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Body Weight Changes and Serum Growth Hormone Comparative Assessment in Female Lactating Wistar Rats (*Rattus norvegicus*) Treated with Metoclopramide and Some Atypical Antipsychotics

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Authors' contributions

This work was carried out in collaboration between all authors. Authors NSE and IGB designed the study and wrote the protocol. Authors CNC, AEO, RAA and AUA managed the literature searches. Authors SS and MY managed the statistical analysis. Authors SAD and ABD handled the experimentation, animals and samples collection while author HDM wrote the first draft of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Aims: The study was aimed at comparative evaluation of body weight changes and the serum growth hormone level in female lactating Wistar rats treated with normal saline, metoclopramide olanzapine and risperidone.
Study Design: A total of twenty (20) Female Wistar rats weighing between 140-180 g were used for the study. The study was an experimental study carried out on lactating rats. Treatment started three days after parturition. Two atypical antipsychotic drugs were administered orally and their effects compared to that of a normal control group and a positive control.

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Methodology: Group I served as the control and was administered 2 ml/kg normal saline. Group II received metoclopramide (5 mg/kg b.w) while group III received olanzapine (5 mg/kg b.w) while group IV received risperidone (5 mg/kg b.w). Administration was carried out by oral gavage using an oral cannula, for the period of fourteen (14) days at 06:00 h daily. At the end of the experiment, blood samples were collected using a 5 ml syringe through cardiac puncture and the sera obtained was used for growth hormone analysis. The weight (g) of the experimental animals were recorded using a digital weighing balance at 06:00h for days 0, 3, 6, 9, 12 and 14.
Results: There was a significant increase in mean serum growth hormone concentration (P<0.05) in the metoclopramide treated group; (19.35±1.14 ng/ml) compared to normal control; (11.53±1.64 ng/ml), olanzapine treated; (11.28±0.35 ng/ml) and risperidone treated; (11.30±0.70 ng/ml). However, there was no statistically significant difference in the olanzapine and risperidone treated groups compared to the normal control (P> 0.05).There was no statistically significant difference (P> 0.05) observed in the body weight changes although at day 14, metoclopramide showed the highest increase (180±1.30 g) compared to the normal control (172±1.83 g), olanzapine (173±2.30 g) and risperidone (175±3.80 g).
Conclusion: Metoclopramide at a dose of 5 mg/kg significantly increases serum growth hormone level (ng/ml) compared to olanzapine and risperidone in female lactating Wistar rats, with a non-significant increase in body weight of the dams.

Keywords: Lactation; olanzapine; risperidone and dopamine.

1. INTRODUCTION

Growth hormone which is also referred to as somatotropin is a peptide hormone which stimulates growth in tissues, cell reproduction and regeneration in humans and other animals. As a single chain polypeptide consisting of 191-amino acid it is synthesized, stored and secreted by the somatotropic cells within the pituitary gland also known as adenohypophysis. Somatostatin which is secreted from the hypothalamus inhibits the release of Growth hormone [1]. Growth hormone which is secreted from the anterior pituitary gland in a pulsatile fashion, acts on target tissues to promote growth. The pituitary gland otherwise known as hypophysis is the major source of growth hormone; however several other tissues synthesize GH, including brain, placenta, mammary and pineal gland [2]. GH is involved in maintaining mammary cell number during lactation of mice. In ruminants, the action of GH on the mammary gland is thought to be mediated mainly by the insulin-like growth factor (IGF) signaling axis. Although the action of GH is mediated mainly through the IGF axis, there is evidence that GH may act independently of IGF-I to stimulate milk production [3,4]. In addition, expression of GH receptor has been detected in mammary tissue. More so, GH receptor belongs to a super family of transmembrane receptors, of which the prolactin receptor is a member [5].

Metoclopramide drug was originally commercialized in Europe as an antipsychotic and later in the US as a gastro-kinetic agent which increases gastrointestinal motility. Its first reported use as a galactogogue was in 1975 [6] and it has since then been evaluated in many clinical trials [7]. It's reported side effects in humans include anxiety, insomnia, severe depression and seizure. Also Infants that consumed milk from treated mother had intestinal discomfort [8]. 10 mg administered by oral route three times daily for 10 days increases milk production [9]. Dopamine D_2 receptor blockade in the brain is a general pharmacodynamic property of all antipsychotics which are mainly of two (2) groups known as 'typical' and 'atypical' antipsychotics. Although with typical antipsychotics the level of D_2 receptor blockade is directly related to the antipsychotic effect, with atypical agents the situation is more complicated [8].

Olanzapine (OLZ) is a thienobenzodiazepine derivate structurally similar to clozapine that is effective in treating schizophrenia and acute manic episodes, and in preventing the recurrence of bipolar disorders [10]. Treatment with OLZ is associated with a higher risk of weight gain and, more extensively, metabolic syndrome than other typical and atypical antipsychotics [11,12]. It also has a low propensity to cause extrapyramidal effects or sustained increases in prolactin levels [13].

Risperidone is a benzisoxazole derivative, and has a very strong affinity for serotonin (5-HT_{2A} and 5-HT_7) and dopamine D_2 receptors (its

affinity for D_3 and D_4 receptors is three times lower) [13]. It is rapidly absorbed after oral administration, with peak plasma concentrations being reached in about one hour; its oral bioavailability is about 70-85%. It mainly undergoes 9-hydroxylation in the liver that yields the active 9-hydroxy risperidone metabolite (9-OH-RSP), a step that is mainly catalysed by CYP2D6 and, to a lesser extent, CYP3A4; alicyclic dehydroxylation and oxidative N-dealkylation are minor metabolic pathways [13]. Therefore this study was aimed at body weight changes and serum growth hormone in female lactating Wistar rats treated with metoclopramide and some atypical antipsychotic drugs.

1.1 Experimental Site

This study was conducted at the Department of Human Physiology, Faculty of Medical Sciences, College of Health Sciences, Ahmadu Bello University. Zaria is located between latitudes 11^0 and 3´ N, and between 7^0 and 42´ E, at an altitude of 670 m above the sea level and 664 km away from the sea, in the Northern Guinea Savanna zone [14]. The research was carried out according to the guidelines of Ahmadu Bello University animal use and care policy.

1.2 Chemicals and Drugs

Olanzapine and risperidone; Stallion Laboratories Pvt. Ltd.: Ahmedabad India. Manufacturing Licence No.: G/898, NAFDAC Reg. No.:A4-1677 and metoclopramide hydrochloride tablets 10 mg; Jiangsu Pengyao Pharmaceutical Inc. China, Manufacturing Licence No.: B131205, NAFDAC Reg. No.: 04-6476 and normal saline, used for this study were purchased from the Pharmacy of the Ahmadu Bello University Teaching Hospital (ABUTH) Shika; 8 km away from Samaru on Latitude 112^o 12'' N and Longitude 07^o 37'' E, Zaria Kaduna state, Nigeria.

1.3 Experimental Design

Twenty female lactating Wistar rats were sourced from the animal house of Human physiology department, faculty of medicine, Ahmadu Bello University. Mating protocol was carried out during which 20 females were divided randomly into four (4) groups of five rats each (n=5). Each group of females was then mixed with a corresponding male group in a ratio of 5:5 (male to female) and allowed to cohabit for mating. At parturition, the 20 females were randomly divided into four (4) groups of five (5) animals each (n=5) and treated as in Fig. 1.

1.4 Evaluation of Serum Growth Hormone Concentration in Female Lactating Wistar Rats

The animals were anaesthetized on day 14 at the termination of the experiment by intraperitoneal injection of ketamine and diazepam at 75 and 25 (mg/kg) respectively. The thorax of the each anaesthetized animal was cut open and with the aid of a 5ml syringe, the pulsating heart of the rat pierced at the left ventricle and blood obtained from which sera was obtained for the determination of growth hormone using the Rat-Growth hormone ELISA kit according to the manufacturer's manual.

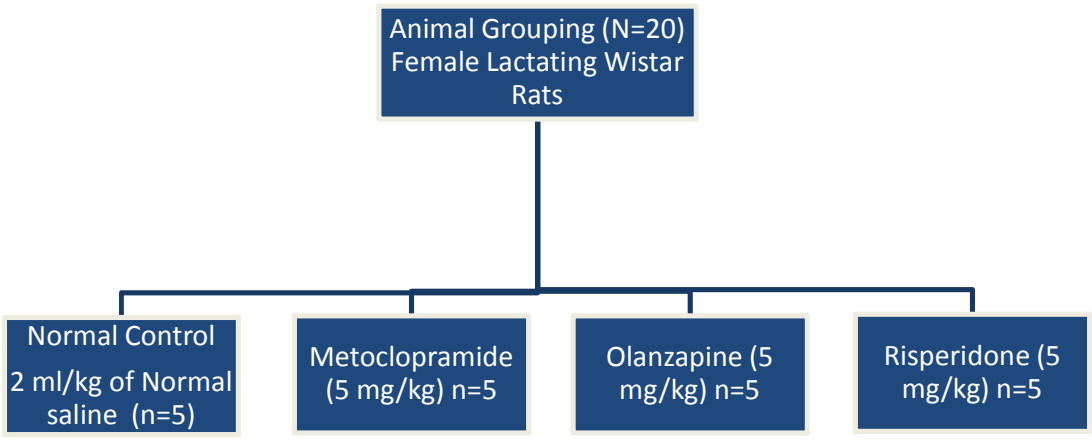

Fig. 1. Animal groupings and treatment

1.5 Statistical Analysis

Data obtained from the study were expressed as mean ± SEM. Statistical analysis was carried out using version 20 of SPSS with the aid of one way analysis of variance (ANOVA) and Tukey *post-hoc* test. Values with ($P< 0.05$) were considered significant.

2. RESULTS

2.1 Effect of Metoclopramide, Olanzapine and Risperidone on Serum Growth Hormone Levels in Female Lactating Wistar Rats

The serum growth hormone level (ng/ml) in female lactating Wistar rats treated with metoclopramide was significantly increased ($P< 0.05$) compared to the normal control; 19.35±1.14 ng/ml vs 11.53 ± 1.1.64 ng/ml respectively. Although changes were observed in the other treated groups, it was however not statistically significant compared to the normal control.

2.2 Effect of Metoclopramide, Olanzapine and Risperidone on Body Weight Changes in Female Lactating Wistar Rats Treated For Fourteen (14) Days

Metoclopramide treated groups showed the highest gain in weight at day 14 of the experiment; 180±1.30 g compared to normal control (172±1.83 g), olanzapine (173±2.30 g) and risperidone (175±3.80 g). Although changes were observed, it was however not statistically significant ($P> 0.05$).

3. DISCUSSION

The levels of serum growth hormone from this present study showed significant increase in the metoclopramide treated group compared to the control ($P< 0.05$). The result obtained from the metoclopramide treated could have been due to a pro-activity of this substance on the growth hormone releasing hormone in the hypothalamus resulting in increased serum growth hormone secretions from the cells in the pituitary gland. It has been shown that doperminergic drugs like metoclopramide can elicit GH secretion through an increased hypothalamic growth hormone releasing hormone [15]. This result has also been corroborated by the increase in weight observed in the metoclopramide treated group which is consequence of the activity of elevated serum level of growth hormone. The action of GH on the mammary gland is thought to be mediated mainly by the insulin-like growth factor (IGF) signaling axis [16]. Metoclopramide is known to elevate serum prolactin during which is responsible for milk synthesis. This action of the said drug could have also indirectly caused the complementary release of growth hormone in response to increased milk synthesis for the purpose of galactopoiesis and mammogenesis.

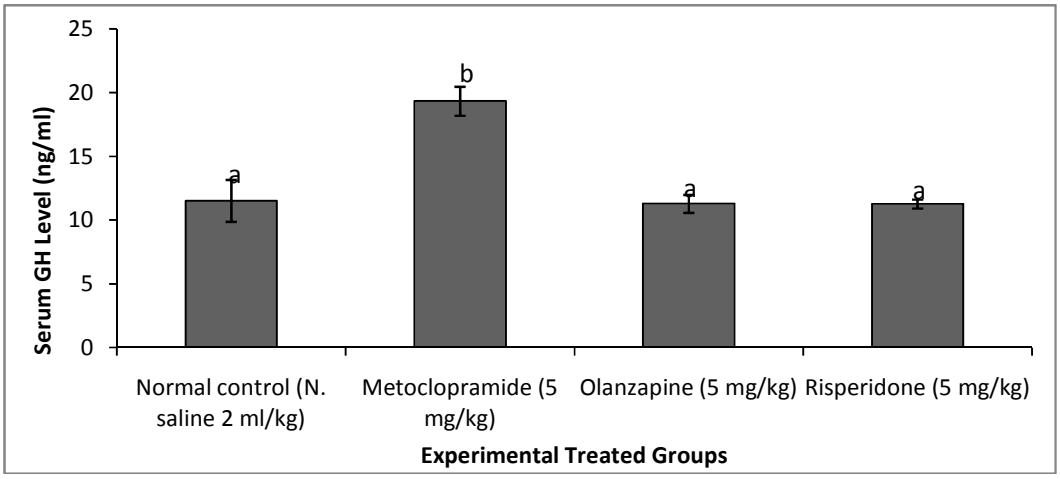

Fig. 2. Serum growth hormone levels in female lactating Wistar rats treated with Normal saline, metoclopramide, olanzapine and risperidone for fourteen (14) days. D= day. Different superscript (a,b) indicates statistically significant changes ($P< 0.05$), N. saline= normal saline, GH= growth hormone. Data was analysed using ANOVA after which Tukey *post hoc* test was carried out on SPSS

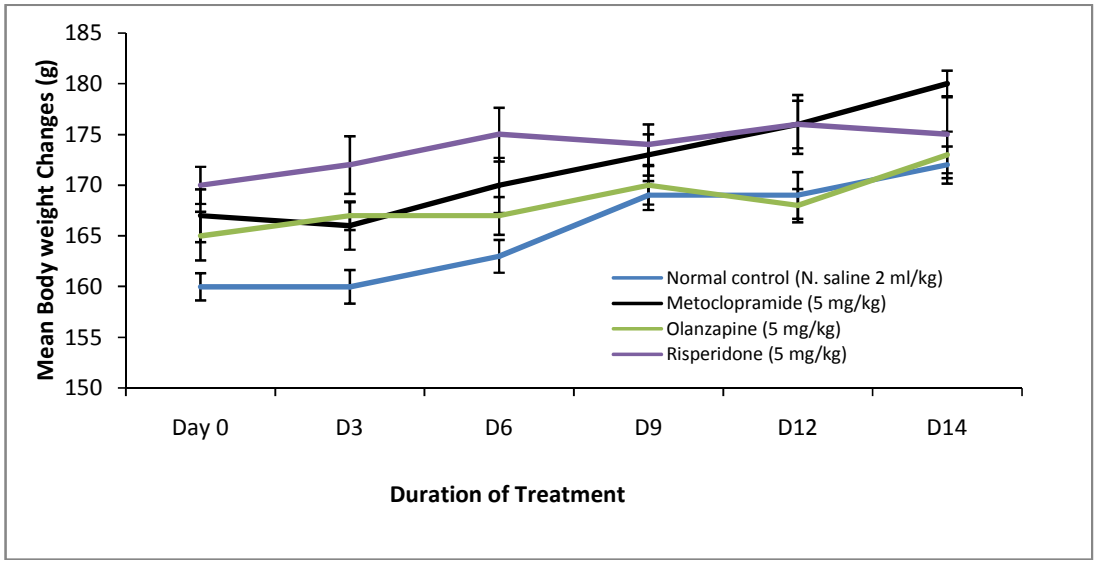

Fig. 3. Showing body weight changes in female lactating Wistar rats treated with Normal saline, metoclopramide, olanzapine and risperidone for fourteen (14) days. D= day. Data was analysed using SPSS while repeated measure ANOVA was employed to check the effect of time

Improved lactation performance can be achieved under conditions that enhance mammary cell proliferation (or decrease apoptosis), biochemical and structural differentiation of mammary epithelium, and synthesis and secretion of milk components. Moreover, any factors involved in the regulation of these processes can directly impact mammary function and milk yield [17,18].

The increase in body weight observed in metoclopramide treatment could also have been from a possible direct action of the drug on the hepatocytes resulting in the secretion of insulin like growth factor-1, which is known to cause the growth of tissues in the body. The increase in boy weight could also have been due to a possible upregulation of GH receptors in the various tissues, hence elevating their susceptibility and response to secreted GH. Although olanzapine and risperidone both act on doperminergic cells like metoclopramide, the mild effect observed in the GH level of these treated groups could have been from their less affinity to D_2 receptors within the adenohypophysis resulting in less effect on the serum GH level compared to the control and metoclopramide. The result obtained on the body weigh in both olanzapine and risperidone treated groups also corroborate with the findings on the serum growth hormone level.

4. CONCLUSION

Metoclopramide elevates serum GH level as well as the body weight of dams during lactation in female Wistar rats more than olanzapine and risperidone.

CONSENT

It is not applicable.

ETHICAL APPROVAL

The research was carried out according to the guidelines of Ahmadu Bello University animal use and care policy. This research is an excerpt from a work we conducted a while back as part of a dissertation during which a proposal was presented to the department and approved taking into consideration the University's ethical standards on the use of animals.

As per international standard or university standard ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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