Effect of Different Concentrations of Tramadol on testes and male hormones in Young and Adult Mice

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Abstract:

This work aims to study the pathophysiological and physiological toxicity effect of tramadol in different concentrations, equivalent to less than 400mg which thought it is safe, on testes and male hormones. Forty-eight male Balb/c mice were used in this work and divided into two age groups; an adult group aged 8-9 weeks and young group aged 4-5 weeks. Every age group was divided into three subgroups (n=8mice). The first group consumed a high concentration of TM, 40mg TM/65kg bodyweight daily which equivalent about 421.2 mg TM/kg bodyweight. The second group was consumed a low concentration of TM, 20 mg/kg daily. The last group consumed only water ad libitum and served as a control group. After one month, the mice were sacrificed. Blood samples were collected and used to determine testes function and concentration of male hormones. Testes were collected and put in 10% formalin for path histological study. Testes of mice consume TM shows many histopathological changes compared to control. Significantly higher FSH, LH, and prolactin and lower testosterone levels in the mice group consumed tramadol compared to control groups. These changes is higher in the mice consume high TM concentration. As conclusion, taking tramadol in long term will have severe effects of testicular tissue which could cause male infertility even if it has given dose is less than 400mg daily which urges attention and not to use this type of drugs for long periods, whatever the reasons and looking for healthy alternatives to it.

Key words: Tramadol, testes, prolactin, mice, histopathology, and physiology


Introduction:

Tramadol (TM), centrally acting opioid analgesic, is utilized widely (1). Long term administration of TM is recorded for pain management, as well as using it as an acceptable alternative for people who suffer from drug addiction behaviour (2).

TM absorption is more than morphine which has reached about 95 to 100% and it is rapidly absorbed in the small intestine to reach the highest peak after five hours (3), it is broadly distributed throughout the body, especially kidneys and liver (4). Tramadol is metabolized in the liver and excreted by the kidneys. Biomagnification takes place in the liver and lades to O-desmethyltramadol. This substance is more effective about 2 to 4 times compared to tramadol itself (5-6-7). In addition, biotransformation produces inactive products, also excreted by the kidneys (8, 9). TM has a dose-based analgesic effect located between the efficacy of codeine and morphine, about 10 to 20% of standard morphine (10). So the dose of tramadol must be regulate depending on the severity of the pain. Total daily dose must not override 400 mg in therapeutic levels of blood between 0.1 to 0.8mg/l (11).

Its acting mode is not fully understood, but there are two acceptable complement mechanisms binding to mu-opioid receptors (MOR) and inhibiting its binding with serotonin and noradrenaline (12). It has been reported multiple cases of toxicity and abuse of tramadol in literatur (13,14). Likewise, fatal cases have been reported as a due to an overdose of tramadol. In these cases, death is attributed to cardiac pulmonary stroke and hepatic failure (15,16,17) likewise hypoglycemia (18).
It is suggested that endogenous opioid peptides may participate in the reproductive function because they are present in different male reproductive tissues. These peptides action are induced by opioid receptors (µ, λ, and κ) which present in spermatozoa membranes of human. Opioids cause loss of sexual desire and impotence in men. It is may also lead to hypogonadism by reducing gonadotropin secretion (GnRH) and testosterone deficiency which results in sterility.

According to a study, a decrease in sperm efficiency and movement was observed, and a decrease in its number. Also, a decrease in the weight of the epididymis was observed, as well as the occurrence of abnormalities in the head of sperm treated with tramadol.

Science TM is becoming more popular with teenagers in most countries around the world nowadays especially among males. The aim of this work was to study the histopathological and hormonal profiles of tramadol toxic effects on testicular functions.

Materials and Methods

Forty eight Balb/c male mice, obtained from the preventive research center/ Baghdad/ Iraq, were used in this study. Twenty four mice were adult aged 8-9 weeks and the other twenty four mice were young aged 4-5 weeks. Every age group was divided to three groups (n=8 mice). The first group was consumed a high concentration of TM, 40 mg TM/ kg body weight daily which equivalent about 421.2 mg TM/ 65kg body weight according to Aghili (11). The second group was consumed a low concentration of TM, 20 mg/kg daily. The last group consumed only water ad libitum and served as control group. After one month of consuming, the mice were sacrificed by cervical dislocation. Blood samples were collected from the eyes in sterile tubes. The testes were collected and placed in a 10% formalin solution and processed through standard procedures. Tissue sections containing paraffin were stained with hematoxylin and eosin and examined by light microscopy (1). Blood samples were centrifuged 10min at 10000 rpm. The serum was collected and used to determine serum FSH; LH; prolactin hormones levels by LH, FSH, Prolactine kit from diaSorin , S. p.A , Italy ; and testosterone hormone by enzyme linked fluorescent assay (ELFA) using the BioMérieux VIDAS Automated Immunoassay System (Biomérieux® S.A., Marcy-l’Etoile, France).

Results were expressed as mean ± standard error (M±SE). These data were analyzed by one-way analysis of variance (ANOVA) followed by Fischer's test for multiple comparisons, using Statviewaversion 5.0. Differences were considered significant when p<0.05.

Results

There was no difference between the histological study of testes in Adult and young groups which were the same, so Figure (1) includes the tissue sections of testes in mice consumed higher concentration of TM (H), consumed lower concentration of TM (L), and control (C). This figure shows reduce in the size of seminal tubes and a decrease in the cell layers number inside the seminal tube and the loss of intercellular bridges, which appears through the emergence of gaps between them. It shows also decreases the number of sperm cells in the center of seminal tubes. These pathohistological changes were very high in the group of mice that consumed tramadol with a high concentration.
Figure 1: Tissue sections of the testes in the control group (C), the high focus group (H) and the low concentration (D). Under x400 magnification power, dyed H&E. ( acquainted ) layers of the spermatic tube. ( acquainted ) Gaps between cells.

FSH, LH, and prolactin levels were significantly higher in the mice group consumed high dosage of tramadol in both young and adult groups compared to how consumed low dosage of tramadol and control groups, while testosterone hormone level was significantly lower in both groups consumed tramadol (high and Low) in young and adult groups compared to control (figure-2)
Discussion:

Since narcotic drugs especially tramadol drugs have been widely used among young people, this work aimed to illustrate the damage to males. We observed few studies describing the role of tramadol on spermatozoa histological and physiological sperm and testicular tissues and sperm production efficiency in testicular in mice.

El-Ghawet was interesting indicated a treatment by tramadol (40 mg /Kg body weight for one month) causes foci of spermatic tubes with marked depletion of sperm cell populations. The connective tissue between the tube becomes hyalinized and shows a relatively low interstitial cells (22). On the other hand, Heidari reported seminal tubes atrophy, interstitial calcification, focal testicular degeneration and single or multiple layers of vicious sperm cells in the group of mice injected with 30 mg/kg of buprenorphine for 15 days compared to the group of mice received by normal saline injection (24). These results were supportive of what we got in the current study, where we noticed, when continuing the dose of tramadol for more than four weeks, a decrease in the tissue layer of the seminal tubes and the appearance of gaps between them. Abul Fotouh also reported that the testicles undergo extensive metastatic testicular degeneration with many sperm cells and the formation of giant sperm cells without spermatogenesis and/or sperm cells are often necrotic after tramadol at a dose of 40 mg/kg body weight (25). Our results came in line with the aforementioned studies regarding the damage to the testicles due to taking over long-term periods but the histological changes was less than previous studies because of the lower dosage we used which was 40-20mg/kg body weight, this dosage which thought it safe. According to our results, we observed the testicular effect from the tissue aspect, as the tissue was affected in a salient way, as in the aforementioned picture, and sperm production decrease more when the groups were exposed to concentration high tramadol.

Figure 2: FSH (A), LH (B), prolactin (C) and testosterone (D) level in the young and adults mice consumed TM high concentration and low concentration and in control group.
*Significant deference between mice consumed TM and control

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Opium use is known to reduce male sex hormone levels. This low hormonal level is believed to be responsible for decreased fertility in male opium users. Testosterone, LH (26, 27), and FSH (27) levels decrease and prolactin (26) and estradiol levels increase after taking Opium. The results of Abdellatif also observed a sharp decrease in testosterone hormone level which was similar to our results (28). This decrease in testosterone hormone which observed in our results could be caused by destroyed Sertoli cells resulting TM consumption and leads to a significant decrease in sperm numbers and a decrease in male fertility (24). This decrease in testosterone hormone levels we observed could lead also to an increase in the FSH level as a negative feedback effect which could cause an increase in LH and prolactin levels, this results was similar with Youssef observing which reported increasing in estradiol and prolactin levels and decreasing in the testosterone, luteinizing hormone, and follicular stimulating hormone levels after tramadol administration (23).

Also in a study conducted in Nigeria where drugs are misused, Osadolar injected and drained rabbits for the same period in our study and found a lower in testosterone hormone to be supportive of our findings regarding sex hormones (29).

According to our current study and with support of previous studies it can be concluded that taking tramadol in the long term will have severe effects of sperm and testicular tissue depends mainly on the dose given as well in the future can occur cases of male infertility even if it has given dose is less than 400mg daily which urges attention and not to use this type of drugs for long periods, whatever the reasons and looking for healthy alternatives to it.

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