EXPLORATION OF TAMSULOSIN EFFECT ON CHOLESTEROL AND TRIGLYCERIDE IN NORMAL RATS

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ABSTRACT

Tamsulosin is used to manage benign prostate hyperplasia (BPH) and among the risk factors of BPH is obesity. The aim of this study was to verify tamsulosin effect on body total cholesterol and triglycerides in normal rats. Normal rats of six different groups (n=8) were orally given daily distilled water (5mg/kg), carvedilol (800µg/kg), tamsulosin doses (6µg, 12µg, 18µg and 40µg/kg) respectively for six (6) weeks. Cholesterol and triglyceride levels were determined at the end of the study.The results showed significant decreased in cholesterol and non-significant decreased in triglycerides levels compared to normal control. It is therefore concluded that tamsulosin has lowering effects on total cholesterol and triglycerides in normal rats. Tamsulosin may be useful in BPH associated obesity.

Keywords: *Tamsulosin; BPH; Cholestrol; Triglycerides; Obesity*

INTRODUCTION

Benign prostate hyperplasia (BPH) is a disease of lower urinary tract symptoms (LUTS) due to the bladder outlet blockage as a result of prostate enlargement (Schiwn *et al*., 2008). Many BPH patients visit hospitals for medical solutions (Karadeniz *et al.,* 2008). About 4.5million people in the United States of America visited hospital for BPH in 2000 (National Kidney and Urologic Diseases Information Clearing House, 2012). In Nigeria, there is no true data on the patients that visit hospitals BPH, but large number visit hospitals (Alhassan *et al.*, 2008 and Anunobi *et al*, 2011). BPH affects large number of people especially old age. Its incidence rate rises to 40%, 50%, 80% and 90%

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by the ages of 50, 60, 70 and 90 years respectively (Tag and Hee 2012). It was reported that about 210 million males (6% of the world population) were affected with BPH related symptoms as of 2010 (Vos, 2012). In Nigeria, the BPH rate was as high as 25% (Ezeanyika *et al.*, 2006). Since BPH is an age related disease, it occurs with co-morbidities such as diabetes mellitusand hypertension (Boyle and Napalkov, 1995; Sarma *et al.*, 2008).

However, alpha-1 adrenoceptors blockers are usually the most common choice for initial treatment of BPH (Black *et al.*, 2006; Marks *et al.*, 2009) as they relax the smooth muscles of bladder neck and the prostate, thereby enhancing urinary flow. Tamsulosin hydrochloride (flomax), a selective alpha-1 adrenoceptor blocker was developed to treat BPH related symptoms (Yamanouchi Pharmaceutical Company Limited, 2000). It selectively blocks subtypes alpha-1a and 1d adrenoceptors predominantly found in prostate, thereby causing prostate smooth muscle relaxation which eventually leads to reversal of BPH related symptoms (Silva *et al.*, 2014).Tamsulosin was found to have worked effectively even in comorbid conditions. Tamsulosin was found to have similar efficacy in treating both diabetic and non diabetic BPH patients (Martin *et al.*, 2000). Similarly, tamsulosin less specificity on subtype alpha-1b adrenoceptor found in vasculature has made it to have lower incidence of orthostatic hypotensionassociated with non-selective alpha-1 adrenoceptorblockers (Abrams *et al*., 1995; Lee, 2000).The ability of tamsulosin to work effectively even in co-morbid conditions has made it to be the initial drug of choice by most BPH patients with co-morbidities (Schulman, 2008).The aim of this study was to determine tamsulosin effect on body total cholesterol and triglycerides in normal rats.

MATERIALS AND METHODS

Experimental animals:

Male albino rats of wistar strain (90 – 120g body weight) bred in Faculty of Veterinary Sciences of University of Ibadan, Nigeria was used. They were kept (two/cage) in standard cages (21.5 x 32 x 14cm) with mesh bottoms (freshly spread with wood saw to absorb urine) and wire mesh covers under a standardconditions of temperature (18 – 29^{o}C), humidity (30 - 70%) and illumination (12:12 hours light/dark cycle, light on at 7am -7pm) for seven (7) days before the beginning of the experiment. Tap water and pelletized grower feeds pellets product of (Vital feeds, product of Grand cereals plc, Jos, Nigeria) were supplied *ad libitum* throughout theexperimental periods. Ethical approval

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was obtained before the commencement of the experiments from the Usmanu Danfodiyo University ethical committee on animal care and use.

Experimental design:
Forty eight (48) normal male albino wistar rats were selected (using Computer random number generator) and randomlydivided into 6 groups (n = 8). Group 1, control (vehicle) received 5ml/kg distilled water. Group 2, positive control received 800µg/kg carvedilol. Group 3, 4, 5, and 6 received tamsulosin at dose of 6µg/kg, 12µg/kg,18µg/kgand 40µg/kg. Similarly, the weight of each rat was measured at the beginning of the study and at each week until the end of the study.

Drugs used:
Tamsulosin hydrochloride powder (product of Sigma-Aldrich, Germany)and Carvedilol powder (product of Sigma-Aldrich, Germany).

Dose preparation and administration:
Human oral therapeutic dose (0.4mg) of tamsulosin was extrapolated to rats based on geometric (body weight) and allometric scaling (body surface area). Geometric doseof 6µg/kg was calculated and increased to 12µg/kg and 18µg/kg using Modified Fibonaccidose escalation method. While allometric dose of 40µg/kg was calculated using body surface area normalization method (Jang-Woo *et al*., 2010). Carvedilol dose of 800µg/kg was selected based on previous study. Both tamsulosin and carvedilol doses were suspended in distilled waterfor oral administration and were given daily for 6 weeks using a metal cannula attached to 1ml syringe (Suresha *et al*., 2013).

Determination of cholesterol and triglyceride:
At 6^{th} weeks, animals were sacrificed after overnight fasting of 8 hours by head concussion and immediately dissected. Blood was collected via cardiac punctureinto plain sample bottles immediately. Blood were then allowed to stand for 30minutes to clot, and then centrifuged for 10 minutes at 4000g to collect serum which was preserved at -20^{o}c.Cholesterol and triglycerides were determined by the calometric method using wet reagent diagnostic kits (Agappe Diagnostics Switzerland GmbH).

STATISTICAL ANALYSIS
All results were expressed as Mean $\pm$ SEM. Results were analyzed using ANOVA, and then followed by Dunnettpost hoc comparison. All statistical calculations and graphs were done using Graphpad prism 6 version for

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windows. The significant level was set at 95 percent (P <0.05) confidence interval.

RESULTS

Effects of chronic administration of tamsulosin on total cholesterol levels at 6th week

Table 1: Effect of various tamsulosin doses on total cholesterol levels at 6th week.

Control (vehicle),5ml/kg	Positive (carvedilol),800µg/kg	Tamsulosin, 6µg/kg	Tamsulosin, 12µg/kg	Tamsulosin, 18µg/kg	Tamsulosin, 40µg/kg
94.0 ± 7.44	81.25 ± 6.89**	89.0 ± 7.21ns	77.13 ± 2.72**	81.57 ± 1.21**	79.0 ± 6.68**

Results expressed as Mean ± SEM. ANOVA was used to analyze the results, and then followed by Dunnett post hoc for comparison.**Significant difference (P <0.01) compared to control (vehicle) group.ns No significant difference between the group (p > 0.05) as compared to control (vehicle).

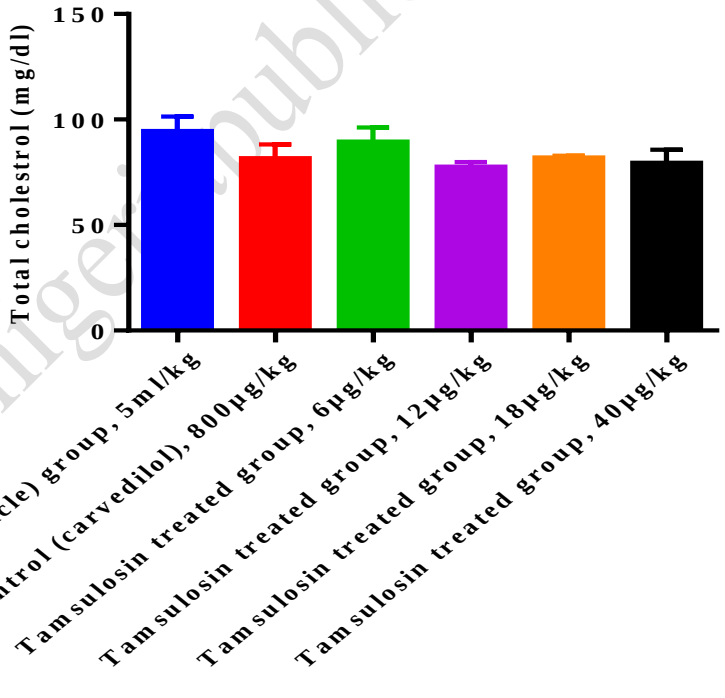

Figure 1: Effect of various tamsulosin doses on total cholesterol levels at 6th week.

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Results expressed as Mean ± SEM. ANOVA was used to analyze the results, and then followed by Dunnett post hoc for comparison. **Significant difference (P <0.01) compared to control (vehicle) group.

Effects of chronic administration of tamsulosin on triglyceridelevelsat 6th week:

Oral administration of tamsulosin for 6 weeks insignificantly ($p < 0.05$) decreased triglyceride levels as compared to control (vehicle) values. Similarly, carvedilol showed insignificant ($p < 0.05$) decreased as compared to control (vehicle) values (Table 2/Figure 2).

Table 2: Effect of various tamsulosin doses on triglyceride levels at 6th week.

Control (vehicle),5ml/kg	Positive (carvedilol),800µg/kg	Tamsulosin, 6µg/kg	Tamsulosin, 12µg/kg	Tamsulosin, 18µg/kg	Tamsulosin, 40µg/kg
83.38 ± 12.78	61.63 ± 5.81^{ns}	61.67 ± 4.67^{ns}	80.88 ± 10.96^{ns}	72.29 ± 5.21^{ns}	58.71 ± 4.10^{ns}

Results expressed as Mean ± SEM. ANOVA was used to analyze the results, and then followed by Dunnett post hoc for comparison.^{ns}No significant differences between the groups ($p > 0.05$) as compared to control (vehicle).

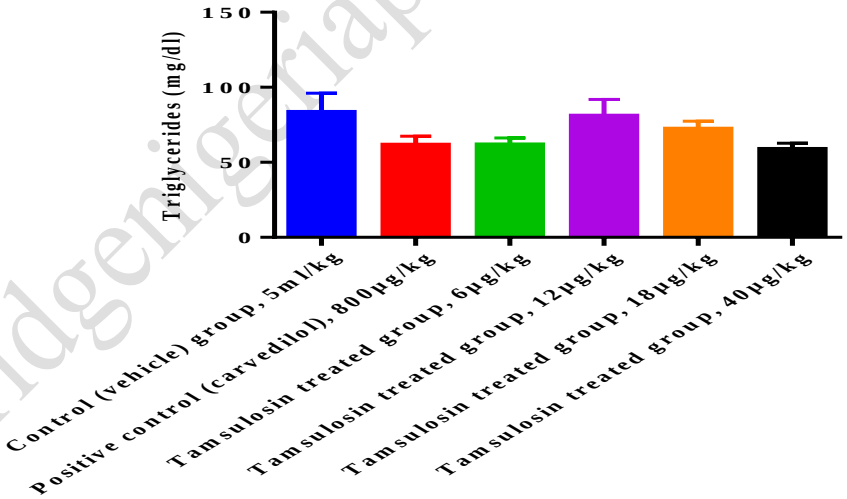

Figure 2: Effect of various tamsulosin doses on triglyceride levels at 6th week.

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Results expressed as Mean ± SEM. ANOVA was used to analyze the results, and then followed by Dunnett post hoc for comparison.^{ns} No significant differences between the groups ($p > 0.05$) as compared to control (vehicle).

DISCUSSION

In a chronic hyperglycemic condition, the ability of liver to get rid of cholesterol from blood stream is blocked due to glycosylation of low density lipoproteins and its receptors which resulted to the onset of atherosclerosis and latercardiovascular diseases which are secondary complications of type-2 diabetes (Shivani *et al*., 2013). Although alpha-1 blockers were reported to have an advantageous effects on total cholesterol and triglycerides (Nitin, 2014),chronic use of alpha-1 antagonist (doxazosin) in hypertensive patients caused significant decreased in total cholesterol (Ishimitsy *et a.*, 1996), while prazosin, indoramin and urapidil were reported to have no effect on cholesterol synthesis of hypertensive patients (Krone *et al.*, 1987). In the present study, chronic oral administration of tamsulosin caused significant reduction in total cholesterol with no effects on triglyceride. Mechanisms through which the alpha-1 blockers affect serum lipid were known. Blockade of alpha-1 receptors causes low density lipoprotein receptors to be up regulated thatleads to suppression of HMG co-A reductase enzymes activity and at the end causes decrease in total cholesterol and low density lipoprotein (Pool *et al*, 1990). Also, alpha-1 blockers affect serum lipids throughaccelerating activity of lipoprotein lipase enzymes that determine the breakdown of very low density lipoproteins (Krone *et al*, 1987).

CONCLUSION

Tamsulosin use for 6th weeks caused reduction in serum cholesterol and triglyceride levels.

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