Nigerian Journal of Pharmaceutical and Applied Science Research, 9(2): 33-39, May 2020 (ISSN 1485-8059. Available at www.nijophasr.com)

Determination of Oral Glucose Tolerance (OGT) of Benign Prostatic Hyperplasia Patients Treated with Tamsulosin in Sokoto State, Nigeria

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ABSTRACT

This study determined the effect of tamsulosin on blood glucose tolerance among patients of benign prostatic hyperplasia/ lower urinary tract symptoms in Sokoto state, Nigeria. Standard methods were used in this study.The result revealed a significant increase ($P<0.05$) in the area under oral glucose tolerance test (OGTT) curve at 2nd month,3rd month, and 4thmonth progressively. Comparisons between mean values at other time points were not significantly different ($P>0.05$). A change ($P<0.05$) in the total area under the OGTT curve was observed in BPH patients aged 55-64 years at 4th month compared to the values of the 0th and 1st months. Comparisons between mean values at other time points were not significantly different ($P>0.05$). At 0th or 1storor 2ndor 3rd or 4th month, there was no significant difference ($P>0.05$) in the total area under the OGTT curve between the three (3) age groups.The results of the study showed that tamsulosin caused hyperglycemiain BPH patients. It is recommended that blood glucose levels in BPH patients using tamsulosin should be monitored to avoid hyperglycemia complications.

Keywords: Tamsulosin, glucose, hyperglycemia, humans, adverse drug reactions

INTRODUCTION

Adverse drug reaction (ADR) refers to any response to a drug which is harmful and unwanted at normal doses used in chemotherapy; or other problem such as sign and symptom or adverse effect to a drug or diseases due to drug (Kahinde and Erah, 2018; Olugbake *et al*., 2019; Umar *et al*., 2016; Dikko *et al.*, 2020). The ADR epidemiology is speeded up by misuse, abuse, error, increased drugs in the market, increased aging groups and polymedicine practices (Dikko, 2019). ADR is a leading cause of iatrogenic diseases worldwide. Adverse drug reactions (ADRs) occurs almost daily in healthcare facilities, and at homes, and can adversely affect a patient's quality of life, often causing significant morbidity and mortality.That is why much attention has been accorded in identifying population at risk, common drugs causing ADRs, and potential causes of ADRs (Dikko *et al*., 2020). ADRs can spur patients to lose confidence in healthcare or drugs; and on the other hand increase selfmedication or precipitate further ADRs. Moreover,cost of ADRs management can be high or precipitate other ADRs,and inturn posing huge burden on the patients, healthcare system, and government (American Society of Health-System Pharmacists,1995; Riedl and Casilas,2003; Muller, 2015; Schatz, 2015). Nevertheless, certain measures are followed to minimize ADRs such as careful medication review, good education to patients and healthcare givers, monitoring and pharmacovigilance among others (Chika *et al*., 2018; Ganiyu and Erah, 2018). Benign prostatic hyperplasia (BPH) is a histologic diagnosis that refers to proliferation of smooth muscle and epithelial cells within the prostatic transition region. It contributes to lower urinary tract symptoms (LUTS) (American Urological Association Education and Research Inc., 2010). BPH associated LUTS are very prevalent among the older men and present an outstanding public health threat.To address the BPH and LUTS, a typical drug widely utilized is the tamsulosin, an alpha-1 adrenoreceptors blocker. Wider acceptance of tamsulosin is increasing among older men; the challenge that is trying to cause an upheaval is reported cases of hyperglycemia associated symptoms among the users (Kang *et al*, 2009; Dankner *et al.,* 2012). Some studies reported that tamsulosin use have higher risk of developing diabetes mellitus (Wei *et al*., 2019).The study objective was to determine the effect of tamsulosin on blood glucose level among patients of HPB and LUTS in Sokoto state, Nigeria.

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MATERIALS AND METHODS

Ethical approval

Ethical approval dated 10th July, 2017 with reference number (UDUTH/HREC/2017/No. 589) was obtained from the Research Ethics Committee of the UsmanuDanfodiyo University Teaching Hospital (UDUTH), Sokoto.

Study setting

The study was carried out between August 2017 and July 2018 at the Institute of Urology and Nephrology of Usmanu Danfodiyo University Teaching Hospital (UDUTH), a tertiary hospital situated in Sokoto, a city in the North-Western Nigeria.

Study population

The study population was only male subjects freshly diagnosed with benign prostatic hyperplasia (BPH) who indicated for medical treatment that attended and received treatment in the Institute during the period of the study.

Sampling technique

BPH patients that satisfied the study inclusion criteria were selected by convenient sampling. Thirty (30) BPH patients (age, $\geq$ 45 yrs.) were consented to be included in the study. Later, Two (2) patients opted out. Thus,twenty-eight (28) patients completed the study.

Study design

Selected patients were asked to fast overnight (10pm-10am) and report back in the morning. On their arrival, oral glucose tolerance test (OGTT) of each participant was recorded to serve as baselines. Soon after that, thirty (30) tamsulosin capsules were given to each patient and asked to take one (1) capsule daily (30 minutes after meal) for a period of one (1) month starting from the day given. The patients were instructed to swallow the capsule and if a dose is missed, it should be replaced as soon as it was remembered. If missed for the whole day, the next dose should continue on a regular schedule. Similarly, each day they were reminded (through their mobile numbers) to take the drug. At the 30th day, they were asked to fast overnight (10pm-10am) and come back to the Institute for the collection of another tamsulosin capsules and analysis of the oral glucose tolerance test (Dikko, 2019).

Determination of oral glucose tolerance (OGT) of BPH patients treated with tamsulosin. OGTT was performed at baseline then at 1st, 2nd, 3rd and 4thcompleted month post treatment. Prior to each OGTT, patients were fasted for 12 hours (10pm-10am). The blood glucose of each patient was measured via fingertip incision at 0hours (pre-glucose load). Then, 75g of anhydrous D-glucose powder dissolved in 250-350mltap water was given to the patient to drink (within 5 minutes time frame) orally, after which blood sample was collected via fingertip incision at 30, 60 and 120 min. A Standardized digital glucometer (Accu check) was used to measure blood glucose levels (Dikko, 2019).

Statistical analysis

All results were expressed as Mean $\pm$SEM. Differences between groups were estimated using either Student t-test or Analysis of Variance (ANOVA). For multiple comparisons,TukeyKramer post hoc test was used. All calculations and graphs were done using GraphPad prism 7.04 version. The significant level was set at 95% ($P < 0.05$) confidence interval.

RESULTS AND DISCUSSION

Oral glucose tolerance test at baseline (0th) and at 1st, 2nd, 3rd and 4th month of the study in benign prostatic hyperplasia patients treated with tamsulosin. A significant increase ($P<0.05$) in area under OGTT curve was observed at 4th month compared to baseline and 1st month values (Figure 1). Other comparisons between mean values at other time points were not significantly different ($P>0.05$).

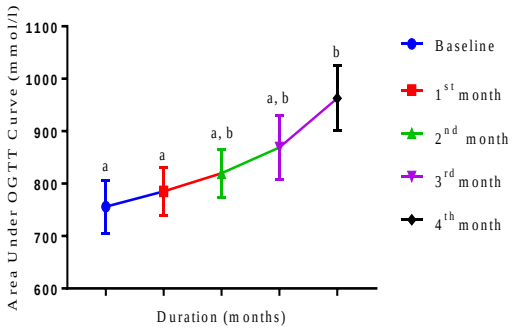
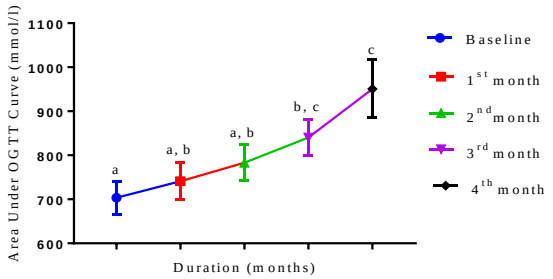


Figure 1: Change in the total area under the OGTT curve with duration of tamsulosin use at baseline (0th) and at 1st, 2nd, 3rd and 4th monthsin BPH patients.

Each bar represents Mean $\pm$SEM (n=28). Student t-test was used.Mean valueswith different lower case letters are significantly different.

Oral glucose tolerancetestat baseline (0th) and at 1st, 2nd, 3rd and 4th months of the studyin benign prostatic hyperplasia patients (45-54 years) treated with tamsulosin

At 3rd month of tamsulosin use, a significant increase in the total area under oral glucose tolerance curve compared to baseline values were noticed (Figure 2). Likewise, at 4th month of tamsulosin use, a significant increase in the total area under oral glucose tolerance curve was observed compared to baseline, 1st month and 2nd month values (Figure 2).Comparisons between mean values at other time points were not significantly different (P>0.05).



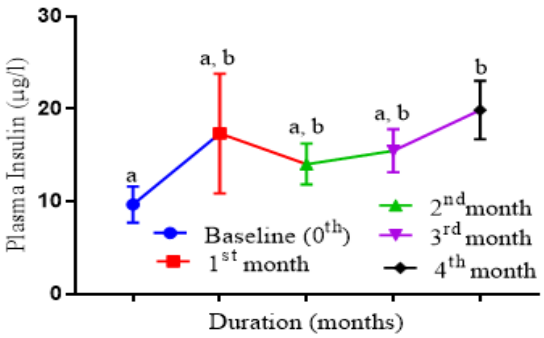


Figure 2: Change in the total area under the OGTT curve with duration of tamsulosin useatbaseline (0th) and at 1st, 2nd, 3rd and 4th months in BPH patients (45-54 years).

Each bar represents Mean (mmol/l) ±SEM (n=28). Student t-test was used.Mean values with different lower case letters are significantly different.

Oral glucose tolerance testat baseline(0th) and at1st, 2nd, 3rd and 4th months of the study in benign prostatic hyperplasia patients (55-64 years) treated with tamsulosin.

A change (P<0.05) in the total area under the OGTT curve was observed in BPH patients aged 55-64 years at 4th month of treatment compared to the value at either the baseline or 1st month of treatment (Figure 3). Comparisons between mean values at other time points were not significantly different (P>0.05; Fig. 3).

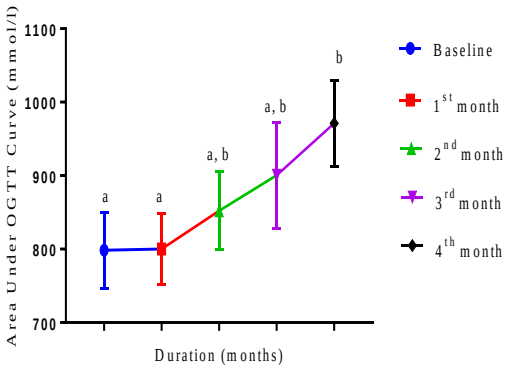


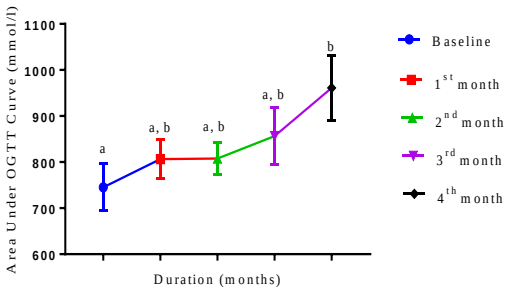
Fig 2: Effect of tamsulosin on plasma insulin at baseline (0th) and at 1st, 2nd, 3rd and 4th months of the study in BPH patients (45-54 years). Each bar represents Mean ± SEM (n=8). Student t-test was used. Mean values with different lower case letters are significantly different.

Figure 3: Change in the total area under the OGTT curve with duration of tamsulosin useat baseline (0th) and at 1st, 2nd, 3rd and 4th months of the study in BPH patients (55-64 years).

Each bar represents Mean (mmol/l) ±SEM (n=28). Student t-test was used. Mean values with different lower case letters are significantly different.

Oral glucose tolerance testat baseline (0th) and at 1st, 2nd, 3rd and 4th months of the study in benign prostatic hyperplasia patients(65+ years) treated with tamsulosin

At 4th month of the study, there was a significant increase (P<0.05) in the total area under oral glucose tolerance curve compared to baseline values (Figure 4). Comparisons between mean values at other time points were not significantly different



Each bar represents Mean ±SEM. Student t-test was used.Mean values with different lower case letters are significantly different.

Figure 4: Change in the total area under the OGTT curve with duration of tamsulosinuseat baseline (0th) and at 1st, 2nd, 3rd and 4th months of the studyinBPH patients (65+ years).

Oral glucose tolerance testat baseline (0^{th}) of the studyin benign prostatic hyperplasia patients of different age groups treated with tamsulosin

At baseline, there was no significant difference (P>0.05) in the total area under the OGTT curve between the three (3)age groups (Figure 5).

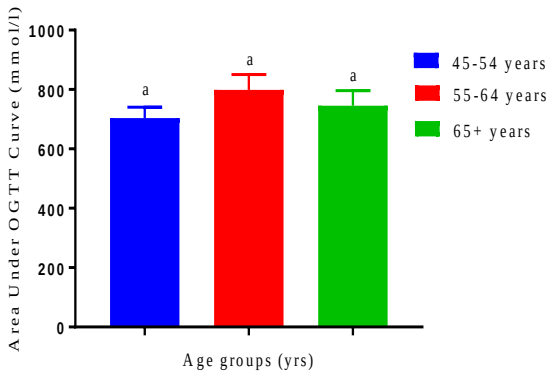


Figure 5: Effect of tamsulosin on the total area under the OGTTcurveatbaseline(0^{th}) of the study in BPH patients of different age groups.
Each bar represents Mean ± SEM. ANOVA was usedfollowed by Tukey Kramer post hoc test.Groups with same lower case letters are not significantly different.

Oral glucose tolerance testat 1^{st} month of the studyin benign prostatic hyperplasia patients of different age groups treated with tamsulosin

At 1^{st} month of the study, there were no significant differences (P>0.05) in area under the OGTT curve between the three (3) age groups (Figure 6).

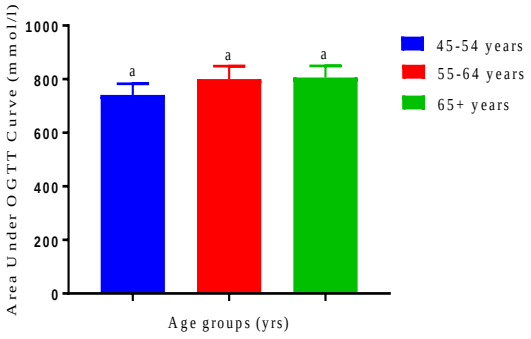


Figure 6: Effect of tamsulosin on the total area under the OGTT curveat 1^{st} month of the study month in BPH patients of different age groups.

Each bar represents Mean ± SEM. ANOVA was usedfollowed by Tukey Kramer post hoc test.Group with same lower case letters are not significantly different.

Oral glucose tolerance testat 2^{nd} month of the studyin benign prostatic hyperplasia patients of different age groups treated with tamsulosin

At 2^{nd} month of the study, there were no significant differences (P>0.05) between the three (3) age groups (Figure 7).

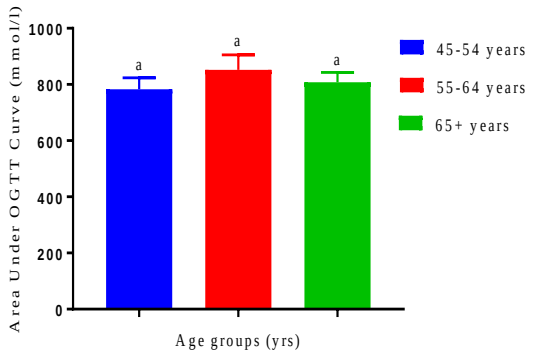


Figure 7: Effect of tamsulosin on the total area under the OGTT curve at 2^{nd} month of the study in BPH patients of different age groups.

Each bar represents Mean ± SEM. ANOVA was used followed by Tukey Kramer post hoc test.Group with same lower case letters are not significantly different.

Oral glucose tolerance testat 3^{rd} month of the studyin benign prostatic hyperplasia patients of different age groups treated with tamsulosin

At 3^{rd} month of the study, there were no significant differences (P>0.05) in area under the OGTT curve between the three (3) age groups (Figure 8).

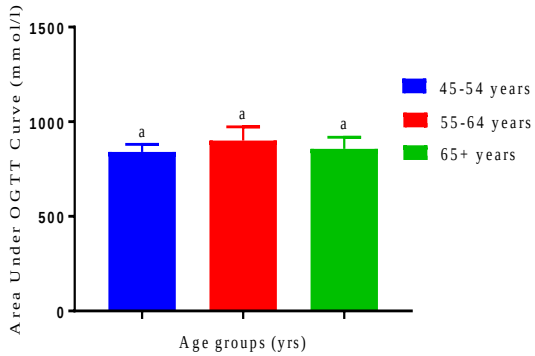


Figure 8: Effect of tamsulosin on the total area under the OGTT curveat 3^{rd} month of the study month in BPH patients of differentage groups.

Each bar represents Mean ± SEM. ANOVA was usedfollowed by Tukey Kramer post hoc test.Group with same lower case letters are not significantly different.

Oral glucose tolerance test at 4th month of the studyin benign prostatic hyperplasia patients of different age groups treated with tamsulosin

At 4th month of the study, there were no significant differences (P>0.05) in area under the OGTT curve between the three (3) age groups (Figure 9).

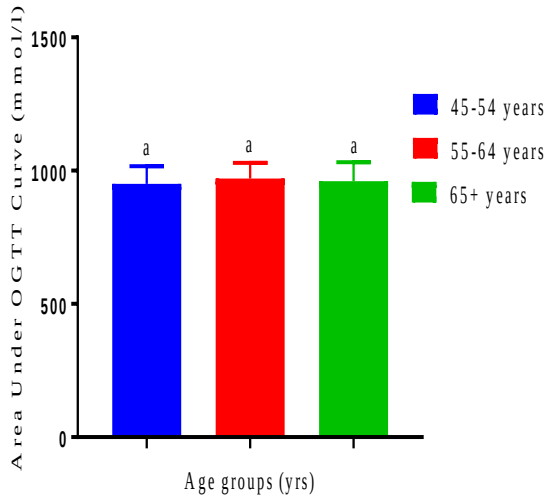


Figure 9: Effect of tamsulosin on the total area under the oral glucose tolerance curveat 4th month of the studyin BPH patients of different age groups.

Each bar represents Mean ± SEM. ANOVA was used followed by Tukey Kramer post hoc test.Group with same lower case letters are not significantly different.

As seen in the study, tamsulosin effect on blood glucose homeostasis was unaffected by the age differences. It was once documented that aging alone have no effect on glucose homeostasis in humans (Despres *et al.*,2007; Szoke *et al.*, 2008). Aging was among the most important demographic factors that elevate the incidence and severity of BPH as prostate size usually correlate closely with age and serious lower urinary tract symptoms are commonly seen as men get older (Dikko *et al*, 2020). Aging also causes functional decline anatomically and physiologically and these changes affect pharmacokinetics and pharmacodynamic properties of drugs (Katzung, 2004). As age increases, renal and hepatic clearances reduce and volume of distribution of some drugs increases, hence delaying their elimination half-lives. These changes might be responsible for theage group of 55-64 years to be more sensitive to tamsulosin effect on blood glucose homeostasis as compared to age group of 45-54 years as evidenced in the present study.It is known that altered sensitivity to some drugs is greatly enhanced with advancing age (Mangoni and Jackson, 2004). Similarly, deterioration in glucose tolerance was known to be associated with advancement in age (Dikko, 2019). This study found that tamsulosin has the capacity to induce hyperglycemia and affect or impair oral glucose tolerance (as shown by the significant increase in the area under the oral glucose tolerance curve) in BPH and SLUTS patients. Many mechanisms are cited as the brain behind these effects. The major reason might be due to effect of tamsulosin in blocking alpha-1 adrenoreceptors in animals, because these receptors play a critical role in glucose homeostasis.Tamsulosin as an alpha-1 receptor antagonist bind selectively and competitively to alpha-1 receptors during BPH and LUTS treatment.Thus inhibiting the alpha-1 receptor mediated route of glucose uptake (Chen *et al*., 2000; Borgsteede *et al*., 2010; Dikko *et al*., 2020).Some studies reported that, people using tamsulosin have higher risk of developing diabetes mellitus (Wei *et al*., 2019). It might be because to the drug increases insulin secretion or increases gluconeogenesis (Siddiqui *et al*., 2013; Lee and Halter, 2017). Thus, tamsulosin is able to cause hyperglycemia because it causes a dysregulation in the mechanisms of glucose homeostasis (Marcovecchio, 2017). Once said, all drugs are poisons underlining the importance of vigilance,and care with drug use, more especially in older population.The incidence of ADRs from established drugs is about 3.1% in children,6-8% in the young adults and middle age, and 20% in old people (Bello and Umar, 2011).This study revealed tamsulosin cause an adverse drug reaction of hyperglgycemia.It is a type A or primary ADR , related to the pharmacology of the drug . Hyperglycemia cause injury to a large number of organs and tissues in the biological system. In acute hyperglycemia, serious complications may arise such as endocrine emergencies in ketoacidosis, hyperosmolar hyperglycemic state; whereas, in chronic case hyperglycemia it is a determinant of vascular complications in diabetes such as retinopathy, nephropathy, neuropathy, and cardiovascular disease (Arief and Kleeman, 2000; Bilbis *et al*., 2012; Isa *et al*., 2013; Muller, 2015; Muhammad *et al*., 2015; Marcovecchio, 2017; Chika *et al*., 2018; Chika and Yahaya, 2019).Considering the hyperglycemic ADR found among patients using tamsulosin, there might be reduced incentive in persistent use of the drug. More and careful monitoring and pharmacovigilance are needed to surf information and help in reducing further consequences of tamsulosin usage among older patients (Umar *et al*., 2010; Muller, 2015; Marchovecchio, 2017; Ganiyu and Erah, 2018 ; Umar *et al*., 2016).

CONCLUSION

The results of the study showed that tamsulosin caused hyperglycemia in BPH patients.

Recommendations

It is recommended that blood glucose fluctuation of BPH patients using tamsulosin should be monitored.Further studies are also recommended to investigate the molecular basis of tamsulosin effect on blood glucose homeostasis using a larger sample size.

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