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Research Article

Effect of Tamsulosin Administration on Oral Glucose Tolerance (OGT) In Normal Wistar Rats

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Summary: The objective of this study was to determine the effect of administration of tamsulosin on oral glucose tolerance in normal Wistar rats. Forty (40) male albino Wistar rats were selected and divided into four (4) groups of ten (10) rats each, viz, GROUP I, II, III and IV. 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).Different treatments of Distilled water, Carvedilol and Tamsulosin were administered once every day orally 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 After the 6th week of the study, all the treatments were withdrawn for a further 2 weeks (7th and 8th weeks). The Animals underwent 8 hours fasting. OGTT was done at baseline (0th), and then at3rd, 6th, 7thand 8th weeks. The blood glucose of all the animals was measured via tip tail incision at 0hours (pre-glucose load). Then, 2g/kg of D(+)-glucose powder dissolved in distilled water was administered to all the animals orally; after which blood samples were measured via tail tip incision at 30, 60 and 120 minutes using standard glucometer. ANOVA and Tukey Kramer post hoc test was used. The results were revealed therein. At the baseline of the study, 2nd, 3rd week, the groups of rats treated with carvedilol (positive control),tamsulosin high dose (40µg/kg) or low dose (12µg/kg) did not show any significant difference ($P>0.05$) in total area under the oral glucose tolerance curve compared to the normal control group and other inter group comparison. At the 6th week of the study, the group of rats treated with carvedilol (positive control), tamsulosin low dose (12µg/kg) and tamsulosin high dose (40µg/kg) revealed significantly higher values ($P<0.05$) of total area under the oral glucose tolerance curve compared to the normal control group. Other inter-group comparisons were not significantly different ($P>0.05$). At the 7th week of the study, the group of rats treated with carvedilol (positive control), tamsulosin low dose (12µg/kg) and tamsulosin high dose (40µg/kg) revealed no significant differences ($P>0.05$) in total area under the oral glucose tolerance curve compared to normal control group and other inter-groups comparison. At the 8th week of the study (two weeks after treatments withdrawal), only group of rats treated with carvedilol (positive control) revealed significantly higher values ($P<0.05$) of total area under the oral glucose tolerance curve than the normal control group. Other inter-group comparisons were not significantly different. The current study revealed that tamsulosin affects the glucose tolerance of the Wistar rats, thereby causing hyperglycemia.

Keywords*: Tamsulosin, hyperglycemia, Oral glucose tolerance test (OGTT, benign prostatic hyperplasia (BP), carvedilol*

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INTRODUCTION

Glucose tolerance impairment is a state of increased risk of progressing to diabetes. It also increases the risk of cardiovascular disease. Thus, it is a risk factor for future diabetes or adverse outcomes (WHO, 2006). The prevalence of impaired glucose tolerance is increasing among the older men across the various continents of the world (WHO, 2006). Presently, oral glucose tolerance test (OGTT) is regarded as the gold standard for the diagnosis of diabetes (Patrick, 2012). OGTT can be affected by many factors such as carbohydrate intake and duration of fasting before the test, the time of the day the test is carried out, carbohydrate intake during test, activity during the test, caffeine consumption or smoking during the fasting. Therefore Wistar rats are the good candidates to manage and monitor larger samples (Patrick, 2012).

Clinically, hyperglycemia is a persistent blood glucose level above 11mmol/l for more than two (2) hours after meals or over 6.9mmol/l after fasting. Hyperglycemia occurs when insulin is unable to stimulate blood glucose uptake in target tissues mainly skeletal muscles. Medical investigations to establish the presence of hyperglycemia includes oral glucose tolerance test (OGTT) which is used to determine how swiftly glucose is cleared from the blood after its ingestion through oral route (Suresha *et al*., 2013). OGTT is a medical investigation primarily adopted to detect glucose intolerance since it shows post-prandial glucose excursion. OGTT is used to test for diabetes, insulin resistance and the inability of the pancreas beta cells to secrete insulin (Dikko, 2019). OGT is the common glucose tolerance test that is widely used to check how body shuttle glucose from blood into the tissues (United States Library of Medicine, 2020). It is indicative when other tests are insufficient in establishing or ruling out the diabetes diagnosis (Jerry, 2018). That is why it was carried out to determine the ability of tamsulosin to cause hyperglycemia in rats.

Adverse drug reactions (ADRs) refers to any undesirable response presented due to a drug by biological system (more especially humans) at normal doses (WHO, 2005; Umar *et al*., 2010; Umar *et al*., 2016). Due to ADRs many drugs were withdrawn from the market during the last century (Preissner *et al*., 2015). Hyperglycemic effect was the adverse drug reaction (ADR) of tamsulosin in benign prostatic hyperplasia (BPH) and associated lower urinary tract symptoms (LUTS) human patients as reported by some past studies (Dikko *et al*., 2020a; Dikko *et al*.,2020b). ADR is one of the leading causes of iatrogenic diseases throughout the world. Globally, it cost about 4 billion USD every year, and leads to about 5% hospital admissions, 28% emergency department's visits, and 5% hospital deaths (Umar *et al*., 2016; Oduala *et al*., 2018). ADRs can cause patients to lose confidence in healthcare or drugs; and on the other hand increase self-medication or precipitate further ADRs. Moreover, cost of ADRs management can be high or precipitate other ADRs, and in turn leading to large burden on the patients, healthcare system, and government (Dikko *et al*., 2020a; Dikko *et al*., 2020b). One of the escalating factors of the trend is the underreporting of ADR from the patients and healthcare givers. Sources that are utilized to detect unidentified ADRs of drugs include anecdotal reports, observational studies, clinical trials, systematic reviews, or animal data (Onakpoya *et al*., 2016). Certain measures are followed to minimize ADRs such as careful medication review, good education to patients and healthcaregivers, monitoring and pharmacovigilance among others (Woodcock, 2016; Chika *et al*., 2018; Ganiyu and Erah, 2018). The objective of this study was to determine the effect of administration of tamsulosin on oral glucose tolerance in normal Wistar rats.

MATERIALS AND METHODS

Animals: Seventy (70) male adult albino Wistar rats were obtained from the breeding units of Faculty of Veterinary Sciences of University of Ilorin, Nigeria. The rats were kept in the animal house of the Department of Pharmacology and Therapeutics, Usmanu Danfodio 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 were supplied ad libitum.

Experimental Design: Forty (40) male albino Wistar rats were selected from the 70 rats purchased, using random number generator (computer software) and divided into four (4) groups of ten (10) rats each, viz, GROUP I, II, III and IV. They were allowed 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)

Different treatments of Distilled water, Carvedilol and Tamsulosin were administered once every day (during the research course) 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 served ad libitum (Suresha *et al*., 2013; Chika *et al*., 2018).

Oral glucose tolerance test (OGTT) in normal rats administered with tamsulosin

OGTT was done at baseline (0th), and then at3rd, 6th, 7thand 8th weeks. Prior to each OGTT, animals underwent 8 hours of fasting. The blood glucose of all the animals was measured via tip tail incision at 0hours (pre-glucose load). Then, 2g/kg of D(+)-glucose powder dissolved in distilled water was administered to all the animals orally (Suresha *et al*., 2013); after which blood samples were measured via tail tip incision at 30, 60 and 120 minutes. A Standardized digital glucometer (Accu check) was used to measure blood glucose levels. Glucometer standardization was done by testing rat plasma with standard (glucose oxidase) and glucometer methods in order to assess their consistency (Suresha *et al*., 2013; Chika *et al*., 2018). ANOVA was used then followed by Tukey Kramer post hoc test.

RESULTS

Oral glucose tolerance test at baseline (0th) of the study in normal rats administered with tamsulosin: At the baseline of the study, the groups of rats treated with carvedilol (positive control),tamsulosin high dose (40µg/kg) or low dose (12µg/kg) failed to show any significant difference ($P>0.05$) in total area under the oral glucose tolerance curve (Fig. 1A) compared to the normal control group and other inter group comparison.

Oral glucose tolerance test at 3rd week of the study in normal rats administered with tamsulosin: At the 3rd week of the study, the groups of rats treated with carvedilol (positive control),tamsulosin high dose (40µg/kg) or low dose (12µg/kg) did not show any significant difference ($P>0.05$) in total area under the oral glucose tolerance curve (Fig 1B) compared to the normal control group and other inter group comparison.

Oral glucose tolerance at 6th week of the study in normal rats administered with tamsulosin: At the 6th week of the study, the group of rats treated with carvedilol (positive control), tamsulosin low dose (12µg/kg) and tamsulosin high dose (40µg/kg) revealed significantly higher values ($P<0.05$) of total area under the oral glucose tolerance curve (Fig. 1C) compared to the normal control group. Other inter-group comparisons were not significantly different ($P>0.05$).

Oral glucose tolerance test at 7th week (one week after tamsulosin withdrawal) of the study in normal rats administered with tamsulosin: At the 7thweek of the study, the group of rats treated with carvedilol(positive control),tamsulosin low dose (12µg/kg)and tamsulosin high dose (40µg/kg)revealed no significant differences ($P>0.05$)in total area under the oral glucose tolerance curve (Fig 1D) compared to normal control group and other inter-groups comparison.

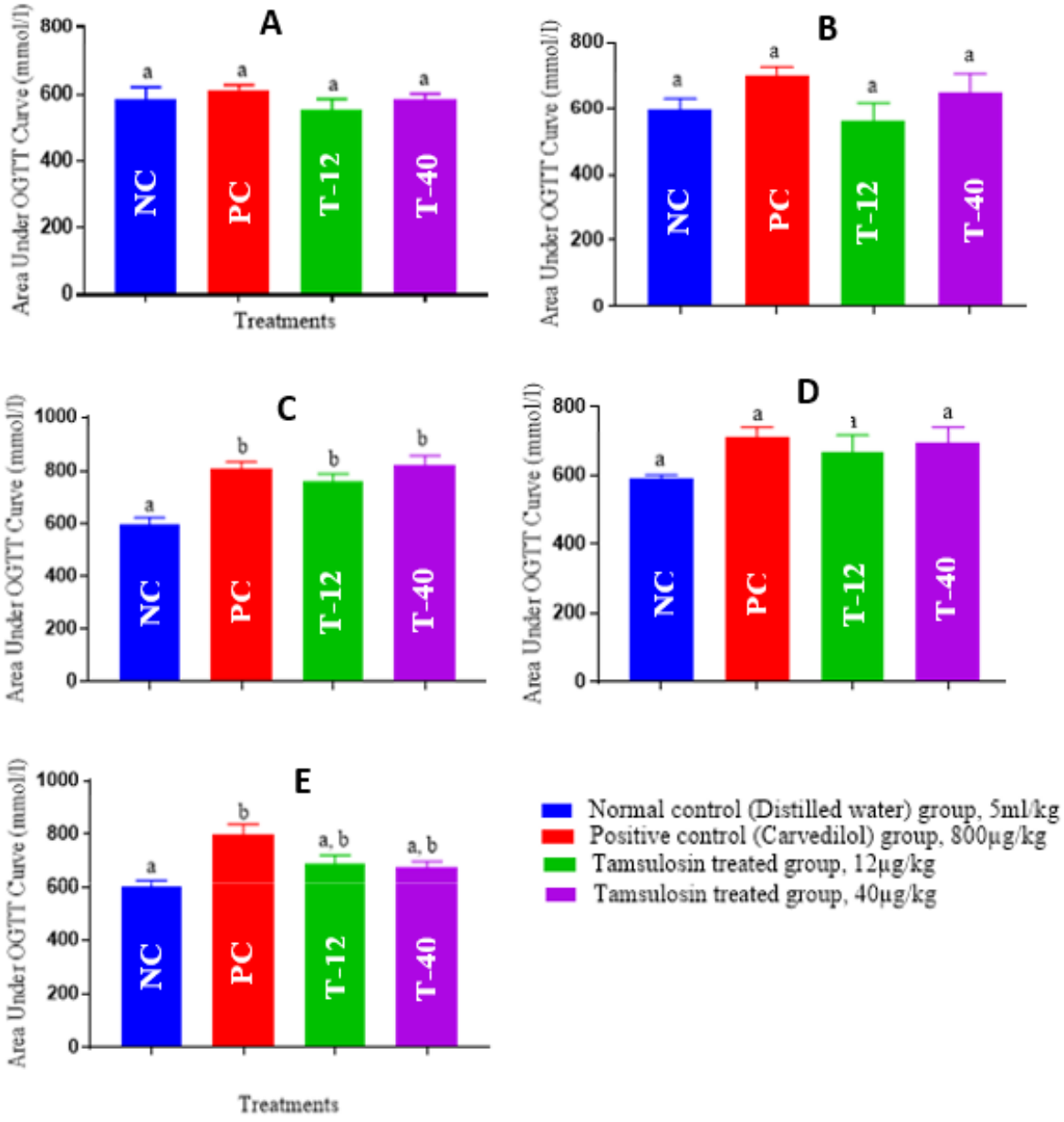

Figure 1:
Effect of tamsulosin on the total area under the oral glucose tolerance curve at baseline or week 0 (A), week 3 (B), week 6 (C), week 7 (D) and week 8 (two weeks after tamsulosin withdrawal) of the study.
Each bar represents Mean ± SEM (n=5). Groups with different lower-case letters are significantly different.
NC – Normal control; PC – Positive control; T-12 – 12µg/kg Tamsulosin treated animals; T-40 – 40µg/kg Tamsulosin treated animals

Oral glucose tolerance test at 8th week (two weeks after tamsulosin withdrawal) of the study in normal rats administered with tamsulosin: At the 8th week of the study (two weeks after treatments withdrawal), only group of rats treated with carvedilol (positive control) revealed a significantly higher values ($P<0.05$) of total area under the oral glucose tolerance curve than the normal control group. Other inter-group comparisons were not significantly different ($P>0.05$; Fig. 1E).

DISCUSSION

The objective of this study was to determine the effect of administration of tamsulosin on glucose tolerance in normal Wistar rats. This study shows that carvedilol and tamsulosin affect glucose tolerance by inducing hyperglycemia in normal rats. Some reports said that tamsulosin cause an impaired oral glucose tolerance and elevated fasting blood glucose in normal rats due to its ability to block L-type voltage gated calcium ion channels (Suresha *et al*., 2013). Calcium ion channels of pancreatic beta-cells are involved in the regulation of insulin secretion (Satin, 2000). Blockage of calcium channel ions by carvedilol might inhibit the influx of intracellular calcium ions thereby impairing insulin secretion, leading to the development of hyperglycemia (Jacob *et al*., 1996). Dikko *et al* (2020) reported that tamsulosin administration in BPH/ LUTS patients lead to impairment of oral glucose tolerance thereby causing hyperglycemic effect.

Moreover, several mechanisms might be the brain behind the observed ability of tamsulosin to cause impairment of glucose tolerance and elevated blood glucose in Wistar rats. It might be due to the reported effect of tamsulosin in blocking alpha-1 adrenoceptors in

experimental animals (Shivaprasad *et al*., 2015). Several studies have reported the important role played by alpha-1adrenoceptors in blood glucose homeostasis in experimental animals and humans through the regulation of blood glucose uptake. Parable, Cheng *et al*. (2000) cited an improvement in glucose uptake into isolated white adipocytes when methoxamine (an alpha 1 agonist) was administered to Wistar rats to stir alpha-1 adrenoceptors; Boschmann *et al*., (2002) and Flechtner-Mors *et al*., (2004) reported some clinical studies revealing that stimulation of alpha-1 adrenoceptors by phenylephrine (an alpha-1agonist) and noradrenaline (non-selective alpha agonist) cause an increase in glucose uptake in human. On the other hand, it has been documented that blockade of alpha 1 receptors leads to impairment in the tissue uptake of blood glucose both invitro and invivo (Cheng *et al*., 2000; Shivaprasad *et al*., 2015). Another possible mechanism for such effects is through increasing insulin secretion. A previous study showed an elevation in plasma insulinlevel (hyperinsulinemia) when alpha-1 adrenoceptors were blocked in experimental rats and humans (Ahrén *et al*., 2008). And this negative effect on glucose tolerance of the rats (which have similar biology with humans) is an ADR that can diminish the enthuastic use of tamsulosin. And it serves as a threat, because hyperglycemia is a factor that goes hand in hand with glucose intolerance, beta-cells inefficiency, and other metabolic syndrome problems threatening public health (Umar etal., 2010; Bilbis etal.,2012).

In conclusion, the current study revealed that tamsulosin affects the glucose tolerance of the Wistar rats, thereby causing hyperglycemia..

REFERENCES

Ahrén, B., Lundquist, I., and Järhult, J. (2008). Effects of α1-, α2- and β-adrenoceptor blockers on insulin secretion in the rat. Acta Endocrinologica105 (1): 78–82.

Bilbis L.S., Muhammad, S.A., Saidu, Y., & Adamu, Y. (2012). Effect of vitamins A, C, and supplementation in the treatment of metabolic syndrome in albino rats .Biochemistry Research International, 1-7.

Boschmann, M., Krupp, G., Luft, F.C., Klaus, S., and Jordan, J. (2002). In Vivo Response to α 1 -Adrenoreceptor Stimulation in Human White Adipose Tissue. Obesity Research 10 (6): 555–558.

Cheng, J.T., Liu, I.M., Yen, S.T., & Chen, P.C. (2000). Role of alpha1A-adrenoceptor in the regulation of glucose uptake into white adipocyte of rats in vitro. Autonomic Neuroscience : Basic & Clinical 84 (3): 140–6.

Chika, A., Onyebuece, D.C., & Bello S.O. (2018). Phytochemical analysis and evaluation of antidiabetic effects in alloxan-induced diabetic rats treated with aqueous leaf extract of *Acanthospermum hispidium.* African Research Journal of Biomedical research 21:81-85.

Dikko, M., Bello, S.O., Chika, A., Mungadi I.A, Sarkingobir Y, & Aliyu, S. (2020a). Determination of Oral Glucose Tolerance (OGT) of Benign Prostatic Hyperplasia Patients Treated with Tamsulosin in Sokoto State, Nigeria. Nigerian Journal of Pharmaceutical and Applied Science Research, 9(2): 33-39.

Dikko, M. (2019). Exploration of gross effect of tamsulosin on glucose and insulin kinetics in ratsand humans. A PhD thesis submitted to the Postgraduate School Usmanu Danfodiyo University Sokoto, Nigeria.

Dikko, M., Bello, S.O., Chika, A, Mungadi, I.A., Sarkingobir, Y., & Umar, AI (2020b). Effect of Tamsulosin use on plasma insulin status in Benign Prostatic Hyperplasia patients in Sokoto, Nigeria. Journal of Applied Science and Environmental Management, 24 (4) 543- 548.

Flechtner-Mors, M., Jenkinson, C.P., Alt, A., Biesalski, H.K., Adler, G., & Ditschuneit, H.H. (2004). Sympathetic Regulation of Glucose Uptake by the α 1 -Adrenoceptor in Human Obesity. Obesity Research 12 (4): 612–620.

Jacob, S., Rett, K., Wicklmayr, M., Agrawal, B., Augustin, H.J., & Dietze, G.J. (1996). Differential effect of chronic treatment with two beta-blocking agents on insulin sensitivity: The carvedilol-metoprolol study. Journal of Hypertension14(4): 489–494.

Jerry, J. (2018). Glucose tolerance testing. Www.medicine.medscape.con. Retrieved 7/5/2020

Onakpoya, I.J., Heneghan, C.J., & Aronson, J.K. (2016). Post-marketing withdrawal of 462 medicinal products because of adverse drug reactions: A systematic review of the world literature. BioMed Central Medicine14 (1): 10.

Patrick, J.P. (2012). Oral glucose tolerance testing. Australian Family Physician, 41(6):391-193.

Satin, L.S. (2000). Localized calcium influx in pancreatic β-cells: Its significance for Ca2+-dependent insulin secretion from islets of Langerhans. Endocrine13 (3): 251–262.

Shivaprasad, G.M., Bharatha, A., Naikwadi, A.A., & Wali R.S. (2015). Effect of tamsulosin a selective α1 -antagonist on glucose homeostasis in rats. International Journal of Pharmacy and Pharmaceutical Sciences 7 (3): 232–234.

Suresha, R.N., Ashwini, V., Pragathi, B., Kalabharathi, H.L., Satish, A.M., & Pushpa, V.H. (2013). The effect of carvedilol on blood glucose levels in normal albino rats. Journal of Clinical and Diagnostic Research 7 (9): 1900–1903.

Uduala, T., Umar R.A., Isah R.A., Bello, M., Aiyelabegan, Isa, L.O., & Oduala G.B. (2018). Use of Gliricidia sepium aqueous leaf extracts as an antisickling agent: Oxidative stress biomarkers in wistar rats exposed to the extract. International Journal of Medical and Health Research4(8):79-83.

Umar, R. A., Hassan, S.W., Ladan, M.J., Matazu, I.K., Shehu, B., Shehu, R.A., Muhammed, L.G., & Molabo, F.I. (2010). Adverse effect associated with administration of antiretroviral drugs (Nevirapine, Lamivudine and Stavudine) to albino rats: Implication for management of patients with HIV/AIDS. Asian Journal of Biochemistry 5(3): 181-187.

Umar, M.T., Bello, S.O., Chika, A., & Oche, O.M. (2016). Attitude of nurses and pharmacists on adverse drug reactions reporting in selected hospitals in Sokoto. Journal of Research in Pharmacy Practice 5:219-2121.

United States National Library of Medicine (2020). Glucose tolerance test: Non pregnant .www.medlineplus.gov. Retrieved 7/5/2020

Woodcock, J. (2016). “Precision” drug development? Clinical Pharmacology & Therapeutics99 (2): 152–154.

World Health Organisation (2005). WHO Draft Guidelines for Adverse Event Reporting and Learning Systems. Geneva, Switzerland: Author. Report No. 80: Retrieved March 16, 2019.

World Health Organisation (2006). Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia. WHO, 20 Avenue Appia, 121 Geneva 27, Switzerland.