



Body Weight Determination and Histological Examination of Livers in Normal Rats Administered with Tamsulosin

¹DIKKO, M; ^{*2}SARKINGOBIR, Y

¹Department of Pharmacy, Sultan Abdurrahman School of Health Technology Gwadabawa, Sokoto state, Nigeria

²Department of Biology, Shehu Shagari College of Education Sokoto, Nigeria

*Corresponding Author Email: superoxidizedismutase594@gmail.com; Tel: +234(0)8135420062

ABSTRACT: The objective of this study was to investigate histopathology of livers and carry out body weight determination in normal rats administered with tamsulosin. Standard methods and procedures were used in this study. The results were revealed. Pertaining weight, at the 3rd, 6th and 8th weeks of the study, no significant difference ($P>0.05$) in weight was found in the group of rats treated with carvedilol (positive control), tamsulosin low dose (12 μ g/kg) and high dose tamsulosin (40 μ g/kg) compared to normal control group, respectively. Other inter-groups comparisons were not significantly different, respectively. Pertaining liver morphology, liver sections of groups revealed no significant histological lesions compared to the normal control group at the 6th and 8th weeks of the study, respectively. This study revealed that the tamsulosin cause no histopathological lesion, thus the drug might be safe to the liver and its biochemical processes.

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Benign prostatic hyperplasia (BPH) is a histological diagnosis that refers to the proliferation of smooth muscles and epithelial tissue in the prostate region (American Urological Association Education and Research, 2010; Dikko *et al.*, 2020a). Lower Urinary tract symptoms (LUTS) include storage and/ or voiding problems that are common among aging men (AUAER, 2010). The spread of BPH and LUTS is increasing with age (Dikko *et al.*, 2020b). It starts as early as at the forties among men. In West Africa the prevalence is about 21% in men of under 60years, and 53% in men of 80 years (Ibrahim *et al.*, 2016). In Nigeria, about 22.3% of the cases of BPH are reported from male patients. According to recent census, 3million men are above 50years, hence, if the life expectancy rise, the prevalence of BPH might rise as well (Udeh *et al.*, 2016). The BPH or LUTS if left untreated, it can progress to complications of obstructive neuropathy, acute urinary retention, and recurrent urinary retention (Udeh *et al.*, 2016). Presently, alpha-blockers are the most common chemotherapeutic drugs used to relieve BPH or LUTS. Tamsulosin is a categorical drug widely used in BPH or LUTS management. Whereas, it's used is reported to be very effective, there is paucity of studies revealing it effects on the liver (Ibrahim *et al.*, 2016). Generally, in toxicological studies, relative weight change in an organ or organism is often associated

with dose-related effects. An increase or decrease in weight easily depicts metabolic disturbance or hypoglycaemia induced by drug (Aghaghowa and Okolocha, 2018). The liver is the largest organ in human body. It carries out multiplicity of vital metabolic functions (Akuyam *et al.*, 2017). It lies below the diaphragm and anterior stomach. It is involved in maintenance of glucose homeostasis, secretion of lipoproteins, excretion of bile, synthesis of albumin, synthesis of prothrombin, synthesis of fibrinogen, synthesis of binding protein. It is also active in metabolism of proteins, carbohydrates, and lipids. In catabolism, it is involved in degradation of hormones, serum proteins, drugs, chemicals and products of microbes etc (Arika *et al.*, 2016; Ozougwa, 2017). Histologically, liver has a basic functional unit called lobule, which consists of plates of hepatocytes, portal triads, central vein, Kupffer cells, little canals and space of Disse (Ozougwa, 2017). Liver disease is echoed as the fifth most common cause of death after heart disease, stroke, chest disease and cancer (Dandare *et al.*, 2015). The trend is never decreasing; rather it is on the increase especially because of recent rise of environmental pollution chemicals interaction with biological systems. Drugs are among the leading causes of liver diseases nowadays (Hadi and Alwan, 2012; Arika *et al.*, 2016). Hepatic injury cause to liver is one of the leading challenges to public health and

*Corresponding Author Email: superoxidizedismutase594@gmail.com; Tel: +234(0)8135420062

pharmaceutical industry as it leads to morbidity, mortality, drug restrictions, drug development termination and even post-market drug withdrawal (Arika *et al.*, 2016). Therefore, the objective of this study was to investigate histopathology of livers and carry out body weight determination in normal rats administered with tamsulosin.

MATERIALS AND METHODS

Animals: Ethical approval was obtained from the Committee of Animal Care and Use, Usmanu Danfodiyo University, Sokoto. Seventy (70) male adult albino Wistar rats (261-294g) were purchased from the breeding units of Faculty of Veterinary Sciences of University of Ilorin, Nigeria. The rats were allowed in the animal house of the Department of Pharmacology and Therapeutics, Usmanu Danfodio University Sokoto, in plastic cages (four per cage) 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 pelletized grower feeds pellets product of (Vital feeds, a product of Grand cereals limited Jos, Nigeria) were supplied *ad libitum* (Dikko, 2019).

Experimental Design: Forty (40) male albino Wistar rats were selected using random number generator (computer software) and divided into four (4) groups of ten (10) rats each, namely, 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). They were left for three (3) days before the commencement of the study. 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*. Weights of the rats in each group were measured at the beginning of the study and each week until the end of the study (Dikko, 2019).

Determination of body weight in normal rats administered with tamsulosin: Rat's weight was determined at baseline (0th) and at 3rd, 6th, and 8th completed week. A large plastic beaker was placed on the electronic weighing scale and tarred it back to 0, and then the beaker was taken off. The rat was placed in the beaker and the beaker was placed back

on the scale. The most frequently observed number was recorded as rat's weight (Dikko, 2019).

Histological (morphological) examination of kidneys and livers of normal rats during and after tamsulosin administration: At the 6th week of the study, five (5) rats from each group were randomly selected after underwent 8 hours fasting. The selected rats were sacrificed by head concussion method and immediately their livers were removed and placed in a chilled fixative of 10% formal-saline. At the 8th week of the study, the remaining rats in each group were sacrificed through head concussion after 8 hours fasting. Immediately, livers were removed and placed in a fixative of 10% formal-saline. In the laboratory, the tissues were dehydrated and cleared using xylene, then, embedded in paraffin, sectioned, and stained with hematoxylin and eosin and viewed under light microscope (Dikko, 2019).

RESULTS AND DISCUSSION

Determination of body weight at baseline (0th) and at 3rd, 6th and 8th week of the study in normal rats administered with tamsulosin: At the 3rd week of the study, no significant difference ($P > 0.05$) in weight 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 6th week of the study, also no significant difference ($P > 0.05$) in weight was observed in the group of rats administered 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 8th week of the study, weight 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) did not revealed any significant differences compared to the normal control group. Other inter-group comparisons were not significantly different ($P > 0.05$; Table 1).

Histopathology analysis of and livers at 6th and 8th weeks of the study in rats treated with tamsulosin: Liver sections of groups showed no significant histological lesions compared to the normal control group at the 6th week of the study (Table 2 and Plates 4- 5). At the 8th week of the study, liver sections of all treated groups showed no significant histological lesions compared to normal control group (Table 2 and Plates 6- 9). The relative weight change is useful in explaining the adverse effect triggered by a drug (Yazici-Tutunis *et al.*, 2016).

Table 1: Effect of tamsulosin on body weight at baseline (0th) and at 3rd, 6th and 8th week of the study 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
0 th	290.8± 3.49 ^a	281.2± 2.84 ^a	283.6± 1.41 ^a	288.6± 2.14 ^a
3 rd	296.5± 3.36 ^a	289.0± 2.12 ^a	287.7± 1.59 ^a	294.1± 1.94 ^a
6 th	303.2± 2.77 ^a	295.2± 1.99 ^a	295.4± 1.92 ^a	299.5± 1.98 ^b
8 th	308.5± 3.88 ^a	304.3± 3.19 ^a	300.0± 2.27 ^a	303.3± 3.19 ^a

Results expressed as Mean (gram) ± SEM (n=10). ANOVA was used followed by Tukey Kramer post hoc test. Groups within the same row with same superscript letters are not significantly different.

Table 2: Effects of the tamsulosin on the liver at 6th week of the study in rats treated with tamsulosin

Groups	Organs	Effects	Plates
Normal control (Distilled water), 5ml/kg	Liver	Appeared normal (5/5)	- Plate 4.2
Positive control (Carvedilol) 800µg/kg	Liver	Appeared normal (5/5)	- Plate 4.5
Tamsulosin treated, 12µg/kg	Liver	Appeared normal (5/5)	- Plate 4.7
Tamsulosin treated, 40µg/kg	Liver	Appeared normal (5/5)	- Plate 4.9

Numbers in parenthesis indicate positive slides over total numbers of slides examined

Table 3: Effect of tamsulosin on liver at 8th week of study in rats treated with tamsulosin

Groups	Organs	Effects	Plates
Normal control (Distilled water), 5ml/kg	Liver	Appeared normal (5/5)	- Plate 4.11
Positive control (Carvedilol) 800µg/kg	Liver	Appeared normal (5/5)	- Plate 4.13
Tamsulosin treated, 12µg/kg	Liver	Appeared normal (5/5)	- Plate 4.15
Tamsulosin treated, 40µg/kg	Liver	Appeared normal (4/4)	- Plate 4.17

Numbers in parenthesis indicate positive slides over total number of slides examined

One observation of the present study was the lack of negative effect of tamsulosin on rats' body weight. This was similar to the past studies which showed that alpha-1 adrenoceptors blockers have an advantageous effect on total cholesterol and triglycerides (Kabra, 2014). This observation might suggest that this drug have normal effect on leptin (a hormone that contribute hugely in weight regulation), dopamine, and serotonin (Yazici-Tutunis *et al.*, 2016). Other researchers have proposed mechanisms via which alpha-1 adrenoceptor blockers affect cholesterol and triglyceride synthesis which include up-regulation of low-density lipoprotein receptors, leading to suppression of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG) activity and consequently leading to a reduction in total cholesterol and low-density lipoprotein (Katzung, 2009). Another proposed mechanism is via blockade of alpha-1 adrenoceptors, which affect serum lipids by increasing the activity of lipoprotein lipase enzymes that determine the breakdown of very low-density lipoproteins (Enroth *et al.*, 2018). Weight is of great concern nowadays. Overweight is associated with obesity, which is a risk factor of many deadly diseases such as diabetes, cancer, hypertension, liver disease, cardiovascular disease and cancer (Yazici-Tutunis *et al.*, 2016). Moreover, present study revealed lack of significant histological lesions in the livers of the tamsulosin and carvedilol-administered rats, indicating that the two (2) drugs are not hepatotoxic. Previous studies echoed that, tamsulosin hardly causes symptomatic liver injury and it is similar to other

alpha-1 adrenoceptors blockers in causing mild and self-limited forms of liver injury (Dikko, 2019). Liver is an organ known to participate fully in blood glucose homeostasis (Dashty, 2013) as well as in drug excretion and biotransformation (Dandare *et al.*, 2015). Liver is considered the most important organ for animal or human growth. It is important to evaluate the state of health of liver since this organ played a role in many disease processes and health either primarily or secondarily because to any liver damage distort metabolic processes essential for health and growth (Suhair and Eman, 2009; Ozougwu, 2017).

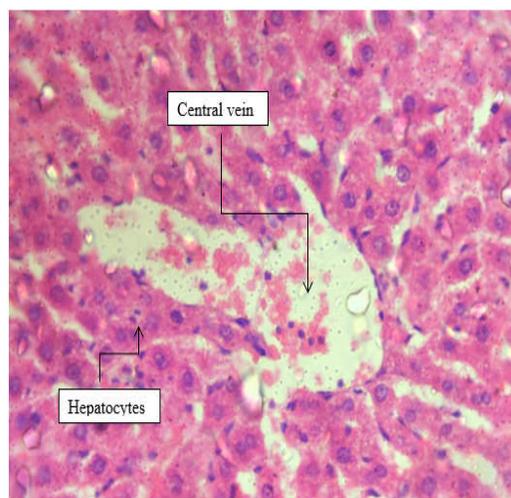


Plate 1: Photomicrograph of the liver of normal rats treated with distilled water (5ml/kg) at 6th week of the study showing central vein surrounded by hepatocytes having regular normal nuclei and cytoplasm. H & E x400

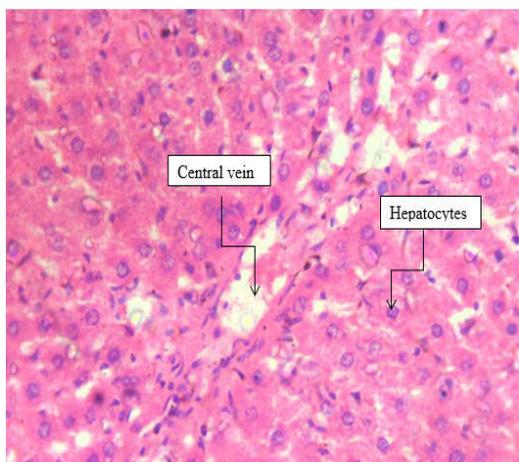


Plate 2: Photomicrograph of the liver of normal rats treated with carvedilol (800µg/kg) at 6th week of the study showing central vein surrounded by hepatocytes having regular normal nuclei and cytoplasm. H & E x400

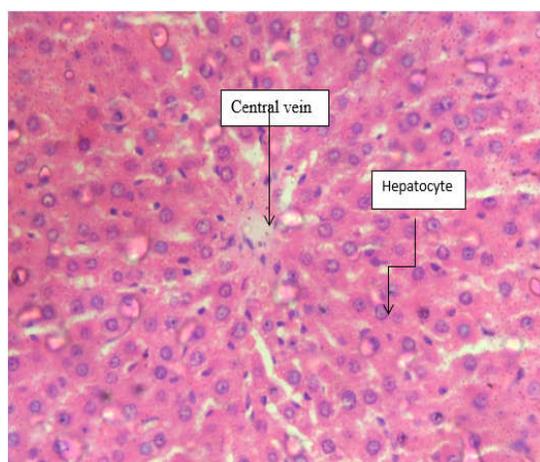


Plate 5: Photomicrograph of the liver of normal rats treated with distilled water (5ml/kg) at 8th week of the study showing central vein surrounded by hepatocytes having regular normal nuclei and cytoplasm. H & E x400

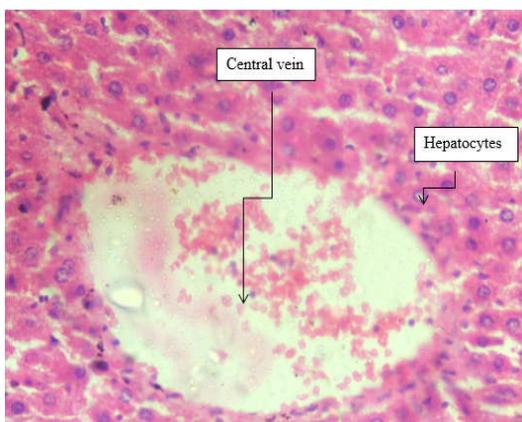


Plate 3: Photomicrograph of the liver of normal rats treated with tamsulosin(12µg/kg) at 6th week of the study showing central vein surrounded by hepatocytes having regular normal nuclei and cytoplasm. H & E x400

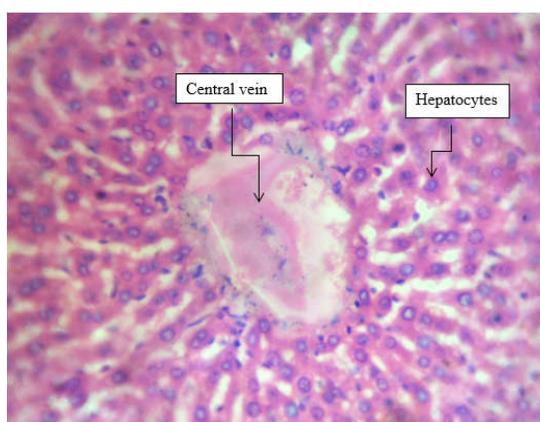


Plate 6: Photomicrograph of the liver of normal rats treated with carvedilol (800µg/kg) at 8th week of the study showing central vein surrounded by hepatocytes having regular normal nuclei and cytoplasm. H & E x400

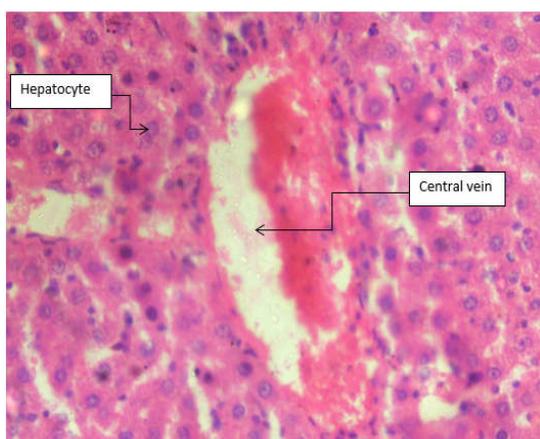


Plate 4: Photomicrograph of the liver of normal rats treated with tamsulosin(40µg/kg) at 6th week of the study showing central vein surrounded by hepatocytes having regular normal nuclei and cytoplasm. H & E x400

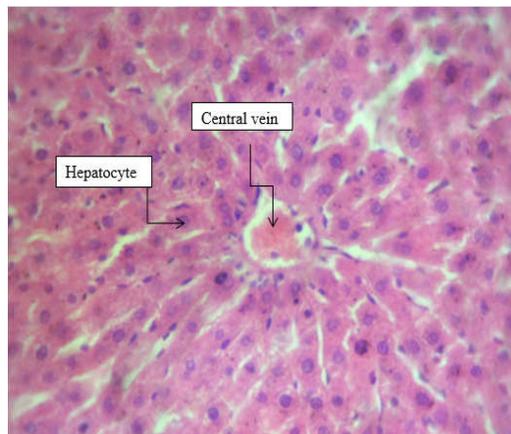


Plate 7: Photomicrograph of the liver of normal rats treated with tamsulosin (12µg/kg) at 8th week of the study showing central vein surrounded by hepatocytes having regular normal nuclei and cytoplasm. H & E x4.

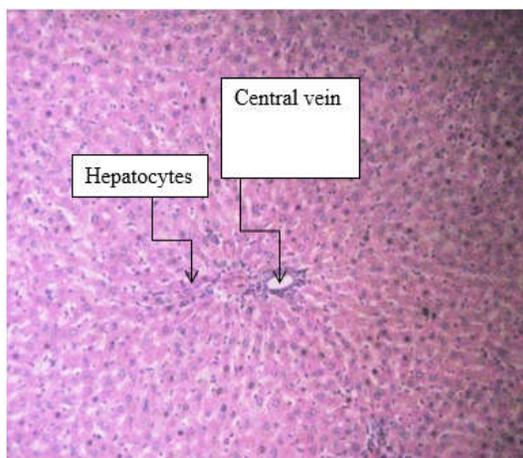


Plate 8: Photomicrograph of the liver of normal rats treated with tamsulosin (40 µg/kg) at 8th week of the study showing central vein surrounded by hepatocytes having regular normal nuclei and cytoplasm. H & E x400.

Histopathological investigations has long been recognized to examine specific organs that are vital in physiological processes such as liver, which carry out many activities within the body such as biotransformation of drugs, chemicals and other xenobiotics. The alterations found in organs through histopathology are easier to identify, and serve as warning portend of damage to organisms health (Hadi and Alwan, 2012; Dandare *et al.*, 2015). Exposure of liver to some chemicals or drugs leads to morphological changes and in turn affects homeostatic balance of many processes (Arika *et al.*, 2016). Drug induced hepatic injury have become a major hurdle to pharmaceutical industry leading drug development termination, post-market withdrawal and many more (Karadeniz *et al.*, 2008; Sharif *et al.*, 2013; Abubakar *et al.*, 2015; Arika *et al.*, 2016; Odusanya *et al.*, 2017; Enroth *et al.*, 2018; Kaplan, 2019).

Conclusion: This study revealed that the tamsulosin cause no histopathological lesion, thus the drug might be safe to the liver and its biochemical processes. It also does not affect the body weight of the rats.

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