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Effect of Tramadol on Hormones and Lipid Peroxidation of male Rabbits

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Abstract

Tramadol manhandle straightforwardly impacts the discharge of luteinizing hormone and follicular stimulating g hormone from the front pituitary organ that diminishes the common discharge of luteinizing hormone in a pulsatile way, resulting in a negative impact on male testiclesdue to lower levels of testosterone hormone. Animals were orally given 40 mg/kg B.W. doses of tramadol. The tried measurements were given to rabbits each other day for 6 weeks. Tramadol significantly decreased body weight (BW), weight of brain, testes, testosterone, estradiol, follicle stimulating hormone (FSH), luteinizing hormone (LH), triiodothyronine (T3) and thyroxin hormone (T4). While, it caused significant increase in thiobarbituric acid-reactive substances (TBARS) concentrations in plasma, testes and brain.

Keywords: Tramadol; Hormone; TBARS; Rabbits

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Introduction

Tramadol may be an engineered centrally dynamic opioid pain relieving utilized to oversee direct to serious torment. It has dual mechanism of action it works by binding to μ-opioid receptors in the brain and spinal cord. These receptors are capable for both the pain-relieving impacts and at higher measurements, the euphoric impacts that abusers look for. In addition, it works as a serotonin-norepinephrine reuptake inhibitor, thereby increasing brain levels of serotonin and norepinephrine [1]. Tramadol is basically utilized within the treatment of muscle torment, joint torment and wound torment It utilize isn't prescribed for children underneath 16 a long time. Patients with therapeutic history of sedate compulsion, liquor abuse, seizure, epilepsy, head harm and metabolic disarranges have more plausibility of seizures when treated with tramadol. Its use is not practiced in patients with kidney disease, liver disease, stomach disorder, mental illness, depression and suicidal ideation as it can worsen the patient's condition. Its utilization is limited in pregnant ladies as well as breast nourishing moms because it may cause birth

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abandons and hurt the hatchling and to the nursing babies. Tramadol is rated as Category C within the pregnancy chance sedate by American Nourishment and Sedate Organization. Due to these effects, physician should avoid prescribing tramadol to pregnant women and nursing mothers [2]. In a test think about, rats were subjected to subcutaneous infusions of tramadol at a dosage that around comparable to verbal dosage of human for a term of eight weeks. Lower luteinizing hormone, and follicular stimulating hormone, and higher prolactin levels were created by treatment with tramadol [3]. Drug-induced rodent hyperprolactinemia at a measurement that did not have a negative impact on total testosterone, estradiol, or inhibin levels have driven to diminish in luteinizing hormone and follicular stimulating hormone, and higher prolactin levels were developed by treatment with tramadol [3]. Drug-induced rat hyperprolactinemia at a dose that did not have a negative effect on total testosterone, estradiol, or inhibin levels have led to decrease in luteinizing hormone and follicular stimulating hormone levels, abnormal testicular histology, irregular acrosomal structure and morphology, and increased fragmentation of DNA [4]. Tramadol mishandle specifically impacts the discharge of luteinizing hormone and follicular stimulating hormone from the front pituitary gland that diminishes the common discharge of luteinizing hormone in a pulsatile manner, resulting in a negative impact on male testiclesdue to lower levels of testosterone hormone [5]. Opioids are known to induce oxidative stress, with multiple studies reporting increased serum and tissue oxidative stress biomarkers and decreased antioxidant defense mechanisms. Diminished brain glutathione, glutathione peroxidase, and superoxide dismutase (Turf) exercises, as well as expanded brain malondialdehyde (MDA), nitric oxide (NO), inducible nitric oxide synthase (iNOS), and 8-hidroxydeoxyguanosine levels, have been portrayed in mice and rodent models more than once managed with 20 to 168 mg/kg tramadol, through distinctive courses [6]. In single introduction measures to 10, 25 and 50 mg/kg tramadol and tapentadol, we found nearly no noteworthy changes in TBARS levels in lung, heart, and brain cortex homogenates. In turn, the protein carbonyl group contents increased in lung and heart tissues at the intermediate and highest doses, whilst they significantly decreased in brain cortex upon tramadol treatment [7]. Subsequently, it may well be hypothesized that delayed organization changes the oxidation status in an opioid- and organ particular way. In fact, LPO was presently initiated in lung and brain cortex, but there appears to be a defensive impact in heart tissue. Reliably with this, 20 mg/kg tramadol anticipated a rise in cardiac tissue MDA levels in a rodent ischemia-reperfusion show. The creators of the ponder propose that tramadol decreases oxidative stretch by rummaging peroxyl radicals and expanding antioxidant capacity [8].

Materials and Methods

In this study tramadol were used. Tramadol was purchased from pharmacy alsalam hospital in El -Beida-Libya. Develop male Modern New Zealand White rabbits (6 months old). Animals were individually housed in cages and weighed weekly throughout 6-weeks experimental period. The objective of this study was to Determine the effects of tramadol (50 mg/kg BW) [9] on hormonal status, antioxidant system in adult male rabbits. respectively. Rabbits were orally administered their respective doses for 6- Week. At the end of the exploratory period body weight of rabbits were recorded.

Creatures were yielded by execution and testes were instantly removed and weighed at that point the organs weight proportion was calculated. Serum was gotten by centrifugation of blood tests at 860×g for 20 min, and was put away at (–20oC) until utilized for investigation Testosterone, Estradiol and Progesterone hormone concentration were assayed by using commercial kit that was supplied by Coat – A – Count testosterone RIA, from Diagnostic

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Systems Laboratories (DSL), from Texas, USA. Follicle Stimulating Hormone (FSH), Luteinizing hormone (LH) levels, Thyroxine (T4) and Triiodothyronine (T3) hormone concentrations were assayed by using commercial kit that was supplied by Coat - A - Count, from Los Angeles, USA. Plasma thiobarbituric acid-reactive substances (TBARS) were measured by the strategy of[10]. Statistical analysis: Data were analysed as a completely randomized design [11] using the General Linear Model procedure of [12]. Means were statistically compared using Least Significant Difference (LSD) test at 0.05 significant levels [11].

Results

The changes in body weight (BW), brain and testes weight of male rabbits throughout the 6-week experimental period of rabbits treated with tramadol were summarized in (Table 1). Table. 2 Ooverall means indicated that treatment with tramadol caused significant ($P<0.05$) decrease in BW, brain and testes weight compared to control animals. Treatment with tramadol caused significant ($P<0.05$) decrease activity of testosterone, oestradiol, progesterone, follicle stimulating hormone (FSH),luteinizing hormone (LH), thyroxin (T_4), triiodothyronine (T_3) in plasma compared to control . Thiobarbituric acid reactive substances (TBARS) are produced by lipid per oxidation (LPO) and are considered as indicators of oxidative stress. LPO was assessed by measuring the concentrations of thiobarbituric acid-reactive substances TBARS in plasma, brain and testes homogenates of male rabbits treated with tramadol. Data in (Table 1) indicated that treatment with tramadol significantly ($p<0.05$) increased TBARS in plasma, brain and testes homogenates.

Table 1: Changes in the body weight, weight of testes, brine and the level of thiobarbituric acid-reactive substances (TBARS) during treatment of male rabbits with 50 mg/kg doses of tramadol.

Parameters	**Animal Groups**	
	Control	**Tramadol**
Body weight (g)	1892 ± 50.79^{a}	1529 ± 64.85^{b}
Brine weight (g)	5.028 ± 0.486^{ab}	3.538 ± 0.502^{b}
Testis's weight (g)	4.432 ± 0.486^{ab}	2.774 ± 0.424^{b}
TBARS Plasma (nmol/ml)	2.673 ± 0.025^{a}	3.113 ± 0.087^{a}
Brain(nmol/gT)	44.9 ± 1.63^{ab}	50.1 ± 1.48^{a}
Testes(nmol/gT)	14.7 ± 1.50^{b}	27.3 ± 2.64^{a}

Values are means ± SEM of 5 rabbits in each group. Mean with different letters **(a- d)** are significantly difference ($p \leq 0.05$) at same raw. Mean with the same letters (a-d) are non-significantly difference ($p \geq 0.05$).

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Table 2: Changes in the hormone during treatment of male rabbits with 50 mg/kg doses of tramadol.

Parameters	Animal Groups	
	Control	Tramadol
Testosterone (ng/ml)	1.570 ± 0.063^{b}	0.987 ± 0.112^{c}
Estradiol (mg/dl)	8.414 ± 0.062^{a}	7.975 ± 0.093^{b}
Progesterone (g/dl)	7.683 ± 0.041^{b}	7.109 ± 0.121^{c}
Thyroxine T_4 (ng/dl)	3.162 ± 0.019^{ab}	2.924 ± 0.093^{b}
Triiodothyronine T_3 (ng/dl)	1.666 ± 0.044^{b}	1.379 ± 0.074^{c}
Luteinizing Hormone LH (mIU/ml)	0.858 ± 0.011^{a}	0.801 ± 0.018^{a}
Follicle Stimulating hormone FSH (mIU/ml)	0.847 ± 0.038^{a}	0.805 ± 0.009^{a}

Values are means ± SEM of 5 rabbits in each group. Mean with different letters **(a- d)** are significantly difference ($p \leq 0.05$) at same raw. Mean with the same letters (a-d) are non-significantly difference ($p \geq 0.05$).

Discussion

The present results indicate that treatment with tramadol caused significant reductions in body weight (BW), testes weight and brain weight (Table 1). The reduction in BW, testes weight and brain of the tramadol treated rabbits is in agreement with those reported in previous studies [13-15]. Also, this study has shown that the treatment of rabbits with tramadol caused significant increases the catabolism of lipids in the adipose tissue, resulting in significant reduction in body weight of rabbits at a later stage during the treatment period. Similar results were reported by [16] in Persea americana leaf extracts treated rats. Opiate use is known to decrease the levels of sex hormones in both sexes and this is thought to be responsible for the diminished fertility of both male and female opiate users [17]. The present study showed that tramadol treated rabbits had lowered plasma levels of testosterone, LH and FSH levels compared with control. The decreased plasma FSH and LH levels were explained by [18]. Testosterone, LH and FSH are vital hormones required for the gametogenic functions of the testis. Acute tramadol administration caused a dose dependent decrease in these hormones (Table 2). [3] earlier reported a decrease in testosterone, LH and FSH of rats that received subcutaneous injections of tramadol (40 mg/kg) for 8 weeks. The hormonal dysfunction could imply that tramadol probably induced toxicity by blocking the release of gonadotropins from the anterior pituitary gland which in turn results in decreased stimulation of testicular leydig cells and decrease in testosterone secretion. These adversely affect spermatogenesis and probably culminated in the observed decline in sperm profile of tramadol treated rats. It is worth noting that garlic prevented tramadol induced decrease in testicular weight and ameliorated tramadol-induced decline in androgen and gonadotropins. [3] earlier reported that long term tramadol administration resulted in increased testicular nitric oxide and oxidative stress. Overproduction of nitric oxide and consequent excessive exposure to oxidative conditions has a potential implication in the reduction of sperm motility [19]. The transformation of testosterone into oestradiol is due to the enzyme aromatase. The present study showed low testosterone and high oestradiol

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levels. Also considering the testosterone -to-oestradiol ratio, it was higher in the control group than in the high dose groups. This finding was explained by [20], who reported that in addition to decreasing testosterone production, morphine, tramadol and buprenorphine also increase aromatization of testosterone to oestradiol. The present results support previous studies concerned with gonadal activity during drug abuse where [21] reported decreased levels of LH and testosterone with increased prolactin hormone after morphine and methadone administration. Also [22,23] observed the reduction of serum levels of LH, FSH and testosterone. Toxic effects of opioids at cellular level may be explained by lipid peroxidation. Biological membranes contain large amount of poly-unsaturated fatty acids, which are particularly susceptible to peroxidative attacks by oxidants resulting in lipid peroxidation. Therefore, lipid peroxidation has been used as an indirect marker of oxidant- induced cell injury [24]. A significant increase in lipid peroxides was reported in rats receiving an acute dose of cocaine [25]. Similarly, lipid peroxides were found significantly increased among heroin users. These findings are in agreement with the present results which showed significant increase in serum MDA levels in both tramadol groups compared to control group, indicating an increase in lipid peroxidation.

Conclusion

It is clear from the obtained results that tramadol induced pronounced hazardous effects in several physio-metabolic functions including body weight and some hormones. There is a significant correlation between tramadol abuse and impaired gonadal and male sex hormone.

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