

Implication of Prolonged Administration of Tramadol on Reproductive Performance of Male Wistar Rats

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Abstract

Original Research Article

Tramadol is a centrally active synthetic opioid analgesic that is used extensively in abolishing pain in animals. The effect of prolonged administration of tramadol on some reproductive parameters of wistar strain albino rats was studied. Fifteen sexually matured male albino rats weighing between 150–200 g were divided into three groups (A, B and C) of five rats in each. Group A (control) was given distilled water while the experimental groups B and C were treated orally with 50mg/kg and 100mg/kg of tramadol respectively for 28 days. The hormone profile of groups B and C male rats showed a significant decrease ($p < 0.05$) in LH, FSH and testosterone value and a significant increase ($p < 0.05$) in prolactin which was dose dependent compared to the control. These findings probably indicate that prolonged oral tramadol administration has a deleterious effect on sex hormone production and can precipitate infertility in the male wistar rats; hence its use must be with caution in animals meant for breeding purpose.

Keywords: Wistar rat, hormone, tramadol.

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INTRODUCTION

Tramadol was first used in therapeutic analgesia in Germany in 1977. Since this time its use has become more widespread and it has been registered and marketed in most countries by 2005 [1]. Tramadol is a centrally acting analgesic, and is increasingly used for analgesia in animal. It has only recently gained significant attention as an analgesic in animal despite its having been used in humans in Germany since 1977 and in North America since the mid 1980's [2]. The LD₅₀ in mice and rats has been determined to be 350 mg/kg and 228 mg/kg, respectively, following an oral dose of tramadol [3]. In addition, an LD₅₀ of 200 mg/kg and 286 mg/kg has been reported in mice and rats, respectively, following a subcutaneous dose [4]. Tramadol has a linear pharmacokinetic profile within the therapeutic dosage range [5]. Tramadol is rapidly and almost completely absorbed after oral administration following a mean absorption delay of approximately thirty minutes. The absorption half-life ($t^{1/2}$) is 23hr 11minutes [6]. Tramadol and its metabolites are excreted mainly by the kidneys with a cumulative renal excretion (tramadol and metabolites) of approximately 95% in animal and approximately 15–19% of an administered dose of tramadol is excreted in the urine as un-metabolized [7]. Tramadol has been

reported by Raffa *et al.*, 1992 [3] to have opioid like effect, hence has some characteristic resemblance as most of the opioid side effects.

The effects of opioid compounds on endocrine function are now fairly well understood and have been termed opioid endocrinopathy. Various studies have demonstrated opioid effects on a variety of hormones including but not limited to testosterone (both total and free) [8, 9], luteinizing hormone (LH) [8, 10], gonadotrophin releasing hormone (GnRH) [11, 12] and cortisol [13]. The majority of work has focused on the androgen hormones because of their linkage to many symptomatic side effects of opioid usage. It was found that unlike morphine, tramadol is unlikely to induce tolerance and physical dependence [14]. Other animal studies reported that tramadol did not precipitate or suppress physical withdrawal symptoms in morphine-dependent rats, mice and rhesus monkeys [15, 16]. The shortage of information on the implication of prolonged oral tramadol administration on the reproductive endocrine function of animal motivated this study. Therefore, the work was designed to investigate the effect of prolong use of tramadol as an analgesic on the endocrine function of the male rats.

MATERIALS AND METHODS

Experimental Animals and Their Management

Fifteen sexually matured male albino rat (wistar strain) weighing between 150g-200g were selected from Animal House at Physiology Department, University of Ibadan, Oyo state, Nigeria and housed at the experimental animal unit of Faculty of Veterinary Medicine, University of Ibadan, Oyo state, Nigeria. The rats were fed *ad libitum* with commercially prepared feed (containing 18% crude protein, 6% crude fibre, 2750k/cal metabolizable energy) and clean water was given *ad libitum*.

Experimental Drugs

Tramadol capsules (Ultram®) made in India were purchased from a reputable Pharmacy in Ibadan, Nigeria.

Experimental Design

Fifteen sexually mature male albino rats (Wistar strains) were used for the study. The rats were divided into two experimental groups (B and C) and control group A comprising five male rats per group. The experimental groups B and C were treated orally with 50 mg/kg and 100 mg/kg of tramadol respectively while the control group A was given distilled water for 28 days.

Blood Collection

Blood was collected through the medial canthus of the rat into the plain sample bottles to harvest the serum for hormone analysis.

Serum Hormone Assay

Serum hormone was assayed from blood obtained from left ventricular puncture. The samples were assayed in batches from a standardized curve using the enzyme linked immunosorbent assay (ELISA) method [17]. The microwell kits used were from Syntro Bioresearch Inc., California USA. Using 10 µl of the standard, the samples and control were dispensed into

coated wells. 100 µl of each hormone conjugate reagent was added followed by 50 µl of anti-hormone reagent. The contents of the microwell were thoroughly mixed and then incubated for 90 min at room temperature. The mixture was washed in distilled water and further incubated for 20 min. The reaction was stopped with 100 µl of 1N hydrochloric acid. Absorbance was measured with an automatic spectrophotometer at 450 nm. A standard curve was obtained by plotting the concentration of the standard against the absorbance and hormones concentration was determined from the standard curve.

Statistical Analysis

Data obtained from this study was analyzed using the statistical package of social science (SSPS) version 17.0 for windows. Analysis of variance (ANOVA) was done at 0.05 level of significance which $p < 0.05$ was said to be statistically significant. The result obtain was represented as means \pm S.E.M.

RESULT

The mean serum testosterone concentration of groups B (50mg/kg) and C (100 mg/kg) were, 3.2 ± 0.04 and 2.6 ± 0.05 ng/ml respectively and these values were significantly lower ($p < 0.05$) than the value of the control (5.2 ± 0.10). The mean serum Luteinizing Hormone concentration of control group, groups B (50mg/kg) and C (100 mg/kg) were 3.20 ± 0.5 ng/mL, 2.1 ± 0.41 ng/mL and 1.28 ± 0.39 ng/mL respectively. Comparing group B and group C with the control, significant reductions ($p < 0.05$) were observed. The same trend was observed with serum Follicle Stimulating Hormone where control group had significantly higher value (3.70 ± 4.57 ng/mL) at $p < 0.05$, when compared with groups B (2.66 ± 2.46 ng/mL) and C (1.18 ± 0.86 ng/mL). The mean serum prolactin of 50 and 100 mg/kg treatment groups were, 2.26 ± 0.53 and 4.12 ± 0.73 ng/mL respectively. Both values were significantly higher than the value obtained for the control group (1.60 ± 4.17) ($p < 0.05$).

Table-1: The hormone profile of male albino rat (wistar strain) exposed to long term tramadol treatment

Parameter	Luteinizing hormone (ng/ml)	Follicle stimulating hormone (ng/ml)	Prolactin (ng/ml)	Testosterone (ng/ml)
Control Group A	3.20 ± 0.55^{ab}	3.70 ± 4.57^{ab}	1.60 ± 4.17^{ab}	5.2 ± 0.10^{ab}
Group B (50mg/kg)	$2.14 \pm .41^a$	2.66 ± 2.82^a	2.26 ± 0.75^a	3.2 ± 0.04^a
Group C (100mg/kg)	1.28 ± 0.39^b	1.18 ± 0.86^b	4.12 ± 0.73^b	2.6 ± 0.05^b

Values with the same superscript in the same column are significantly different ($p < 0.05$)

DISCUSSION

The consequence of chronic drug therapy resulting into sexual dysfunction has been reported with a wide range of drug. Chowdhuru 1987 [18] reported that about 15% of the 200 most commonly prescribed drugs such as sedatives, tranquilizers, hypnotics, narcotics and cannabis can have adverse effect on male

reproduction. The reproductive adverse effect of antihypertensive, antipsychotics and antidepressants drug has also been reported by Maclean and Lee [19]. Several chronic uses of opiates has also been reported to decrease the level of sex hormones in both sexes resulting into diminished fertility of both male and female opiate users. This present study investigating endocrine function upon prolonged treatment with

50mg/kg and 100mg/kg body weight of tramadol revealed deleterious effects of the drug on some sex hormone production of male rats. Several studies concerned with the gonadal activity during drug therapy corroborates with the present results. The decrease in serum level of LH, FSH and testosterone with an increase in prolactin secretion after morphine and methadone administration has been reported by Chowdhury [18] and Bowman and Rand [20] reported an increase in prolactin after sertraline administration. Another independent investigation reported a reduction in serum level of LH, FSH and testosterone and the induction of prolactin secretion after prolonged paroxetine treatment [21]. The reduction in serum level of FSH, LH and testosterone with an increase in treatment dosage may signify that the drug on long term use cause gonadal degeneration leading to low production of the gonadotropins which may ultimately lead to low libido and infertility. Also the observed decrease in FSH, LH and testosterone which is dose dependence reflects lack of steroid negative feedback mechanism and failure of the hypothalamo-pituitary-gonadal axis due to the prolonged usage of the drug [22]. In conclusion, the prolonged use of the tramadol at 50mg/kg and 100mg/kg in the albino rat revealed malfunctioning of the reproductive endocrine thereby resulting into hormonal imbalance which may lead to infertility in the male rat. Therefore prolonged used of tramadol should be cautiously monitored in animal meant for breeding purpose.

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