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Effect of Tamsulosin on Fasting Blood Glucose and Plasma Insulin Levels in Normal Wistar Rats

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Abstract

This paper aimed to determine levels of fasting blood sugar and plasma insulin in normal rats administered with tamsulosin. Standard methods and procedures were followed to achieve the objective of this paper. At the 3rd week of the study, group of rats treated with tamsulosin high dose (40µg/kg) revealed a significant increase in fasting blood glucose (FBG) ($P<0.05$) (5.31±0.12 mmol/l) compared to normal control and tamsulosin low dose (12µg/kg) groups (4.69±0.16), but showed no significant difference compared to positive control group(4.83±0.08). At the 6th week of the study, a significant increase ($P<0.05$) in FBG was noticed in the group of rats treated with carvedilol (positive control) (5.70±0.19mmol/l), tamsulosin low dose (12µg/kg)(5.67±0.16) and high dose tamsulosin (40µg/kg) (6.02±0.23mmol/l) compared to normal control group. Other inter-groups comparisons were not significantly different ($P>0.05$). At the 7th week of the study, only group of rats treated with tamsulosin high dose (40µg/kg) maintained significant higher values ($P<0.05$) (5.23±0.12mmol/l) in FBG compared to normal control group. Other inter-groups comparisons were not significantly different ($P>0.05$). At the 8th week, FBG of the group of rats treated with carvedilol (positive control), and groups treated with either tamsulosin low dose (12µg/kg) or tamsulosin high dose (40µg/kg) did not show any significant difference compared to the normal control group. Other inter-group comparisons were not significantly different ($P>0.05$). For insulin level observations, at the 6th week of the study, groups of rats treated with either carvedilol (positive control), low dose tamsulosin (12µg/kg) or high dose tamsulosin (40µg/kg) revealed a significantly higher elevation ($P<0.05$) 0.13± 0.01 µg/l, 0.12± 0.02 µg/l, 0.12± 0.01 µg/l) in plasma insulin levels than the normal control group(0.05± 0.01 µg/l).Other inter-group comparisons were not significantly different ($P>0.05$). At the 8th week, only group of rats treated with carvedilol (positive control) showed a significant higher value ($P<0.05$) (0.09±0.002 µg/l) of plasma insulin compared to normal control (0.04± 0.0 µg/l). Other inter-group comparisons were not significantly different ($P>0.05$). The results of the study showed that tamsulosin caused hyperglycemia as well as insulin resistance in both normal rats.

Keywords: Tamsulosin; hyperglycemia; fasting blood sugar; plasma insulin

Introduction

Benign prostate hyperplasia (BPH) and associated lower urinary tract symptoms (LUTS) are highly prevalent among older men and represent a huge challenge to public health worldwide. Particularly in Nigeria, 1 in every 4 older men above 50 years present 1 or more BPH symptoms (Egan, 2016).To address this challenge the leading conventional chemotherapy involved the use of tamsulosin (Dikko, 2019; Dikko and Sarkingobir, 2020). After tamsulosin was approved, there are a number of adverse drug reactions (ADRs) that are being reported due to its use (Kang *et al*., 2009). These ADRs include skin rash, respiratory symptoms, constipation, vomiting, and visual problems; which are associated with hyperglycemia or hyperinsulinemia (Dikko, 2019; Dikko *et al*., 2020a). These are symptoms similarly reported in people with hyperglycemia or diabetes (Usman and Mohammed, 2015; Abubakar*et al*., 2016). On the other hand, hyperglycemia is a risk factor of BPH and metabolic syndrome. Carvedilol, a non-selective β-blocker, with α_1-adrenoceptor and moderate calcium channel antagonistic property was reported to have a negative effect on glucose homeostasis in experimental animals that is why it was used as positive control (Bilbis*et al*., 2012; Alwachis*et al*., 2014; Dikko, 2019)**.** Hyperglycemia developed into diabetes mellitus. Diabetic patients have >2× risk of developing heart failure (HF). Cardiovascular outcomes, hospitalization, and prognosis are worse for patients with diabetes mellitus relative to those without. Because of the structural and functional

changes that characterize diabetic cardiomyopathy, and a complex underlying, and interrelated pathophysiology (Bilbis *et al*., 2012; Abdussalam *et al*., 2019; Kenny and Abel, 2019).Thus it is pertinent to conduct an investigation on the effect of tamsulosin on blood glucose, and plasma insulin levels. The objective of this paper was to determine the effect of tamsulosin administration on blood glucose and insulin levels in normal rats.

Materials and Methods

Animals

Male adult albino Wistar rats were purchased from the Faculty of Veterinary Sciences of University of Ilorin, Nigeria. The rats were kept at the animal house of the Department of Pharmacology and Therapeutics, Usmanu Danfodiyo University Sokoto, in plastic cages, with bottoms (freshly spread with a wood saw to absorb urine) at room temperature with 12 hours light/12 hours dark cycle. Cages were cleaned daily and disinfected weekly with 70% alcohol. The rats were left for fourteen (14) days acclimatization. Tap water and grower feeds pellets product of were supplied *ad libitum*.

Experimental Design

Forty (40) male albino Wistar rats (278-307g) were selected at random and divided into four (4) groups of ten (10) rats each, namely, GROUP I, II, III and IV. They were left for three (3) days before the commencement of the study

- **Group I** (Normal control): Distilled water(5ml/kg)
- **Group II** (Positive control): Carvedilol(800µg/kg
- **Group III** (Tamsulosin treated): Tamsulosin (12µg/kg)
- **Group IV** (Tamsulosin treated): Tamsulosin(40µg/kg)

All treatments (Distilled water, Carvedilol and Tamsulosin) were administered once daily through oral route using metal cannula attached to a 2ml syringe for the period of six (6) weeks. After the 6th week of the study, all the treatments were withdrawn for a further 2 weeks (7th and 8th weeks). During the withdrawal period, only water and food were provided *ad libitum* to the rats (Dikko, 2019).Carvedilol, a non-selective β-blocker, with α_1-adrenoceptor and moderate calcium channel antagonistic property was reported to have a negative effect on glucose homeostasis in experimental animals that is why it was used as positive control(Dikko, 2019)**.**

Determination of fasting blood glucose of normal rats administered with tamsulosin

Blood was collected via tail tip incision at baseline (0th) and at 3rd, 6th, 7th and 8th completed weeks. Before each collection, animals fasted for 8 hours. A standardized digital glucometer was used to determine fasting blood glucose levels (Dikko, 2019).

Determination of plasma insulin of normal rats administered with tamsulosin

At 0th, 6th and 8thcompleted week of the study, all the animals were fasted for 8 hours. After which 50ul blood was collected via tip tail by nicking the tip tail with a scalpel blade and gently stripping the tail. Blood was collected into chilled heparinized capillary tubes placed on ice. The tubes were then sealed using plasticine and then taken immediately to laboratory for processing. The samples were centrifuged using the microhaematocrit machine at 7000 rpm for 5 minutes to separate plasma from blood cells. Plasma was collected by cutting the tube at a level between plasma and blood cells. ELISA kit was used to determine the plasma insulin (Dikko, 2019).

Results

Fasting blood glucose (FBG) at baseline (0th) and at 3rd, 6th, 7th and 8th week of the study in normal rats administered with tamsulosin

At the 3rd week of the study, group of rats treated with tamsulosin high dose (40µg/kg) revealed a significant increase in FBG ($P<0.05$) compared to normal control and tamsulosin low dose (12µg/kg) groups, but showed no significant difference compared to positive control group (Table 1). At the 6th week of the study, a significant increase ($P<0.05$) in FBG was noticed in the group of rats treated with carvedilol (positive control), tamsulosin low dose (12µg/kg) and high dose tamsulosin (40µg/kg) compared to normal control group. Other inter-groups comparisons were not significantly different ($P>0.05$; Table 1). At the 7th week of the study, only group of rats treated with tamsulosin high dose (40µg/kg) revealed significant higher values ($P<0.05$) in FBG compared to normal control group. Other inter-groups comparisons were not significantly different ($P>0.05$; Table 1). At the 8th week of the study, FBG of the group of rats treated with carvedilol (positive control) as well as groups

of rats treated with either tamsulosin low dose (12µg/kg) or tamsulosin high dose (40µg/kg) failed to reveal any significant differences compared to the normal control group. Other inter-group comparisons were not significantly different (P>0.05; Table 1).

Table 1: Effect of tamsulosin on fasting blood glucose in normal rats administered with tamsulosin.

Week	Normal control (Distilled water), 5ml/kg	Positive control (Carvedilol), 800µg/kg	Tamsulosin treated group, 12µg/kg	Tamsulosin treated group, 40µg/kg
0th	4.60± 0.13^{a}	4.30± 0.12 ^{a}	4.32± 0.11^{a}	4.28± 0.07^{a}
3rd	4.57± 0.17 ^{a}	4.83± 0.08$^{a, b}$	4.69± 0.16^{a}	5.31± 0.12^{b}
6th	4.62± 0.14^{a}	5.70± 0.19^{b}	5.67± 0.16^{b}	6.02± 0.23^{b}
7th	4.58± 0.07^{a}	5.06±0.10 $^{a, b}$	5.04± 0.21$^{a, b}$	5.23± 0.12^{b}
8th	4.62± 0.09^{a}	4.94± 0.10^{a}	4.98± 0.17^{a}	5.13± 0.33^{a}

Results expressed as Mean (mmol/l) ± SEM (n=10). ANOVA was used followed by Tukey Kramer post hoc test. Groups within the same row with different superscript letters are significantly different.

Determination of plasma insulin at baseline (0th) and at 6th and 8th weeks of the study in normal rats administered with tamsulosin

At the 6th week of the study, groups of rats treated with either carvedilol (positive control), low dose tamsulosin (12µg/kg) or high dose tamsulosin (40µg/kg) revealed a significantly higher elevation (P<0.05) in plasma insulin values than the normal control group. Other inter-group comparisons were not significantly different (P>0.05; Table 2). At the 8th week of the study, only group of rats treated with carvedilol (positive control) maintained a significant higher value (P<0.05) of plasma insulin compared to normal control. Other inter-group comparisons were not significantly different (P>0.05; Table 2).

Table 2: Effect of tamsulosin on plasma insulin in normal rats administered with tamsulosin

Week	Normal control (Distilled water), 5ml/kg	Positive control (Carvedilol) 800µg/kg	Tamsulosin treated group, 12µg/kg	Tamsulosin treated group, 40µg/kg
0th	0.04± 0.01 ^{a}	0.03± 0.01^{a}	0.03± 0.01^{a}	0.05± 0.01^{a}
6th	0.05± 0.01^{a}	0.13± 0.01^{b}	0.12± 0.02^{b}	0.12± 0.01^{b}
8th	0.04± 0.01^{a}	0.11± 0.02^{b}	0.09±0.002$^{a, b}$	0.06± 0.01$^{a, b}$

Results expressed as Mean (µg/l) ±SEM (n=10). ANOVA was used followed by Tukey Kramer post hoc test. Groups within the same row with different superscript letters are significantly different.

Discussion

The present studies show an elevation in fasting blood glucose of normal rats treated with tamsulosin drug as indicated by table 1. Several mechanisms might be responsible for the observed ability of tamsulosin to cause elevated blood glucose in Wistar rats. The findings might be due to the documented effect of tamsulosin in blocking alpha-1 adrenoceptors in experimental animals (Shivaprasad *et al.,* 2015). Several studies have tried to elucidate the important role played by alpha-1adrenoceptors in blood glucose homeostasis in experimental animals and through the regulation of blood glucose uptake. Cheng *et al*. (2000) reported an improvement in glucose uptake into isolated white adipocytes when methoxamine (an alpha 1 agonist) was administered to Wistar rats to stimulate alpha-1 adrenoceptors. Shi *et al.* (2017) echoed an improvement in glucose tolerance and cardiac glucose intake when alpha-1 adrenoceptors were stimulated in transgenic mice. Similar findings have also been reported in some clinical studies showing that stimulation of alpha-1 adrenoceptors by phenylephrine (an alpha 1agonist) and noradrenaline (non-selective alpha agonist) resulted in an increase in glucose uptake in human adipose tissue(Boschmann *et al.,* 2002; Flechtner-Mors *et al.,* 2004). On the other hand, it has been documented that blockade of alpha 1 receptors leads to impairment in the tissue uptake of blood glucose (Cheng *et al.,* 2000; Shivaprasad *et al.,* 2015). Another possible explanation by which the drug

produces such outcomes is by increasing insulin secretion, as evidenced by the increase in plasma insulin in the normal rats treated with tamsulosin. A one study revealed an elevation in plasma hyperinsulinemia) when alpha-1 adrenoceptors were blocked in experimental rats(Ahrén *et al.,* 2008)**.** It is popular that hyperinsulinemiais risk factors for the of insulin resistance (Ducluzeau *et al.,* 2002). Insulin resistance connotes the inability of insulin to bring normal cellular glucose uptake at a certain insulin level. During insulin resistance, pancreatic cells continue to release more insulin in response to the rising level of blood glucose stimulus, which in turn lead to hyperinsulinemia(Siddiqui *et al.,* 2013).

As seen in the present study, the effect of carvedilol in increasing fasting blood glucose unhalts even after withdrawal of the drug, while the fasting blood glucose of the animals treated with tamsulosin were not significantly different from that of the normal control group. This portend that, the hyperglycaemic effect of tamsulosin may be reversible after the removal of the drug. Studies said the effect of some drugs failed to seized even after withdrawal because some coupling molecules were still present in the activated form,while the effects of other drugs tend to cease as soon as the drug is dissociated from their receptors (Katzung, 2004; Suresha *et al*., 2013; Dikkko, 2019).

According to the results of this study tamsulosin cause hyperglycemia and increased plasma insulin. These effects are diabetes preludes or portends (Abubakar*et al*., 2016; Muhammad *et al*., 2015; Isa *et al*., 2013; Chika and Yahaya, 2019).The increased in glucose level is the stimulator of increased in insulin release by the beta cells of the pancreas; but the persistent increased insulin level show that the insulin has a lesion in its normal mechanism of action, hence the continuous high level. And high insulin level coupled with high glucose is delineation in type 2 diabetes mellitus (type 2 DMM).Type 2 DMM is more prevalent in adults. Hence, the use of tamsulosin in older men could easily predispose them to diabetes mellitus (especially the type 2).Diabetes is an eminent threat to public health worldwide. It causes much morbidity, death, health spending, and reduced life expectancy of its patients (Usman *et al*., 2015; Isa *et al*., 2013).Thus, this ADR recorded by tamsulosin could be a factor that may discourage its continuous use in the Benign prostate hyperplasia (BPH) chemotherapy (Umar *et al*., 2010; Umar *et al*., 2016; Dikko *et al*., 2020).There is need to give more monitoring and supervision unto people who use tamsulosin.

Conclusion

The results of the study showed that tamsulosin caused hyperglycemia as well as insulin resistance in normal rats. However, the induced hyperglycemia disappeared after tamsulosin withdrawal for two weeks in normal rats.

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