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The effect of 200mg dosage of tramadol on the Seminiferous tubules and Spermatozoa production of a male wistar rat

[1]Okaba E.A and [2]Ebisintei P

1,2 Department of Biological Sciences, Faculty of Basic and Applied Sciences, University of Africa, Toru – Orua. Bayelsa State.

Summary: Tramadol hydrochloride is a synthetic opioid analgesic that is centrally acting drug widely used in the treatment of acute and chronic pain but its now a commonly abused erotic drug that recently has gained popularity among young men. This study aimed to evaluate the chronic toxic effects of tramadol on the reproductive system and sperm production of male albino rats. This experiment was carried out on 40 rats divided into two groups. The first group (control group) included 20 rats and received normal saline 0.1% ml/day orally for 8 weeks. The second group (tramadol group) included 20 rats and received tramadol 200 mg/kg subcutaneously three times per week for 8 weeks. Blood samples were obtained from the animals and analyzed for serum testosterone, FSH, LH and prolactin levels. Also, the testes were excised and examined for histopathological changes.

Keywords: Tramadol, Follicle stimulating hormones, Luteinizing hormone, Testosterone

Introduction

Tramadol hydrochloride is a synthetic opioid analgesic that is centrally acting drug widely used in the treatment of acute and chronic pain of moderate to severe intensity associated with a variety of diseases including diabetic neuropathy, neuropathic pain, and perioperative pain
(Azari et al, 2014). It is used also for premature ejaculation and as an antidepressant (Barber J, 2011). In addition, it is used in the treatment of diabetic neuropathy (Lindsay TJ et al, 2010) and postherpatic neuralgia. Tramadol is a centrally acting analgesic with a dual mode of action, including an opioid and non-opioid component. It is an agonist of the opioid receptors, but in addition, it also inhibits the serotonin and norepinephrine reuptake enhancing the inhibitory effects on pain transmission in the spinal cord (Oliva P et al, 2002)

Tramadol is generally considered as a medicinal drug with a low potential for dependence relative to morphine. Nevertheless, physical dependence of the opioid type can occur with tramadol when used for a sustained period of time. Physical dependence on tramadol may occur when used within the recommended dose range of tramadol. In many individuals with tramadol misuse, a substance abuse history is

found. Orally administered tramadol can produce opioid-like effects (both mentally and physically). Tramadol is generally considered a medicine with a lower abuse potential compared to morphine, but abuse of tramadol can occur. At supra-therapeutic doses and rarely at therapeutic doses, intoxications may occur (WHO, 2017).

Symptoms of tramadol intoxication are similar to those of other opioid analgesics but may include serotonergic and noradrenergic components. Symptoms include central nervous system (CNS) depression and coma, tachycardia, cardiovascular collapse, seizures, and respiratory depression up to respiratory arrest. Fatal intoxications are rare and appear to be associated with large overdoses of tramadol and co-ingestion of other drugs (including alcohol). Tramadol is used worldwide and is listed in many medical guidelines for pain treatment. It is mentioned as a step-2 analgesic in the WHO guidelines for cancer pain relief (WHO, 2017).

Materials and Methods

Materials

Animals

This study was carried on 40 adult male albino rats. Strict care and hygiene were maintained to keep them in normal and healthy conditions. Food and water were given *ad libitum*.

Drugs and chemicals

Tramadol: the drug was in the form of tramadol hydrochloride tablets (200 mg/tablet). It was provided by Hilek Pharmaceutical Co. (Biogbolo, Yenagoa). Each tablet is suspended in 20 ml distilled water to produce the desired concentration.

Experimental protocol

The animals were divided into two groups as follows:

- Group I (control group): it included 20 animals. They received 0.1 ml of physiological saline solution by oral route for 8 weeks.

Group II (tramadol-treated group): it included 20 animals. They received tramadol at a dose of 200mg/kg body weight daily (nearly 10 mg/rat) orally by intragastric gavage needle for 8 weeks.

Methods

This experimental work is a toxicological study of a commonly used erotic drug on the reproductive system of male albino rats. It was carried out in accordance with the national and institutional ethics for the care and use of laboratory animals. The study included biochemical analysis of the serum levels of testosterone, prolactin, FSH and LH in the rats after subcutaneous injection of tramadol, in addition to histopathological examination of the excised testes.

At the end of the determined period for each group, animals were anesthetized using ether inhalation, and then were killed. Both testes of each animal were excised.

Results

Hormone	Control group	Tramadol group	P value
FSH (mIU/ml)	0.104 ± 0.008	0.062 ± 0.003	0.058
LH (mIU/ml)	0.52 ± 0.007	0.088 ± 0.016	0.003
Testosterone (ng/ml)	5.34 ± 0.094	2.274 ± 0.140	0.009
Prolactin (ng/ml)	1.06 ± 0.094	4.42 ± 0.328	0.165

Biochemical findings

The results revealed that administration of tramadol 200 mg/kg three times per week for a period of 8weeks statistically reduced the serum testosterone level accompanied by an increase in the serum prolactin level and a decrease in the serum LH levels compared to the control group (Fig 1). Concerning FSH, a decrease in the serum level was observed in the tramadol group but with a borderline significance ($P = 0.058$).

Histopathological findings

The testicular sections prepared from the control group showed normal appearance of the seminiferous tubules and interstitial tissue. The tubules were lined with germinal cells and supporting sertoli cells. The germinal cells were arranged in several layers from the basement membrane towards the lumen of the tubules. These layers are formed of a series of spermatogenic cells at different stages of maturation including spermatogonia, primary spermatocytes, secondary spermatocytes, spermatids and mature sperms. The interstitial tissue stroma between the seminiferous tubules contained the interstitial cells of Leydig.

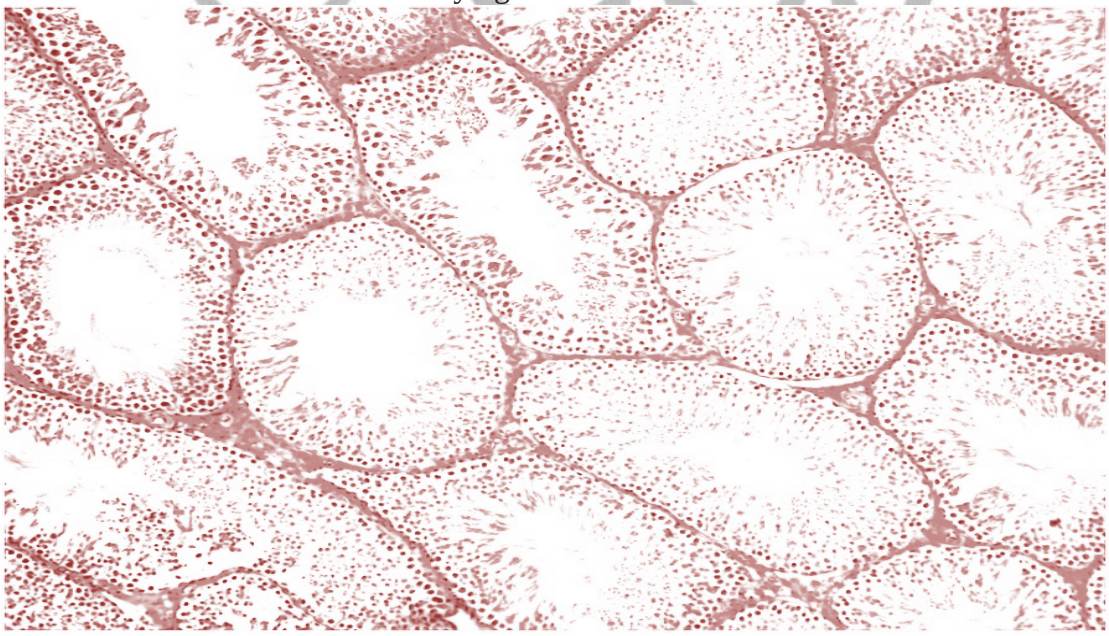

Fig 1: Testicular section from the control group showing normal seminiferous tubules with normal spermatogenesis (H & E, × 100)

Sections prepared from the animals administered with tramadol revealed distinct histological changes with abnormal appearance of the germinal epithelium. The majority of the seminiferous tubules exhibited damage with disorganized spermatogenic cells that showed prominent multiple desquamations and vacuolar degeneration. Numerous apoptotic and multinucleated giant cells were also seen. Many spermatogenic cells appeared with pyknotic nuclei. Furthermore, absence of spermatozoa was clearly recognized. The interstitial tissue showed marked edema and vascular congestion. In addition, foci of dystrophic calcification were found in some cases. Leydig cells were markedly reduced

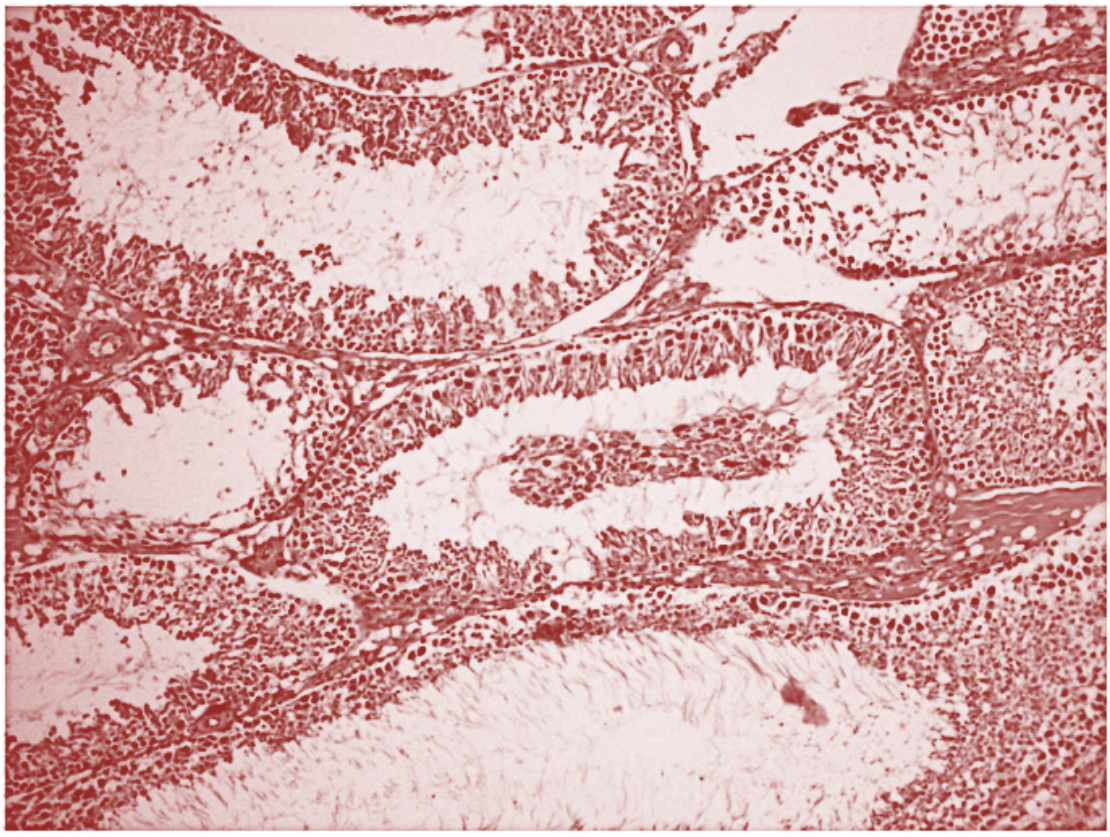

Fig 2:Testicular section from the tramadol group showing disorganized spermatogenesis with focal exfoliation of desquamated germinal cells in the lumen of seminiferous tubules (H & E, × 100)

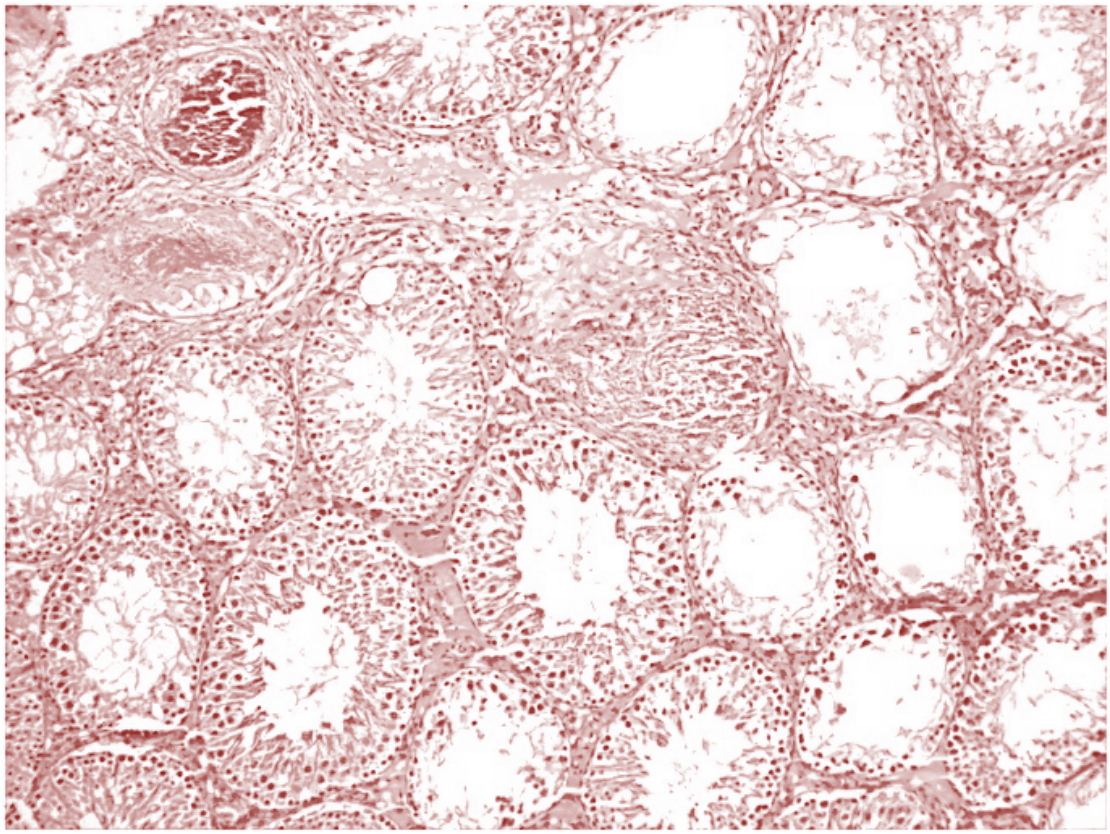

Fig 3. Testicular section from the tramadol group showing vacuolar degeneration with absent spermatogenesis in some seminiferous tubules. Focal calcification was also regarded (H & E, × 100)

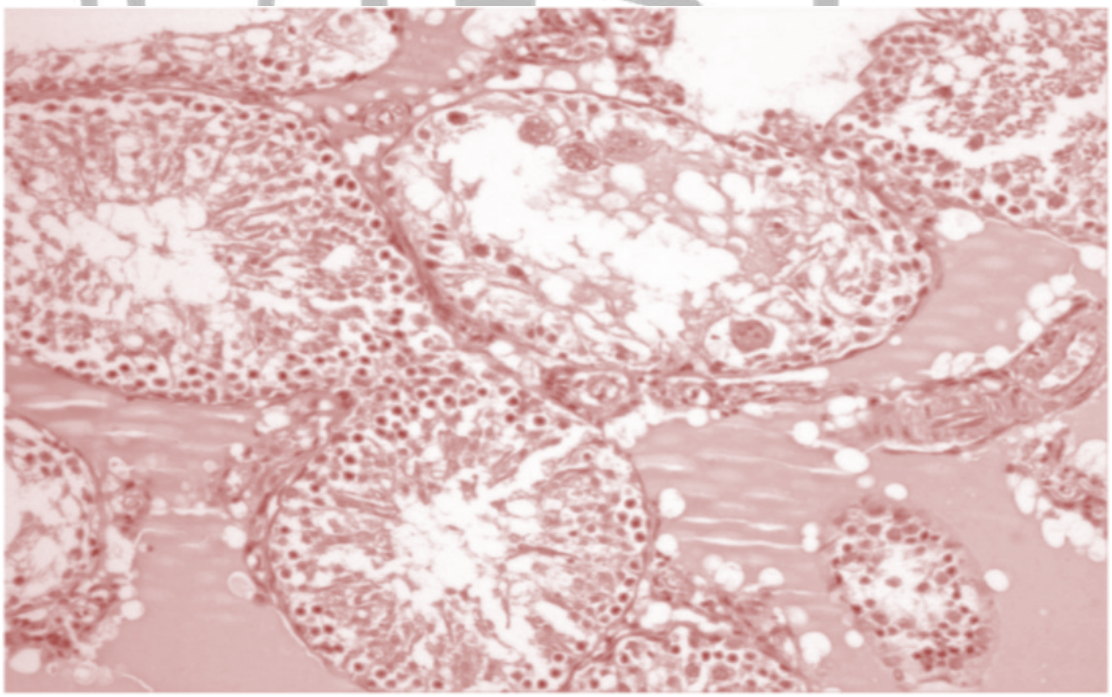

Fig4. Testicular section from the tramadol group showing focal vacuolar degeneration with prominent intratubular giant cells and interstitial oedema (H & E, × 200)

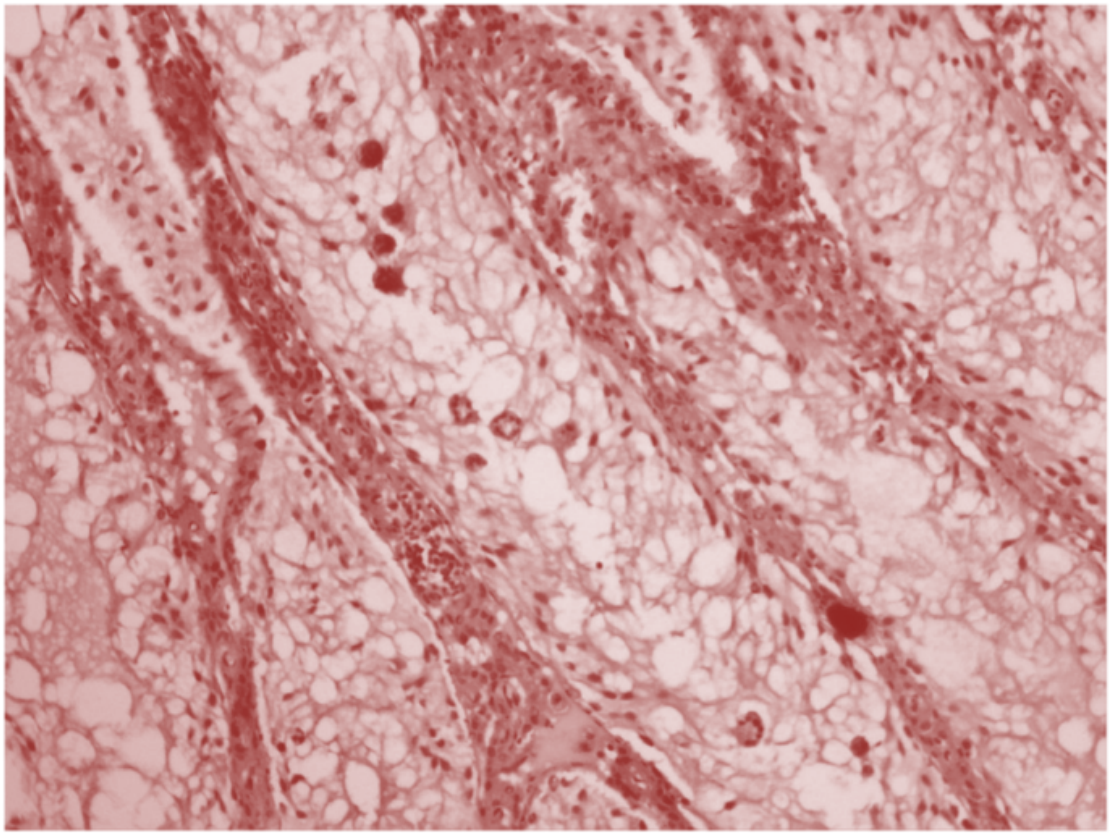

Fig 5: Testicular section from the tramadol group showing vacuolar degeneration with intratubular apoptotic bodies and abnormal giant cells (H & E, × 200)

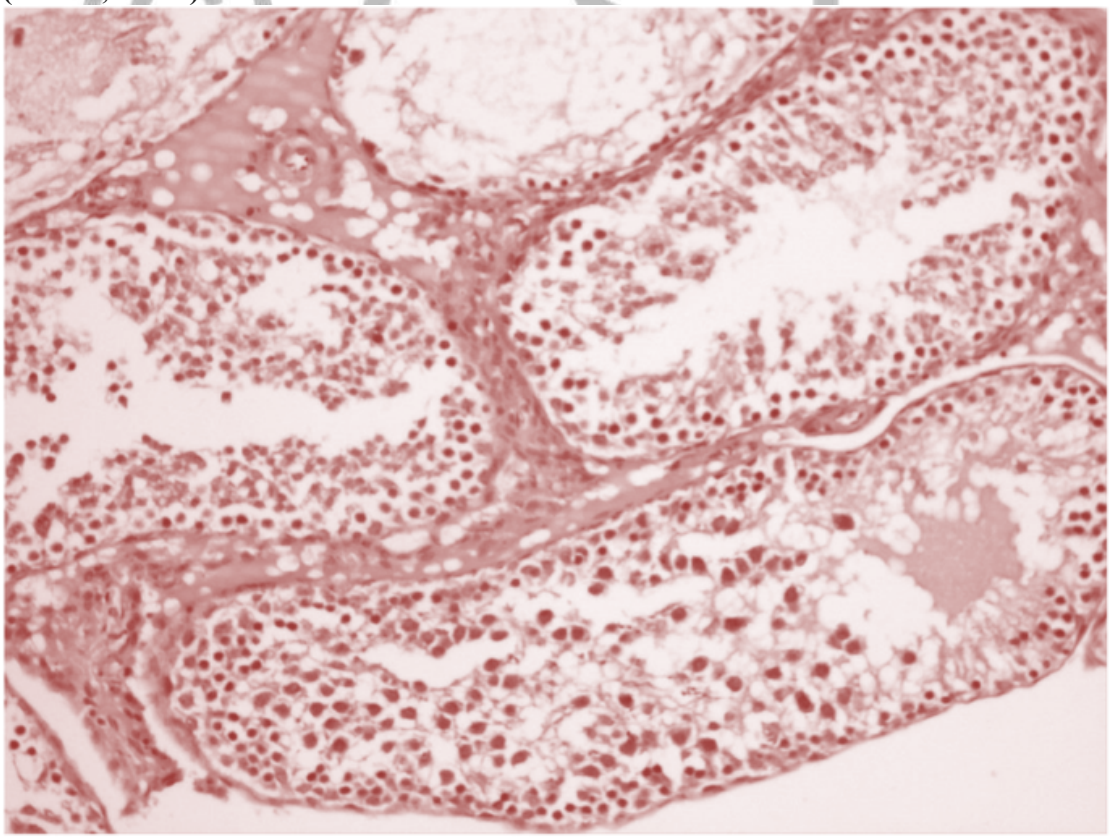

Fig 6: Testicular section from the tramadol group showing disorganized spermatogenesis, vacuolar degeneration, interstitial oedema and reduced number of Leydig cells (H & E, × 200)

Discussion

Sex-enhancing drugs have become some of the most prescribed and abused pharmaceuticals in the last years. Indeed, it is reasonable to believe that recreational use of erotic medications may exceed their recommended medical use (Nna VU et al, 2014).

Several studies on the effect of chronic consumption of opioids on the male reproductive system have revolved around testicular oxidative stress as the mediator of reproductive toxicity. Opioids are among the most useful therapeutic drugs for pain management but their side effects have been a wide subject of research. However, one of their side effects, namely male hypogonadism, has not been fully elucidated.

The current study revealed that rats treated with tramadol had lower serum levels of testosterone ($P = 0.009$), FSH (with a borderline significance) ($P = 0.058$) and LH ($P = 0.003$) and an increased prolactin level ($P = 0.165$) compared with the control rats. The reduced serum levels of FSH and LH were explained by Bliesener et al. (who showed that the opioid effect on the gonadotropin-releasing hormone (GnRH) is mediated partly through the increased prolactin levels.

Pimpinellei et al. (Pimpinellei et al, 2006) reported that increased prolactin synthesis could directly inhibit testosterone synthesis. Moreover, El-Gaafarawy reported the reduction of serum levels of FSH, LH and testosterone and the induction of prolactin secretion following paroxetine (opioid with tramadol-like action acting on opioid receptors) treatment (El- Gaafarawy, 2006). The results suggest that tramadol administration might influence the release of testosterone via the hypothalamo-hypophyseal-gonadal axis. In addition, it is well known that LH is regulated by numerous neurotransmitters, including endogenous opioid peptides (Gore AC, 2001). The present results were also explained by Katz (Katz N, 2005). The long-term effects of opioids on the endocrine system include reducing testosterone levels by central reduction of LH release. There are peripheral effects on the testis as well since tramadol also increases aromatization of testosterone to estradiol (Ceccarelli I, et al, 2006). It is noteworthy that in our study the reduction in FSH was with a borderline significance ($P = 0.058$). This reduction may not be sufficient enough to reach a marked statistical significance but it may be of biological significance. Negative feedback effect may also play a role in this effect.

Opioids are well known to affect sexual drive in male humans and rodents (Cicero T, 2002). Studies have shown that opioids decrease the levels of sex hormones and result in diminished fertility of both males and females (Mckim W, 2003). Studies have detected a significant association between chronic tramadol administration and impaired quality of sperm parameters including a reduction in sperm count, motility and vitality in mice (Azari et al, 2014). Furthermore, Babaei et al. (Babaei et al, 2012) showed that long-term administration of buprenorphine could reduce the serum testosterone level, damage spermatogenesis and affect fertility in male rats.

Conclusions

In conclusion, the data obtained from this study shows that long-term administration of tramadol has adverse effects on adult male rats on the biochemical and histopathological levels and also the spermatozoa production rate. It is thus advisable that tramadol abuse should be avoided without medical description and tramadol should not be used as a sex-enhancing drug. However, further studies on the effect of tramadol on sex hormone levels and changes in the quality of sperm parameters are recommended.

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