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The Effects of Long-term Administration of Tramadol on Epididymal Sperm Quality and Testicular Tissue in Mice

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Abstract

Objective- The objective of the present work was to investigate the effects of tramadol administration on sperm quality and testicular tissue in mice.
Design- Experimental study
Animal- Sixty-three mature male mice
Procedures- Mice were randomly divided into three experimental groups (n=21) and the following treatments were intraperitoneally administered, 3 times a week, for 6 weeks: Control male mice were given physiological saline. Two other groups were given different doses of tramadol including 10 mg/kg (group T1) and 20 mg/kg (group T2). Seven mice in each group were sacrificed at weeks 3, 6 and 12 after the beginning of treatments. Left testes were removed for epiddydimal sperm quality and histopathological evaluations.
Results- The results showed that sperm concentration, motility and vitality in group T1 and T2 were significantly decreased ($P<0.05$) in comparison with group control at weeks 3 and 6, but the mentioned parameters were recovered significantly at week 12.
Microscopic examinations revealed that tramadol in both doses damaged the testicular tissue at weeks 3 and 6, so that more degenerative changes were observed in group T2 at week 6. Most of histopathological parameters returned to the normal structure in groups T1 and T2, at week 12.
Conclusion and clinical relevance- According to the results of present study, it can be concluded that long-term administration of tramadol have adverse effects on sperm quality and testicular tissues and these effects are dose dependant. Also the negative effects of tramadol on testes are reversible.
Key words- Tramadol, Testis, Histopathology, Sperm quality, Mice.

Introduction

Tramadol, synthetic codeine analog, is a weak μ-receptor agonist and centrally acting analgesic.[1] It has received widespread acceptance in human medicine since it was first introduced in 1977 in Germany.[2] The mechanism of tramadol analgesic action is complex. Most reports suggest that the analgesic activity and other clinical effects of tramadol are a result of opioid and non-opioid mechanisms.[3] Tramadol inhibits the neuronal reuptake of norepinephrine and serotonin as do the antidepressant drugs, and may actually facilitate releasing of 5-hydroxytryptamine. It is thought that these effects on central catecholaminergic pathways contribute significantly to the drug's analgesic efficacy.[1,3] The analgesic potency of tramadol is equal to meperidine and 5 to 10 times less than morphine in humans.[4] Tramadol is recommended for the management of acute and chronic pain of moderate to severe intensity associated with a variety of diseases or problems, including osteoarthritis, fibromyalgia, diabetic neuropathy, neuropathic pain, and even perioperative pain in human patients.[1] Also, tramadol is the primary drugs used in the treatment of opiate addicted. Although tramadol appears to have a low potential for abuse, but there are evidences of abuse, addiction, and withdrawal, even in patients without a history of such problems.[5] Long- term administration of

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tramadol is recorded for management of pain, as well as its use as an acceptable alternative in persons with drug-seeking behavior is controversial.[3]
Endogenous opioid peptides are present in various tissues of the male reproductive tract, suggesting that they may be involved in the reproductive function.[6] These peptides induce their effects through opioid receptors (κ, λ, and μ) that are present in human spermatozoa membranes.[7] Opiates cause loss of libido and erectile and ejaculatory dysfunctions among men.[8] opiate abuse may result in hypogonadism, primarily by decrease in release of gonadotropin-releasing hormone (GnRH), testosterone deficiency and infertility.[9,10] Several studies have demonstrated that long time administration of opiate compounds had deleterious effects on sperm cell motility and morphology.[11] Chronic opiate consumption increases DNA damage in sperm in male rats.[12] Oxidative stress induced by opiate exposure is a significant factor in the etiology of male infertility and can lead to an increased DNA fragmentation.[13]
Regarding to the potential adverse effects of opiate on male fertility, the current study was designed to investigate the epididymal sperm quality and testicular tissue damages following long term administration of tramadol in male mice.

Materials and methods

Animals

In this study, the experimental protocol was approved by the Ethics Committee of Faculty of Veterinary Medicine, Shahid Bahonar University of Kerman, Iran. Male NMRI mice were obtained from Research Center of Kerman University of Medical Sciences, Iran. The mice were fed with standard commercial laboratory chow (pellet form, Javeneh Khorasan Co., Mashhad, Iran) and water ad libitum and housed under standard laboratory conditions (12 h light: 12 h dark and 22 ± 2 °C) during the experimental period.

Study design

Sixty-three mature male mice (8 week old, 25–30 gr) were randomly divided into three experimental groups with twenty-one mice in each of them. Group T1: received Tramadol (50 mg/1 ml, Tehran Chemie, Iran) at dose of 10 mg/kg, and group T2: received Tramadol at dose of 20 mg/kg, every other day, during 42 days of experimental period by intra-peritoneal injection. Total volume injected in all groups was equalized by addition of sterile saline. Group control, received normal saline using the same volume and similar method. Seven mice in each experimental group were euthanised with sodium thiopental (Sondos Co.; Sandoz GmbH, Kundl, Austria) on 3, 6 and 12 weeks after the beginning of treatment, and their left testes were removed for sperm quality and histopathological evaluations.

Sperm quality analysis

Sperm samples were obtained from each group at the end of 3rd, 6th and 12th weeks. Samples of mature sperm were collected from the cauda region of epididymis by mincing it finely in PBS at 37°C. Sperm quality was determined by three parameters: Sperm concentration, motility and vitality. Sperm concentration was analyzed using the haemocytometer method. Sperm suspensions from the caudal epididymis were diluted 1:200 with fixative solution (sodium acid carbonate-formaldehyde solution) and counted according to the procedure indicated in the WHO laboratory manual. The diluted samples were put into the counting chamber and the number of sperm was counted using a haemocytometer with improved doubles Neubauer ruling under a light microscope. The sperm concentration was expressed as $\times 10^6$/ml. Sperm motility was analyzed and averaged by counting the motile and non-motile spermatozoa and expressed as the percent motility. To analysis of sperm motility one drop of sperm suspension were placed on the slide and covered with a cover slip and examined under the microscope using ×40 objective.
Sperm vitality was performed by the eosin-nigroson staining. The slide, sperm suspension and stain kept warm (37°c) in an incubator during the experiment. One drop of sperm suspension was mixed with two drops of 1% eosin Y. After 30 sec, three drops of 10% nigrosin were added and mixed well. A smear was made by placing a drop of mixture on a clean glass slide and allowed to air dry and examine under oil immersion (1000×) with a light microscope. Pink-stained dead sperm and unstained live sperm were counted under the light microscope. The vitality of sperm was expressed as the percent of viable spermatozoa[14].

Histopathological study

After necropsy, the testis samples from the animals of each group were preserved in 10% neutral buffered formalin for microscopic examination at weeks 3, 6 and 12. Formalin-fixed samples were processed by the standard paraffin wax technique, sectioned in 5 μm thicknesses, stained with haematoxylin and eosin (H&E) and examined at100 and 400× magnifications using a standard light microscope.

Statistical analysis

The results of sperm quality evaluations were analyzed by SPSS 16.0 (SPSS Inc., Chicago, IL, USA) package. Evaluation of significant difference between the means of different experimental groups was performed with using one-way analysis of variance (one-way ANOVA) followed by the Tukey's test as post hoc. Values were

expressed as mean ± SEM. The significance considered level was $P<0.05$. The histopathologic observations were subjectively evaluated between the groups.

Results

Sperm quality analysis

Results of sperm quality analysis are presented in the Table 1. The obtained data showed that the sperm concentration, motility and vitality in the groups T1 and T2 significantly decreased in compared to the control group at each evaluated time ($P<0.05$). There were no significant differences between the groups T1 and T2 in all evaluated data at 3 weeks after treatment with tramadol ($P<0.05$). At 6th week, sperm motility percentage and sperm count significantly ($P<0.05$), and sperm vitality percentage insignificantly ($P>0.05$) decreased in the group T2 in comparison with the group T1. At 12th week, there were no significant differences between the groups T1 and T2 in all evaluated data ($P>0.05$). Improvement in sperm quality parameters was seen at week 12 compared to 3th and 6th weeks, in the groups T1 and T2; so that more noticeable improvements were observed in the group T2.

Histopathological observation

In this study, histopathologic findings revealed normal histological structure in Control group. Testes were composed of well-organized circular or oval seminiferous tubules and surrounded by thick basement membrane. The tubules were covered with seminiferous epithelium including active spermatogenesis, spermatogonia, primary and secondary spermatocytes, and spermatids that placed in concentric layers (Fig 1).

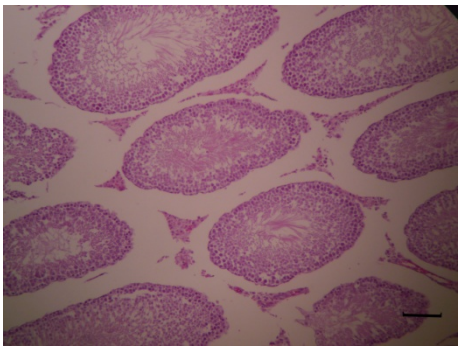

Figure 1. Control group: Normal seminiferous tubules with organized epithelium. H&E. Bar=100 µm

Leydig cells and small blood vessels were component of interstitial tissues. Histopathologically, testes of all treated groups with tramadol (T1 and T2) showed damaged germinal layer and atrophy of some seminiferous tubules. Basement membrane was interrupted. The germinal epithelium of affected tubules appeared disorganized and spermatogenesis was reduced. The affected tubules showed necrotic spermatocytes with nuclear changes such as karyolysis and karyorrhexis and were absence of spermatids and spermatozoa. Germinal cells of some tubules were sloughed and scattered into the lumens. Intra-epithelial spaces were increased. Some sertoli cells had large cytoplasmic vacuoles (Fig 2, 3, and 4).

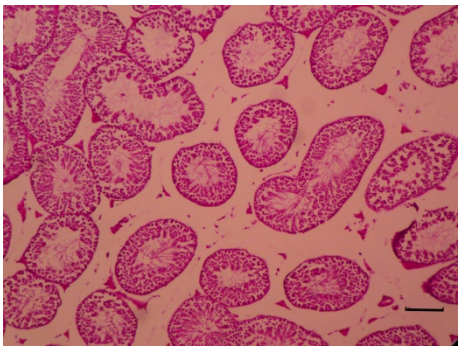

Figure 2. Tramadol 0.1 (3 weeks): Photomicrograph showing seminiferous tubules with mild degenerative changes in the germ cells. H&E staining. Bar=100 µm

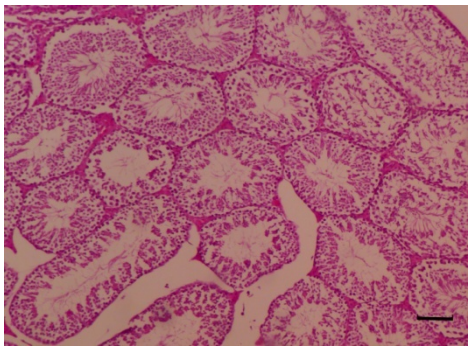

Figure 3. Tramadol 0.2 (3 weeks): Photomicrograph showing seminiferous tubules with moderate degenerative changes in the germ cell layers. H&E staining. Bar=100 µm

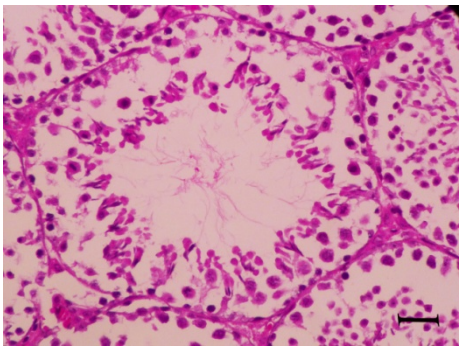

Figure 4. Tramadol 0.1 (6 weeks): Seminiferous tubules show severe degenerative changes with vacuolated epithelium. H&E staining. Bar=25 µm

Some seminiferous tubules had normal architecture and mature sperms were present in their lumens. More degenerative and necrosis of germinal epithelium, and reduction of mature spermatozoa was noticeable in group T2 at week 6 (Fig 5).

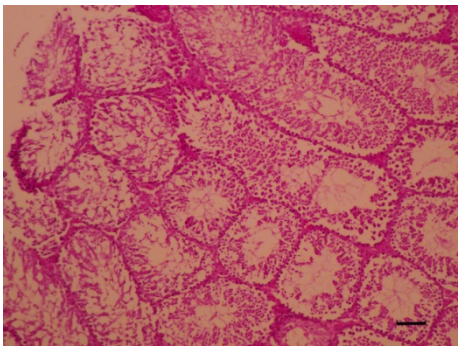

Figure 5. Tramadol 0.2 (6 weeks): Seminiferous tubules show severe degenerative changes with vacuolated epithelium. H&E staining. Bar=100 µm

Microscopic examination at 12th week revealed that the testes had returned nearly to the normal structure in both groups T1 and T2. Germinal layer of seminiferous tubules restarted spermatogenesis. Spermatogonia, spermatocytes, and spermatids were organized again (Fig 6).

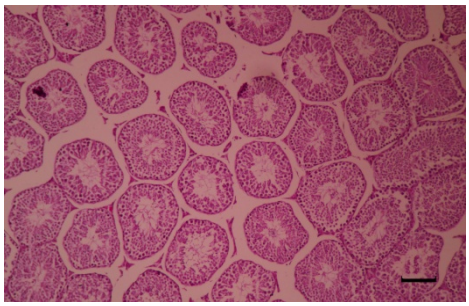

Figure 6. Tramadol 0.1 (12 weeks): Seminiferous tubules are regenerated and show normal structure. H&E staining. Bar=100 µm

Table 1. Mean ± SE of sperm motility, sperm count and sperm vitality following administration of tramadol (10 and 20 mg/kg) in mice

	Week 3			Week 6			Week 12		
Parameters		**T1**	**T2**		**T1**	**T2**		**T1**	**T2**
	Con			**Con**			**Con**		
Motility (%)	68.44 ± 0.91^{a}	46.67 ± 5.59^{b}	32.78 ± 4.87$^{b\bullet}$	77.78 ± 0.88^{a}	51.11 ± 4.77^{b}	36.11 ± 4.91$^{c\neq}$	71.44 ± 1.73^{a}	61.11 ± 4.91^{b}	60.67 ± 3.82$^{b\bullet\neq}$
Count (×10^{6})	63.22 ± 4.77^{a}	22.44 ± 3.59^{b*}	12.11 ± 1.4$^{b\bullet}$	61.33 ± 1.05^{a}	28.33 ± 3.69^{b}	19 ± 1.33$^{c\neq}$	69.22 ± 4.56^{a}	39.33 ± 3.65^{b*}	40.33 ± 4.51$^{b\bullet\neq}$
Vitality (%)	78.33 ± 2.04^{a}	56.44 ± 1.6^{b}	56.22 ± 1.92$^{b\bullet}$	76.89 ± 1.93^{a}	52.33 ± 1.96^{b*}	46.67 ± 1.51$^{b\bullet\neq}$	77.78 ± 2.37^{a}	61.89 ± 1.62^{b*}	61.11 ± 1.7$^{b\neq}$

- Same superscript signs in same line, show significant difference ($p< 0.05$) between the weeks for each individual group.
- Different alphabetic letters, show significant difference ($p< 0.05$) between the groups for each individual week.

Discussion

Our study detected significant association between tramadol administration and impaired quality sperm parameters. The results of sperm quality analysis showed a significant decrease in sperm concentration, motility and vitality that indicate the possibility of adverse effects of long term administration of tramadol on epididymal spermatozoa of mice. Our results demonstrated that negative effects of tramadol on spermatozoa was dose dependant, so that 6 week administration of high dose of tramadol (20 mg/kg) had more deleterious effects on epididymal sperm quality. Our results also showed the negative effects of tramadol on spermatozoa in both doses were reversible. All sperm quality parameters become close to the normal values 6 weeks after the end of drug consumption (at week 12) in mice.

The cycle of spermatogenesis in the mouse normally lasts 35-36 days. This process has been described as five phases. Every nine days, a population of diploid stem cells (spermatogonia) undergoes mitosis to produce type A spermatocytes. The formation of this group of cells marks the beginning of the cycle (day 0). During next seven days, type A spermatocytes undergo five mitoses to produce a population of type B spermatocytes. During the next 14 days, the diploid spermatocytes undergo first and second meiosis to form haploid secondary spermatocytes, then spermatid. The spermatid mature in the seminiferous tubules into spermatozoa. The spermatozoa are released in to seminiferous tubule, and they migrate to the epididymis.

Maturation and migration are completed in 14 days[15]. Sperm count in mice was normally determined about 0.06×10^9 per ml of semen[16].

In previous studies, it has been showed that narcotics markedly reduce the structural and functional integrity of the secondary sex organs by causing pronounced reduction in serum testosterone levels. These drugs inhibit the secretion of luteinizing hormone (LH) by acting either in the hypothalamus or directly in the pituitary gland, which leads to reduced serum testosterone levels.[10,17,18]

It is well known that opiates influence sexual drive in male humans and rodents.[19] Mckim,[20] stated that opiates decrease the levels of sex hormones in both sexes and resulte in diminished fertility of both male and female. In study of El-Gaafarawi,[3] long term administration of tramadol significantly decreased serum luteinizing hormone (LH), follicle stimulating hormone (FSH), and testosterone in serum of male rats. The same results were presented by Chowdhury,[21] following long term administration of morphine. Heidari et al.,[22] demonstrated chronic administration of methadone had deleterious effect on testicular tissue in male rats. Babaei et al.,[23] showed that long tem administration of buprenorphine could suppress plasma testosterone, damage spermatogenesis, and affect male fertility in mice. Although, long-term effects of opioids at cellular level are not clearly understood,[24] but their toxic effects may be explained by lipid peroxidation.[25] Spermatozoa are highly susceptible to peroxidative damage due to the high content of polyunsaturated fatty acids within their plasma membrane.[26] Therefore, lipid peroxidation has been used as an indirect marker of oxidant-induced cell injury.[25] Increased lipid peroxidation and altered membrane function can render sperm dysfunctional through impaired metabolism, motility, acrosome reaction reactivity, and fusogenic capacity as well as oxidative damage to sperm DNA.[27] Superoxide dismutase (SOD) protects human spermatozoa from the oxidative damage.[28] Safarinejad et al.,[29] demonstrated significant decrease in SOD activity in semen of opiate consumers. A significant increase in lipid peroxides was reported in rats receiving an acute dose of cocaine.[30] Similarly, lipid peroxides were found significantly increased among heroin users.[31] El-Gaafarawi,[3] showed significant increase in serum malondialdhyde levels in rats administered tramadol, indicating an increase in lipid peroxidation. Significant decrease in sperm quality and increase in spermatozoa DNA fragmentation in the seminal fluid of opiate consumers was reported in Safarinejad et al.,[29] study. Chronic exposure to heroin causes decrease in sperm motility because it has been extensively linked to the oxidative stress.[7] Increase in sperm DNA damage was observed following amphetamine compounds administration in experimental animals.[12]

The pathological manifestations during this study are indicative of tramadol toxic effects on male reproductive organ; similar results have been described in naturally occurring cases in opioiods consumers.[32] The data obtained form histopathologic examination in the current study showed that tramadol at doses of 10 and 20 mg/kg after 6 weeks caused frank testicular atrophy correspondingly reduced sperm density in epididymal lumen, lowered motility, and induced structural abnormalities in the sperm. The deterioration of seminiferous germinal epithelium or a spermicidal effect of tramadol may be responsible for such effects.

On the other hand, same as sperm quality examination of present study, the results of 6 weeks recovery period indicated that all histopathologic parameters following administration of 10 and 20 mg/kg tramadol tended to returned to the normal structure. This may indicate that tramadol toxic effects induced by mentioned doses were not persisted after drug cessation.

Reuhl et al.,[32] showed thickening of the basement membrane of seminiferous tubules, reduction of tubular diameter and height of the germinal epithelium, cell-maturation arrest, and highest proportion of interstitial tissue in drug abusers. It is known that changes in the thickness of the basement membrane can impair testicular metabolism, and thus promotes enhanced germinal cell hypoplasia and tubular atrophy. The extent of testicular damage is closely related to the duration of drug consumption.[33] Administration of amphetamine compounds induces apoptosis in the seminiferous tubules in testes of mice, and changed testes histopathology in experimental animals.[12,34]

Recently chronic administration of tramadol on testicular function was investigated in the study of Ahmed and kurkar,[35]. In their study, the rat received 40 mg/kg of tramadol as subcutaneous for 8 weeks. Their result revealed that tramadol increased the expression of endothelial nitiric oxide synthase in testicular tissues. Also, tramadol caused decrease in sperm count, motility, and numbers of primary spermatocytes, rounded spermatid and leydig cells. They concluded that long term administration of tramadol affects the testicular function of adult male rats and these effects may be through overproduction of NO and oxidative stress induced by this drug. Our study showed even lower doses of tramadol (10 and 20 mg/kg, IP) had adverse effect on testicular function and structure in mice, but after 6 weeks recovery all the parameters tended to return to the normal situation.

Generally, the results of sperm quality parameters in the present study showed that the adverse effects of tramadol on the sperm quality and testicular tissues were dose dependant and this negative effect was reversible.

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چکیده

اثر مصرف طولانی مدت ترامادول بر کیفیت اسپرم اپیدیدیمی و بافت بیضه در موش سوری

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هدف– هدف از این مطالعه بررسی اثرات مصرف داروی ترامادول بر کیفیت اسپرم و بافت بیضه در موش سوری بوده است.
طرح مطالعه- مطالعه تجربی
حیوانات- ۶۳ سر موش سوری نر بالغ
روش کار- موش ها بطور تصادفی به سه گروه مساوی تقسیم شدند. گروه کنترل: نرمال سالین، گروه T1: ۱۰ میلی گرم به ازای کیلوگرم وزن بدن و گروه T2: ۲۰ میلی گرم به ازای کیلوگرم وزن بدن داروی ترامادول هفته ای ۳ بار به صورت داخل صفاقی برای مدت ۶ هفته دریافت کردند. ۷ سر موش از هر گروه در هفته های ۳، ۶ و ۱۲ کشته شدند و بیضه سمت چپ جهت ارزیابی کیفیت اسپرم اپیدیدیمی و مطالعه آسیب شناسی بیضه خارج شدند.
نتایج- نتایج نشان داد که تعداد، درصد تحرک و درصد زنده مانی اسپرم در گروههای T1 و T2 در هفته های ۳ و ۶ به طور معنی داری در مقایسه با گروه کنترل کاهش یافت. ($P<0.05$) اما در هفته ۱۲ بهبودی معنی داری در پارامترهای مذکور مشاهده شد.
مطالعه میکروسکوپیک نیز نشان داد که هر دو دوز ترامادول در هفته ۳ و ۶ سبب تخریب بافت بیضه شد که بیشترین تخریب در گروه T1 در هفته ۶ بوده است. اکثر پارامترهای هیستوپاتولوژیک در هفته ۱۲ در گروههای T1 و T2 به سطح نرمال برگشته بودند.
نتیجه گیری- بر اساس نتایج مطالعه حاضر این چنین می توان نتیجه گیری نمود که مصرف طولانی مدت ترامادول اثرات مخرب بر کیفیت اسپرم و بافت بیضه داشته که این اثرات وابسته به دوز می باشد و همچنین اثرات منفی ترامادول بر بافت بیضه قابل برگشت است.
کلید واژگان- ترامادول، بیضه، هیستوپاتولوژی، کیفیت اسپرم، موش سوری