed the elevation of mean sodium level in test animals was non significant when compared with controls.

Potassium: The mean plasma potassium concentration following the administration of drug on day 10 reached to a peak value of 29.32±1.53 meq L\(^{-1}\) in test rabbits which was significantly higher (p<0.05) than control value i.e., 5.0±0.12 meq L\(^{-1}\). From day 10 onwards mean potassium concentration in test animals continued to fall up to 13.65±1.88 meq L\(^{-1}\) in test animals, but did not reach to initial level of 4.62±0.19 meq L\(^{-1}\) on day 0 (Fig. 1b).

Calcium: The mean plasma calcium concentrations in control and test rabbits were 3.36±0.03 meq L\(^{-1}\) and 3.34±0.06 meq L\(^{-1}\) on day 0, respectively. After the administration of drug, test animals showed a reduction in mean calcium level (Fig. 1c), which became more significant (p<0.05) as treatment continued. On day 27 the mean calcium level in test group was 1.6±0.26 meq L\(^{-1}\) which was approximately half to its initial mean level.
Fig. 2: Comparison of mean serum enzymes in control and test rabbits following the daily oral administration of 0.6 mg atenolol

AST: In test rabbits, mean serum AST level on day 0 was 33.05±0.76 IU L⁻¹, which significantly (p<0.05) started to reduce, depending on the duration of drug administered daily for 27 days. The mean serum AST level in test animals on day 27 was 10.95±0.69 IU L⁻¹, showed a two third fall from the mean initial concentration (Fig. 2a).

ALT: A consideration of Fig. 2b, indicates that mean serum ALT concentration of test rabbits, was 10.47±0.38 IU L⁻¹ on day 0, started to elevate significantly (p<0.05) from day 7 following the administration of drug. On day 27 the mean level of ALT in test animals was 18.57±1.14 IU L⁻¹, which is about, two folds to its mean initial concentration.

DISCUSSION

The findings of present study suggest that atenolol may control blood pressure through the suppression of renin-angiotensin-aldosterone pathway (Takahashi et al., 1989). However the non significant increase of sodium concentration in plasma suggests that atenolol has mild diuretic effect resulting in dehydration (Hawks, 1988). Normally sodium reabsorption by aldosterone is in exchange for potassium ions but in the present study potassium concentration reached to maximum on day 10 following the treatment, again reduced significantly (p<0.05) indicating an indirect negative effect on sodium reabsorption to control blood pressure (Lijnen et al., 1990). The diuretic effect of β-adrenergic blocker also leads to hypocalcaemia which is evident by significant low levels of plasma calcium concentration, particularly in the later part of experiment suggesting the reduction of blood pressure during β-adrenoreceptor blockade is accompanied by a reduction of calcium concentration (Baumgart et al., 1986). A significant (p<0.05) alteration in serum AST and ALT concentrations according to Chemecky and Berger (2001), are indicative of the effects of β-blocker on liver and probably resulting in liver damage.

Thus it is concluded that β-adrenergic blocker for the treatment of hypertension should be used with caution as they cause electrolyte imbalance involving kidneys and liver. For the management of hypertension the recommendations include to moderately restrict sodium intake, increase potassium, calcium and magnesium intake (Davis and Jones, 2002). However current evidences suggest that potassium, calcium and magnesium may represent the important components of the diet rich in fruits and vegetables. The combination of these nutrients is of crucial importance for the achievement of optimal blood pressure reduction (Suter et al., 2002).

REFERENCES


