Department of Human Anatomy,

Faculty of Basic Medical Sciences,

Afe Babalola University, Ado-Ekiti,

(ABUAD),

Ekiti State.

October 14, 2019

The Chairman ,

Research Ethics Committee,

ABUAD,

Ekiti State.

Dear Sir.

**APPLICATION FOR ETHICAL APPROVAL**

We are the Group 2, 300-level student of the Department of human Anatomy, ABUAD. The research we wish to conduct for our research class focuses on “ ***Effects of the Analgelsic Tramadol on the reproductive system of male Wistar rats*** “. This project will be conducted under the supervision of our course Lecturer Mr. Shola Azeez of the Department of Human Anatomy, ABUAD.

We are hereby seeking ethical approval to carry out this research. Attached herewith is a copy offer proposal outlining our work plan, the materials and methods, which we plan to employ.

Upon completion of the study. We undertake to provide bound copies of the project research and to submit manuscripts to peer-reviewed journals for publication.

Thank you for your time and consideration on this matter.

Yours faithfully,

**Group 2 of 300-level Anatomy students**  .

**Group 2 Members**

1. Afeno-Eboh Voke 17/MHS01/026
2. Amusan Opemipo Fiyinfoluwa 17/MHS01/061
3. Daniel Gimbiya Natasha 17/MHS01/094
4. Emmanuel Emele Uchechukwu 17/MHS01/112
5. Imoyin-Omene E. 17/MHS01/159
6. Inokoba Tovia 17/MHS01/162
7. Kwame-Okpu E. A. Ogheneovu 17/MHS01/174
8. Manger Bernard Aondona 17/MHS01/184
9. Obasi Kosisochukwu Cindy 17/MHS01/218
10. Oferiofe Israel Ovwie 17/MHS01/231
11. Ogwu Isaac Daniel 17/MHS01/235
12. Cynthia Eleojo Peter 17/MHS01/283
13. Rimamchatin Peculiar 17/MHS01/287
14. Nwachukwu Chinaza 17/MHS03/033
15. Bello Aisha 17/MHS07/005
16. Saliu Halima 17/MHS01/294
17. Shaldas Usiju Shaldas 17/MHS01/296
18. Shigaba Anna Nama 17/MHS03/030
19. Chika Chieze 17/MHS03/011
20. Kehinde Henry Aina 16/MHS01/019

A

LITERATURE REVIEW

ON

THE

EFFECTS OF THE ANALGELSIC ‘TRAMADOL’

ON

THE

REPRODUCTIVE SYSTEM

OF MALE WISTAR RATS

INTRODUCTION

Tramadol is a centrally active synthetic opioid analgesic that is used extensively. It’s mode of action is not completely understood, but two acceptable complementary mechanisms are binding to mu opioid receptors (MOR) and inhibition of reuptake of noradrenaline and serotonin. (Raffa et al; 1992). The drug exerted hypoglycemia in users (Grandvuillemin et al; 2006) which influence growth hormone (GH) secretion suggesting that their GH deficiency has a hypothalamic rather than pituitary origin (Tennesse et al; 2003). From literature, multiple cases of toxicity and abuse of tramadol have been reported. The main symptoms of tramadol toxicity include central nervous system depression, nausea and vomiting, tachycardia, and seizures [Shadnia et al; 2008). Fatal cases have been reported as a result of tramadol overdose. In those instances, death has been attributed to cardiopulmonary arrest and hepatic failure as well as hypoglycemia (Mugunthanet al; 2012).

The tramadol absorption is about 95-100% and it is absorbed rapidly in the small intestine and reaches its highest peak after 5 hours (Lintz et al; 1981). It is widely distributed throughout the body, especially liver and kidneys (Jellinek et al; 1990).

 TOXICITY OF TRAMADOL ON MALE REPRODUCTIVE SYSTEM

The toxicity of tramadol on the male reproductive system has been shown in some researches using the seminiferous tubules with marked testis as the organ of study. As reported by (Ghawet et al; 2015), tramadol treatment caused focal disorganization of depletion of the spermatogenic cell populations. Exfoliation of the damaged spermatocytes and spermatids were detected within the tubular lumina of many of the seminiferous tubules. The intertubular connective tissue became hyalinized and showed comparative reduction of interstitial cells. Following flowcytometric analysis, there was a marked increase of apoptic spermatogenic cells.

Also, according to another research carried out on the reproductive system to discover the effects of (tramadol) treatment on testicular functions in adult male rats,tramadol-treatment led to a decrease of testosterone and total cholesterol and increased level of the the testicular levels of nitric oxide and lipid peroxidation, and decreased the anti-oxidant enzymes activities significantly compared with the control group. These may facilitate the damage of spermatogenic cells via increase of reactive species(Ahmed et Kurkar; 2014). Finally, it was concluded that chronic administration of tramadol lead to reproduction dysfunction and increased average of infertility.

It was also identified in another research done by (Azari et al; 2014) that tramadol toxicity caused a decrease in sperm motility, vitality and microscopic examinations revealed that tramadol damaged the testicular tissue.
According to the results of that study, it can be concluded that long-term administration of tramadol has adverse effects on sperm quality and testicular tissues and these effects are dose dependent. Also, the negative effects of tramadol on testes are reversible.

AIM(S) OF STUDY

This research is aimed at assessing the effects of the analgesic, tramadol on the reproductive system of male whister rats.

sOBJECTIVES OF STUDY

To determine the effect of tramadol on the sperm count and concentration.

To check if tramadol has any effect on the penis of rats histologically.

MATERIALS AND METHODS

Purchase of Medications

Analgesic (Tramadol) and Anesthetics to be used will be purchased from Mctanax Veterinary Pharmacy, Ibadan, Nigeria.

Animal Care, Grouping and Housing

Twenty (20) adult male whister rats weighing approximately 150g will be purchased for this research from the University of Ibadan where they have been born and bred. They will be housed in standard cage of five animals/cage. Feed and water will be given *ad libitum*.

The animals will divided into two (2) groups; Control male (Group A) and Tramadol treatment male (Group B) and treated thus;

1. Group A (n=10); will be administered normal saline for thirty days as control.
2. Group B (n=10); will be administered Tramadol doses (40mg/kg body weight) for thirty (30) days. Doses calculated using Paget and Barnes (1964) species introversion table of dosage.

All administrations will be done orally using oral cannula.

Animal Sacrifice

The animals will be sacrificed twenty four (24) hours after last administration. The animals will be eutanized by the inhalation of an anesthetic (Halothane), after which the penis, testes, epididymis, and seminal vesicle will be incised and processed for histological investigation and flow cytometric analysis of apoptosis.

Statistical Analysis

The data obtained during this research will be expressed as mean ± standard error of mean (SEM). Parametric data will be analyzed with one – way analysis of variance (ANOVA) and *P*  value set at 0.05.

Expected Outcome

Tramadol is expected to have an effect on the sperm count and concentration, and also have a histological effect on the penis of the animals.

Publication Policy

A write up regarding this research will be submitted to the Department of Anatomy , College of Medicine and Health Sciences , Afe Babalola University in partial fulfillment of the requirement for the award of the degree of bachelor of science in anatomy.

Project Timeline

Approval – March 1st – March 20th

Acquiring of materials – March 22nd – April 3rd

Bench work – April 4th – May 10th

 Analysis of results – May 11th – May 20th

Preparation of Reports – May 20th – July 1st

Presentation of results – July 5th

Review of literature – July 6th – July 15th

Preparation of final thesis – July 16th – August 16th

Revision of thesis – August 16th – August 18th

Correction of thesis – August 19th – August 21st

 Submission of corrected thesis – August 25th

Budgets

|  |  |  |
| --- | --- | --- |
| **S/N** | **Items** | **Amount (#)** |
| 01 | Animals | 20,000 |
| 02 | Animal feed | 5,000 |
| 03 | Normal Saline | 1,000 |
| 04 | Medications to be administered | 40,000 |
| 05 | Miscellaneous | 25,000 |
|  | **Total** | 91,000 |

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