EFFECT OF THE ANALGESIC TRAMADOL ON SOME BIOLOGICAL ASPECTS

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Tramadol is a centrally acting, binary analgesic which is neither an opiate – derived nor a non steroidal anti-inflammatory drug. It is used for treatment of moderate to severe pain. The present study investigates some biological aspects such as teratological effects, chromosomal aberration and histopathological changes induced by the use of drug at therapeutic doses 40, and 80mg/kg body weight/day. ALT, AST activities and creatinine concentration in male rats serum were carried out. The results showed statistically significant increase in dead and resorbed embryos, decrease in the fetal body weight, crown rump, and length of rat embryos. Fetuses have incomplete ossification of skull, central disc, toes, and ribs. Examination of bone marrow metaphases revealed structural and numerical chromosomal aberrations. These chromosomal aberrations are centromeric attenuation, centric fusion, ring shape, end to end association, gap, break and stickiness. In addition, numerical chromosomal aberration were observed as polyploidy. Vacuoles and some spermatogonia leaving the basement membrane are observed with a decrease in amount of sperms in the lumen of seminiferous tubules and a decrease in number of germ cells. Necrotic cells appeared in Leydig cells with disorganization of some germinal cells. There was significant increase in ALT, AST enzymes activitiy and creatinine concentration.

Introduction

Tramadol is a centrally acting, binary analgesic which is neither an opiate – derived nor a non steroidal anti-inflammatory drug. It is a synthetic morphine – like analgesic used for the treatment of moderate to severe pain. The majority of tramadol activity depends on the

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formation of active metabolite. Tramadol's major active metabolite, O-desmethyltramadol shows higher affinity for μ- opioid receptor and has twice the analgesic potency of the parent drug[1]. Its analgesic activity is mediated through an agonist action at all types of opioid receptors with some receptor selectivity. In addition it inhibits nor-adrenaline uptake and stimulates serotonin release[2]. Bioavailability of a 100 mg oral dose is approximately 75 % and occurs at approximately two hours after a single 100 mg oral dose in healthy subjects. Tramadol plasma levels were maintained at a plateau level about 200 ng / ml from 4 to 16 h after dosing, while for the reference formation, that level was sustained from 4 to only 6 hours.[3]

Constipation, nausea, sedation, sweating, pruritus, and dry mouth have been reported with tramadol use for long time. Respiratory depression was observed at relatively low doses of tramadol and its metabolite[4]. Tramadol is also associated with a small risk of seizures (fits) and its use is contraindicated in people with a history of epilepsy[5]. The metabolite O- desmethyltramadol is more potent in peristalsis than its parent compound. The action of all tramadol forms depends on opioid receptors, and that of (+) - and (-) – tramadol also involves adrenoceptors[6]. Weakly mutagenic results are occurred with the use of tramadol in the presence of metabolic activation in the mouse lymphoma assay and micronucleus test in rats[7].

So, the present study has been conducted to investigate some biological effects induced by the analgesic tramadol and the risk of its toxicity on male and female rats *(Rattus norvegicus)*. Studies on pregnant animals are carried out to determine the risk of birth defects and other reproductive effects.

Materials and Methods

Drugs

Tramadol HCl (Tramal) , 50 mg capsules was obtained from Mina Pharm, Egypt. Its chemical name is (±) cis-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride. The molecular weight of tramadol hydrochloride is 299.8. It is a white, bitter, odorless, crystals . It is readily soluble in water and ethanol.

Animals and Treatments

Female adult rats *(Rattus norvegicus)* weighing 150 – 200 g under routine laboratory care, were mated in the proportion of 2 females for every male over night. Each morning a vaginal smear was taken to check for the presence of sperms. Day 0 of pregnancy was considered to be the day on which sperms were found in the vagina.

15 pregnant female rats were randomly divided into 3 groups. Group one and group two were administered oral therapeutic doses of Tramadol HCl in distilled water equivalent to 40 and 80 mg/kg body weight /day respectively for 14 days from 5th day to 19th day of gestation. The doses were calculated for rats according to Paget and Barnes (1964)[8] species interconversion table of dosage. The third group was served as control.

At the same time, 80 male rats (*Rattus norvegicus)* weighing 150 – 200 g were divided into three groups, group one and two (60 rats) were administered oral therapeutic doses of Tramadol HCl dissolved in distilled water (40 and 80 mg/kg body weight /day) and the third one (20 rats) was served as control. All rat groups, except for colchicine, were sacrificed two hours after drug administration at the time points. Blood samples were collected, sera were separated and kept at -20 °C until analysis. Right testes were removed and prepared for histopathological examination.

Biochemical analysis

Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) activities were measured using the method of Thomas (1998)[9].

Creatinine were measured using the method of Fossati *et al.*, (1983)[10].

Teratological study

Females were sacrificed on day 19 of gestation and fetuses were counted and weighed, the number of alive, resorbed, and dead fetuses were recorded. Fetuses were examined externally to investigate any abnormalities. Also, fetuses were stained in Alizarin red – S according to Weesner and Parry (1986)[11] and their skeletons were examined.

Cytogenetic study

After treatment, male rats were injected intraperitoneally with colchicine (4mg/kg body weight) and sacrificed two hours latter. The femur bones were quickly separated.

Chromosomes of bone marrow cells were prepared according to the modified method of Luck and Tice (1987)[12]. Chromosomal aberration assay was performed by screening fifty well metaphases per animal for scoring different types of aberrations[13].

Histopathological Examination

Treated and control male rats were sacrificed on 10, 20, and 30 days of treatment, and right testes were picked out. Testes were fixed in 10% neutral buffer formalin. Paraffin sections of 4 – 6 micrometer thickness were prepared and stained by Hematoxilyne and Eosin for morphological study[14].

Statistical analysis

Data of different groups were compared using Student "t" test. Differences at $p \leq 0.05$ were considered significant.

Results

Table(1) shows Significant increase ($p \leq 0.05$) of serum ALT and AST activities after administration of tramadol 40 and 80 mg /kg body weight/day respectively and elevated serum creatinine levels. The intensity of the effect increased by increasing duration of time and dose.

Table (2) indicates statistically significant increase in dead and resorbed embryos with tramadol treatment. The resorbed embryos number were increased according to the dose.

Morphological examination showed that oral administration of tramadol 40 and 80mg /kg body weight / day respectively to pregnant females for 14 days from 4 – 19 day of gestation induced statistically significant decrease ($p \leq 0.05$) in the fetal body weight and crown rump length of rat embryos [Table (3) and Figure (1)].

Skeletal system observations of 19 days of gestation showed that fetuses whose their mothers were treated with oral doses of tramadol 40 and 80mg /kg body weight respectively from 4 – 19 day induced statistically significant decrease ($p \leq 0.05$) in body weight and crown rump. The defects noticed in the embryos were incomplete ossification of skull, central disc, toes, and ribs [Table (4) and Figure (1)].

Cytogentic data obtained from treated male rats with tramadol 40 and 80mg /kg body weight respectively for 10,20 and 30 days and fifty metaphase spread examined in every rat were shown in Table (5).

Examination of bone marrow metaphases revealed structural and numerical chromosomal aberrations. These chromosomal aberrations are centromeric attenuation, centric fusion, ring shape, end to end association, gap, break and stickiness . All chromosomal aberration were significantly increased ($p \leq 0.05$) in rats after 20 days treatment and increased by increase duration of time [Table (6), Figure (2)]. In

addition, numerical chromosomal aberration were observed as polyploidy [Figure (2)].

Histological examinations of testes of male rats received oral daily tramadol 40 and 80mg /kg body weight respectively for 10, 20 and 30 days were shown in Figure (3). Clear small vacuoles in seminiferous tubules were shown after 10 days of treatments. On the 20 days large vacuoles and some spermatogonia leaving the basement membrane, decreased amount of sperms in the lumen of seminiferous tubules were also shown, and hypertrophy of germ cells were observed in rats with tramadol at dose 80mg /kg body weight and decrease in the number of germ cells. Where after 30 days of administration, necrotic cells appear in Leydig cells with disorganization of some germinal cells in addition to the findings observed in 10 and 20 days.

Table (1)
Effect of Tramadol Administration on AST, ALT and Creatinine of Male Rats Serum

Drug	Days	AST U/L			ALT U/L			Creatinine mg/dl		
		Doses			Doses			Doses		
		Control	Low Dose	High Dose	Control	Low Dose	High Dose	Control	Low Dose	High Dose
Tramadol	10	119 ±2.17	138.1* ±1.4	206.2** ±1.5	38.4 ±2.14	47.5* ±0.12	59.3** ±0.16	0.65 ±0.3	0.70 ±0.2	0.80** ±0.1
	20		202.2** ±1.5	225** ±1.2		53.7** ±0.12	68.1** ±0.15		0.75* ±0.11	0.82** ±0.11
	30		232.5** ±1.5	240** ±2.0		55.4** ±0.17	77.5** ±0.17		0.76** ±0.17	0.88** ±0.17

* = Significant ($p \leq 0.05$) ** = Highly significant ($p \leq 0.01$)
Data are expressed as the mean ± S.D. of 5 rats.
Control = the average of the results of control groups were used in the statistical analysis as there was no difference between them.

Table (2)
Effect of Tramadol on the Fetuses at 19 Day of Gestation

Drug	Doses	No. of implantation sites		Avarage Total Alive		Avarage Total Mortality		Avarage Total Resorbed	
		Main	%	Main	%	Main	%	Main	%
Control	0	7	100	6.9	98.57	0.0	0.0	0.1	1.43
Tramadol	Low	5	71.43	3.9	53.57	0.4	5.71	0.7	10.0
	High	4	57.14	3.1	44.29	0.55	7.85	0.35	5.00

Table (3)
Effect of Tramadol on the Length of the Crown Rump, and Total Body Weight of the Fetuses at 19 Day of Gestation

Drugs	Doses	Crown – rump Length , mm of Fetus	Total Body Weight , g
Control	0	52±0.26	8.1±0.17
Tramadol	Low	29**±0.04	4.01**±0.11
	High	23**±0.05**	2.81**±0.09

** = Highly significant ($p \leq 0.01$)

Table (4)
Teratogenic Effect of Tramadol on Skeletal System of the Fetuses at 19 Day of Gestation

Skeletal Defect	% of Examined fetuses	
	Doses	
	Low	High
Skull		
Incomplete Ossification	55.31	78.11
Complete Ossification	44.69	21.89
Sternebrae		
Fused	14.12	50.10
Absence	19.72	29.45
Normal	66.16	20.45
Ribs		
Irregular shape	24.53	20.58
Missing	20.80	41.23
Incomplete Ossification	28.71	21.26
Complete Ossification	26.06	16.93
Vertebrae Centra		
Absence	18.18	38.46
Scoliosis	44.82	43.67
Normal	37.00	17.87
Fore Limbs		
Incomplete Ossification	65.74	73.82
Complete Ossification	34.26	26.18
Hind Limbs		
Incomplete Ossification	64.54	77.38
Complete Ossification	35.46	22.62

Table (5)

Effect of Tramadol on Mitotic Index of Bone Marrow in Male Rats

Drugs	Days	No. Of Dividing Cells/1000 Cells/ Rat		
		Doses		
		Control	Low Dose	Hight Dose
Tramadol	10	83.9±1.82	63.8±1.00**	50.3±2.13**
	20	76.6±2.04	54.5±1.41**	48. 5±2.60**
	30	80.7±1.41	48.7±1.16**	42.8±2.62**

** = Highly significant (p≤0.01)

Results are expressed as the mean ± S.D. of the 5 rats

Table (6)

Chromosomal Aberration of Male Rats Bone Marrow Cells Treated with Tramadol

Chromosomal Aberrations	Control	Treated					
		10 Days		20 Days		30 Days	
		Low Dose	High Dose	Low Dose	High Dose	Low Dose	High Dose
a- Structural aberrations							
Gap	0	0	0	0	3.6** ±0.11	3.0** ±0.01	4.2** ±0:2
Stickiness	0	0.8** ±0.02	2.0** ±0.02	4.0** ±0.1	4.1** ±0.2	4.0** ±0.1	3.6** ±0.2
Centromeric atenuation	0.1 ±0.01	0.8** ±0.01	2.0** ±0.1	2.1** ±0.1	3.0** ±0.2	3.0** ±0.02	3.0** ±0.02
Centric fusion	0	0	3.6** ±0.1	2.5** ±0.1	3.0** ±0.3	3.5** ±0.01	4.0** ±0.1
End to End	0	2.0** ±0.10	2.1.1** ±0.1	1.1** ±0.2	1.6** ±0.02	3.3** ±0.01	2.5** ±0.01
Deletion	0	0	2.0** ±0.02	1.0** ±0.01	2.1** ±0.02	1.2** ±0.01	3.0** ±0.02
Ring – Shaped	0	0	1.4** ±0.01	1.2** ±0.01	1.8** ±0.02	1.6** ±0.01	3.1** ±0.02
b- Numerical aberration							
Hyperploidy	0	0	0	0	1.0** ±0.01	1.1** ±0.01	2.0** ±0.01

** = Highly significant (p≤0.01)

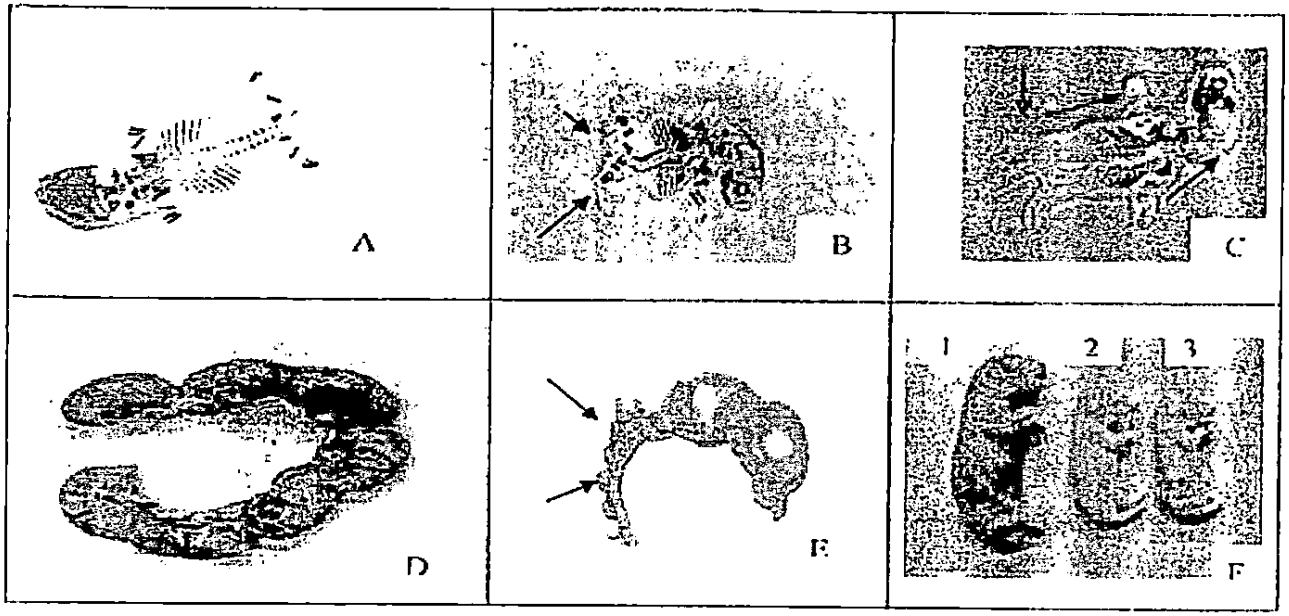

Figure (1): Photographs of control fetus, fetuses maternally and uterus of control and treated rat with tramadol showing retardation of growth, incomplete ossification of bones and resorbed embryo. (A) Control skeletal system of 19 days rat fetus. (B) Skeletal system of 19 days fetus of treated rat with 40 mg/kg tramadol. (C) Skeletal system of 19 days fetus of treated rat With 80 mg/kg body weight tramadol. (D) uterus of control rat (E) uterus of treated rat with 80 mg/kg tramadol. (F) 1- Control rat fetus. 2- Rat fetus treated With 40 mg/kg tramadol. 3- Rat fetus treated With 80 mg/kg tramadol.

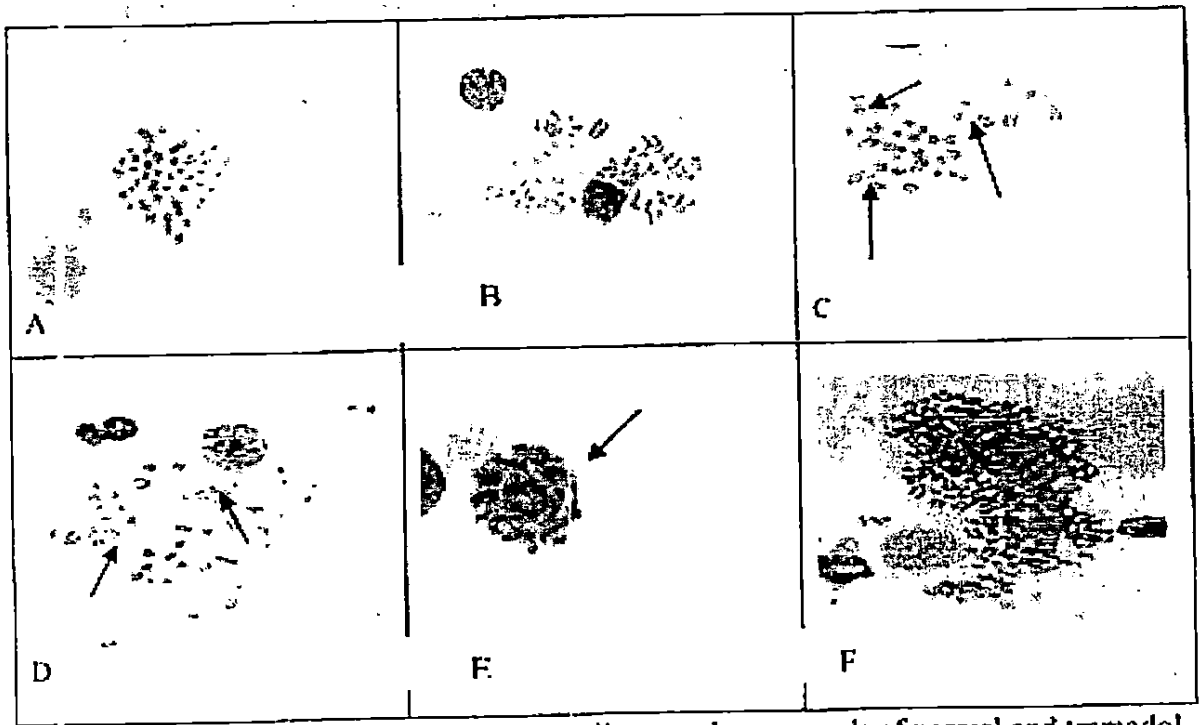

Figure (2): Photographs of bone marrow cells metaphase spreads of normal and tramadol treated male rats with 40 and 80 mg /kg body weight showing. **A** : Normal metaphase spreads **B** : Centromeric attenuation **C** : Centric fusion and end to end **D**: Ring shape and deletation . **E** : Stickness **F** : polyploidy

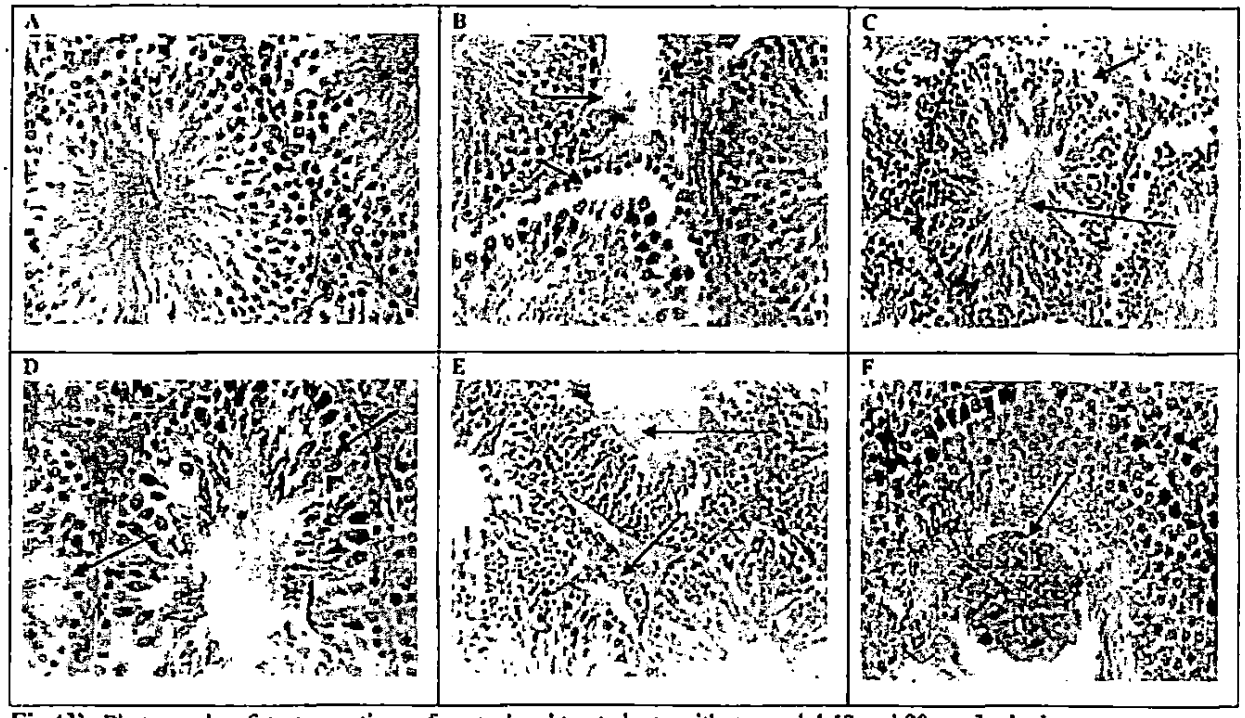

Fig (3): Photographs of testes sections of control and treated rats with tramadol 40 and 80 mg /kg body Weight showing A: control testis. B: Spermatogonia living the basement membrane and small vacuoles in the leydig cells. C: Decrease in number of sperms degeneration of germ cells. D:Hypertrophy of germ cells. E : Necrotic cell in the leydig cells and decrease in number of sperms. F : Disorganization of germinal cells.

Discussion

There are many possible risks to the fetus whenever drug medications are prescribed to the pregnant women. Possible effects include abortion, malformation, intrauterine growth retardation, functional defects, carcinogenesis and mutagenesis. The risk of malformation is greatest when the fetus is exposed to the drug at two and eight weeks after conception [15].

Tramadol is a synthetic opioid. It inhibits noradrenaline uptake and stimulates serotonin release[16]. The results of teratological study revealed statistically significant increase in dead and resorbed embryos number. Resorbed embryos were increased according to the dose with statistically significant decrease in the fetal body weight, crown rump, and length of rat embryos. The defects noticed in skeletal system observation of 19 days of gestation fetuses had incomplete ossification of skull, central disc, toes, and ribs. These results are inagreement with the results of Schardein (1993); Briggs (1994) and Erhart and Frank (1994)[17] who reported that there are several case studies demonstrated congenital defects in infants of heroin-addicted mothers. Effect of maternal heroin addiction may persist in the offspring for an extended period of time, resulting in poor growth and development[18]. Behavioral abnormalities, including impaired organization and perception skills, impaired motor inhibition and mental retardation, have been described[19]. The results of the present study are also inagreement with Grond and Sablotzki (2004)[20] who reported that tramadol has been shown to be embryotoxic and fetotoxic in mice, rats and rabbits at maternally toxic doses 3 to 15 times the maximum human dose or higher. Embryo and fetal toxicity consisted primarily of decreased fetal weights, skeletal ossification and increased supernumerary ribs at maternally toxic dose levels.

Examination of bone marrow metaphases revealed structural and numerical chromosomal aberrations. These chromosomal aberrations are centromeric attenuation, centric fusion, ring shape, end to end association, gap, break and stikness. In addition, numerical chromosomal aberrations were observed as Polyploidy. These results of chromosomal assay in bone marrow cells of rats confirmed the genotoxicity of tramadol and its ability to induce chromosomal damage. It is well known that DNA is the principal target for induction of structural chromosomal aberration[21]. Such aberration can result from DNA fragmentation due to clastogensis induced by drug administration[22]. The results of chromosomal aberration are completely inagreement with result of Grond and Sablotzki (2004)[23]. Who reported that mutagenic results are occurred with the use of tramadol in the presence of metabolic activation in the mouse lymphoma assay and micronucleus test in rats.

The toxic effect of chemical substances or drugs on different tissues is usually manifested in the histological preparation in the form of cells degeneration, vacuolization, pyknosis, accumulation of fat and necrosis. This is mainly considered as a reflection of direct damage in cell and tissues[24]. In clinical medicine, serum enzymes activities and concentrations of metabolic products has been used for detecting both the site and extent of an organ injury[25]. The histological changes observed in the present study of testes cells were vacuoles and some spermatogonia leaving the basement membrane, decrease amount of sperm in the lumen of seminiferous tubules were also shown and hypertrophy of germ cells with decrease in their number with necrotic cells appear in Leydig cells and disorganization of some germinal cells. These histopathological changes in testes are in accordance with those reported by Robison, et al., (1984) and Gershbein and Pedroso (1985)[26] who showed that when drug given to the mice, isolation bloodlines significant for hepatocellular oedemes were noticed.

Procedure for classification of the seminiferous tubules according to the presence of the most advanced germ cell is often performed to evaluate spermatogenesis[27], and it is based on the finding that seminiferous tubules have spermatides as the most advanced germ cell in the rat[28]. Tramadol increased lipid peroxidation, induced hepatic and renal damage and sexual dysfunction in male rats treated with tramadol for one month[29].

Conclusion

The present results showed that tramadol exerted embryotoxic and fetotoxic effects in the pregnant rats. It also increased the risk of congenital malformation, therefore, the drug should not be used in the pregnant women prior to, or during labor unless the potential benefits outweigh the risks.

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تأثير مسكن الترامادول على بعض المؤشرات البيولوجية

مجدى حسن

يهدف هذا البحث إلى دراسة التأثيرات المحتمل حدوثها على بعض المؤشرات البيولوجية التى قد تصاحب الإعطاء المتكرر للجرعات العلاجية من عقار الترامادول المسكن ، من خلال دراسة تأثير العقار على إناث الفئران الحوامل ، وأجنتها ، ودراسة تأثير العقار على العوامل الوراثية ، وأنسجة الخصية ، وبعض وظائف الكبد والكلية فى ذكور الفئران .

وقد استخدم لهذه الدراسة إناث وذكور الفئران ، حيث قسمت الإناث الحوامل والذكور إلى ثلاث مجموعات : أعطيت المجموعتان الأولى والثانية منها (الإناث والذكور على التوالى) جرعات من عقار الترامادول المذاب فى ماء مقطر تعادل ٤٠ ، ٨٠ مجم/كجم من وزن الجسم على التوالى من اليوم الرابع إلى اليوم التاسع عشر من الحمل ، وأعطيت الفئران الذكور الجرعات لمدة ٣٠ يوما ، وتركت المجموعة الثالثة من الذكور والإناث كمجموعة ضابطة .

وقد أوضحت النتائج نقصا ذا دلالة معنوية فى أوزان وأطوال أجنة الفئران ، وزيادة ذات دلالة معنوية فى الأجنة الممتصة والميته ، وكذلك نقص فى نمو الهيكل العظمى لهذه الأجنة .

أما بالنسبة لنتائج ذكور الفئران ، فقد أظهرت زيادة معنوية فى محتوى مصل دم من أنزيمات الترانس امينار والكرياتينين ، وأن التأثير يزداد بزيادة المدة والجرعة . كما لوحظ وجود تلف فى أنسجة الخصية والخلايا المكونة للحيوانات المنوية ، وضمور فى الأنابيب المنوية وخلايا ليدج . كما أوضحت النتائج وجود تشوهات تركيبية وعددية فى الكروموسومات ، وكانت على شكل تباعد سنترومرى ، والتحامات سنترومرية ، وانتقاصات كروموسومية حلقية ، والتصاق كروماتيدى بين الكروموسومات ، وكسر ، وانقسام متضاعف .

وقد خلصت الدراسة إلى أن استعمال عقار الترامادول أثناء الحمل له تأثير مميت على الأجنة ، وكذلك يؤدى إلى خلل فى وظائف الكبد والكلية وتلف فى أنسجة الخصية ، وإلى إحداث تشوهات كروموسومية ، وأن التأثير يزداد بزيادة المدة والجرعة ، وأنه لايجب إعطاؤه أثناء الحمل إلا إذا كانت هناك ضرورة قصوى .