Effects of Tramadol on Fertility Hormones (Follicle Stimulating Hormone, Leutinizing Hormone, Prolactin, Testosterone, Estrogen and β-HCG) in Laboratory Rabbits

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Author’s Contributions

This work was carried out in collaboration between both authors. Author HBO designed the study, wrote the protocol, draft of the manuscript and supervised the work from the beginning to completion while author JAOE managed the literature searches, performed the study analysis and the statistical analysis. Both authors read and approved the final manuscript.

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ABSTRACT

Drug abuse in Nigeria has been indicated to be on the rise in recent years. The use of hard drugs and misuse of prescription drugs for nonmedical purposes cuts across all strata, especially the youths. Tramadol (2[(Dimethylamin) methyl]-1-(3-methoxyphenyl)cyclohexanol) is known for its analgesic potentials. This potent opioid pain killer is misused by Nigerian youths, owing to its suspicion as sexual performance drug. This study therefore is aimed at determining the effect of tramadol on hormone levels its improved libido properties and possibly fertility. Twenty seven (27) European rabbits weighing 1.0 to 2.0 kg were used. Animals were divided into four major groups consisting of male and female control, and male and female tramadol treated groups. Treated groups were further divided into oral and intramuscular (IM) administered groups. Oral groups were administered 25 mg/kg b.w. of tramadol per day while the IM groups received 15 mg/kg b.w. per
day over a period of thirty days. Blood samples were collected at the end of the experiment for progesterone, testosterone, estrogen (E2), luteinizing hormone, follicle stimulating hormone (FSH), β-human chorionic gonadotropin and prolactin estimation. Tramadol treated groups were compared with control groups at the end of the study, as well as within group comparison was done. From the results, FSH was found to be significantly reduced (p<0.05) while LH increased significantly (p<0.05). A decrease was observed for testosterone (p<0.001), and estrogen, FSH, progesterone also decreased (p<0.05). Significant changes weren’t observed when IM groups were compared with oral groups. This study does not support an improvement of libido by tramadol, though its possible usefulness in the treatment of premature ejaculation may have been established, but its capabilities to induce male and female infertility is still in doubt.

**Keywords:** Benin City; Nigeria; animal model; drug abuse.

1. INTRODUCTION

Drug abuse is the recurrent use of illegal drugs, misuse of prescription and/or over the counter drugs with negative consequences. Drug abuse in Nigeria has been indicated to be on the rise in recent years. NDLEA pointed that Kano State has the highest drug abuse rates based on the number of seizures, arrests of addicts and convictions of arrested dealers [1]. This use of hard drugs as well as misuse of prescription drugs for nonmedical purposes cut across all strata especially the youths. Among the drugs being used are alcohol, caffeine, cannabis, opiates and prescription and over the counter drugs. Such abused drugs include alcohol, tobacco, heroin, opiates e.t.c. [2]. Youths are known to continue using these drugs despite the major risk behaviours with its accompanied physical and mental health complications [3]. Of growing interest is the increased demand for tramadol which is an opiate analgesic medication. 2[(Dimethylamin)methyl]-1-(3-methoxyphenyl)cyclohexanol also known as tramadol is a common over the counter drug sold in pharmaceutical shops and retail medicine outlets in Nigeria. It is an opioid pain medication for the treatment of moderate to moderately severe pain. Available dosage forms include capsules, tablets and extended release formulations and injections [4].

Tramadol is frequently been abused in Northern Nigeria by youths for lasting energy [7] and sexual performance drug [8]. The use of this potent opioid pain medication as sexual enhancer and proposed management of premature ejaculation as proposed by [9-13] as well as the effectiveness of tramadol in the treatment of premature ejaculation as show by [14] have given rise to this study. This study aims at evaluating the toxic effects of tramadol on sex hormone profile of male and female Oryctolagus cuniculus (European rabbits) with a view to ascertaining if any its effects on libido and possibly fertility.

2. MATERIALS AND METHODS

2.1 Dosing and Experimental Animals

Twenty seven (27) European rabbits aged between 4-6 months, weighing 1.0 to 2.0 kg purchased from local market in Benin City were used for this study. The drug tramadol HCl (Ampoule) 100 mg/2 ml manufactured by Gland Pharma Limited, India was administered intramuscularly while Nkoyo tramadol (Tramadol capsule B.P. 100 mg) manufactured by Mancare Pharma Pvt. Ltd. Vasai, India was administered orally. Rabbits were left in the animal’s house for two week before experimentation to adapt and acclimatize to laboratory conditions of natural light and dark cycle and given free access to commercial balanced diet and tap water ad libitum all through the experimental period. Animals were divided into four groups consisting male and female controls, and male and female tramadol treated groups. Tramadol treated groups were further divided into oral and intramuscular (IM) groups. IM groups were inoculated with 15 mg/kg b.w./day for thirty days while orally groups were administered 25 mg/kg b.w./day for thirty days.
2.2 Measurement of Hormone Levels

Blood samples were collected from tramadol treated groups and control groups at the end of the experiment into plain sample bottles and serum transferred into a second plain bottle after allowing to clot. Samples were stored at -70°C until ready for assay. Human prolactin, follicle-stimulating hormone, luteinizing hormone, testosterone, progesterone, estradiol (E2) and human chorionic gonadotropin (HCG) were determined using i-chroma immunoassay analysis system [15].

2.3 Statistics

GraphPad Prism (version 6.04; GraphPad Software, USA) was used for statistical analysis. Error bars were reported as means ± SEM. Statistical significance was determined using Student t-Test, and one-way ANOVA to compare tramadol treated groups and controls groups as well as tramadol Oral administered groups with Intramuscular administered groups and with controls; and Two-way ANOVA to compare male and female tramadol treated groups with male and female control groups respectively. Statistically significant levels of p<0.05 was used.

2.4 Ethics

This study was approved by Ministry of Health, Benin City, Edo State of Nigeria.

2.5 Informed Consent

It was not possible to get informed consent from the rabbits, however all the rabbits were given adequate care and treatment as if they were human beings.

3. RESULTS

Effect of tramadol on FSH, LH, Prolactin, Testosterone, Estrogen and β-HCG was estimated. All β-HCG levels were <5.0 mmol/L. Fig. 1, shows the assessment of LH and FSH in serum. When tramadol treated groups were compared with control groups, FSH was found to be significantly reduced (p<0.05) while LH increased significantly (p<0.05). But on comparison of male and female treated groups with control groups (Fig. 3), and Oral and IM groups with control groups as well as among themselves (Fig. 2), p-values showed no significance both for LH and FSH (p>0.05).

![Fig. 1. LH and FSH estimation of control groups and tramadol treated groups](image-url)

* Error bars represent Mean ± SEM (*p<0.05)
Fig. 2. LH and FSH estimation of control groups, oral and IM tramadol treated groups

Error bars represent Mean ± SEM

Fig. 3. LH and FSH estimation showing male and female comparison

Error bars represent Mean ± SEM
Increased Prolactin level was observed when tramadol treated groups were compared with control groups (Fig. 4) although this increase wasn’t significant (p>0.05). Testosterone levels on the other hand showed significant decrease on comparison of tramadol treated groups with control groups (p<0.01). Within group (male and female treated groups against male and female control groups) comparison, and oral against IM and control groups comparisons show no significant difference for prolactin and testosterone (p>0.05) (Fig. 6 and Fig. 5 respectively).

**Fig. 4. Prolactin and testosterone estimation of control groups and tramadol treated groups**

*Error bars represent Mean ± SEM. (**p<0.01)*

**Fig. 5. Prolactin and testosterone estimation of control groups, oral and IM tramadol treated groups**

*Error bars represent Mean ± SEM*
On Estradiol estimation, a significant decrease was observed (p<0.05) (Fig. 7). When Oral and IM groups were compared with Control groups (Fig. 8) and on comparison of male and female treated groups with control groups (Fig. 9), no significance was observed (p>0.05).

Determination of progesterone in tramadol treated and control groups showed significant decrease (p<0.05) (Fig. 10). When comparisons were made between Oral and IM groups, significance was observed between oral administered groups and control groups (p<0.05) although no significance was noticed between IM and oral comparisons or IM and controls (p>0.05) (Fig. 11). When comparisons were made between groups of male and female treated animals and control groups for male and female animals, only male treated groups with male control showed significance (p<0.05) (Fig. 12).

4. DISCUSSION

Opioids are known to do well in relieve of pain. This they do by turning on opioid receptors in the brain, gastrointestinal tract and spinal cord. But on long term usage, opioids have been reported to have negative effects on hormone levels.

These effects include decreased levels of sex hormones including testosterone and estrogen. Cortisol and dehydroandrosterone sulfate (DHEAS) decreases have also been reported [16].

A significant decrease in testosterone, progesterone and estrogen levels were seen in this study which correlates with [16] suggesting that long term opioid therapy results in clinically relevant suppression of both hypothalamic-pituitary-adrenal and —gonadal axes with suppression in testosterone, estrogen and cortisol. This effect as seen in this sub-acute study may be attributed to suppression of the hypothalamic-pituitary-gonadal axis (HPG axis) by opioids [17,18]. Testosterone and estrogen (the male and female principal sex hormones) are produced by the testes and ovaries respectively by the action of FSH and LH (referred to as gonadotropins) which are produced by the pituitary gland following the stimulation of gonadotropin-releasing hormone (GnRH) which in turn is produced by the hypothalamus. It is expected that as the level of sex hormones rises a negative feedback loop should trigger the hypothalamus to reduce production of GnRH.

Fig. 6. Prolactin and testosterone estimation showing male and female comparison

Error bars represent Mean ± SEM
Fig. 7. Estradiol estimation of control groups and tramadol treated groups

$\text{Error bars represent Mean} \pm \text{SEM}$

Fig. 8. Estradiol estimation of showing control groups, oral and IM tramadol treated groups

$\text{Error bars represent Mean} \pm \text{SEM}$
Fig. 9. Estradiol estimation showing male and female comparison

*Error bars represent Mean ± SEM*

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Fig. 10. Progesterone estimation of control groups and tramadol treated groups

*Error bars represent Mean ± SEM*
Fig. 11. Progesterone estimation of control groups, oral and IM tramadol treated groups

Error bars represent Mean ± SEM (*p<0.05)

Fig. 12. Progesterone estimation showing male and female comparison

Error bars represent Mean ± SEM
This study shows a reduction in sex hormones without an adequate increase in gonadotropins which should have been a proper hypothalamic pituitary regulation. A reduction in sex hormones by opioids have been reported previously by [17] who demonstrated a reduction in testosterone levels in the blood of Sprague-Dawley rats following treatment with morphine; as well as in a study of opioid induces endocrinopathia [18].

Reduction in LH and FSH levels by opioids have been reported previously by [18,19]. This study showed a reduction in FSH levels which correlates with previous studies indicating that tramadol interferes with proper hypothalamic pituitary regulation. This study showed an increased LH levels which is in contrast to Todd and colleague report of an inhibition of LH by opioids. But in justification of [18], conclusion of an incomplete understanding of the effect of opioids on LH and subsequently sex hormone release. Suggestions are that this interferences experienced may be due to alterations in sex hormone-hypothalamic feedback process.

This study has shown a direct interference of tramadol consumption with pituitary release of LH and FSH which could interfere with the menstrual cycle in women [18] by blunting of the normal pulsatile release of LH and direct negative effects on the testes of males resulting in testosterone decrease and a reduction in testicular interstitial fluids [20]. A reduction in testosterone levels will eventually lead to decrease in sexual drive as well as sustenance of erection.

Also, a malfunction in HPG axis can result in big changes inside the body. These changes may lead to opioid-induced hypogonadism and other effect may include sluggish libido, erectile dysfunction for the males, irregular menstrual cycles in females and possibly infertility in both male and females.

5. CONCLUSION

Although tramadol is being recommended in the treatment of premature ejaculation, and is used locally by youths for sustained libido, this subacute toxicity studies showed tramadol as having no significant contributory effects on libido at the concentration consumed through an alteration in sex hormone patterns but that tramadol may cause changes in sex hormone levels and alter feedback regulations of the pituitary on the hypothalamus. Tramadol may also have direct effect on the testes and ovaries causing reduced testosterone and estrogen secretions. Also, long term use could result in opiate induced endocrinopathy which could predispose users to cases of infertility for both male and females.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

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