

Biochemical Toxicity Induced By Tramadol Administration In Male Rats

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Abstract

Introduction: Tramadol is a centrally acting analgesic used for treatment of moderate to severe pain. There has been some controversy regarding the dependence liability of long-term use of this medication. The present work was conducted to assess the biochemical toxicity profiles of tramadol during therapeutic use. Liver and kidney functions, sex hormones activity and some metabolic parameters were studied in male rats.

Methods: Rats were divided into three groups. Group one received vehicle (saline), group two and three received oral doses of tramadol equal to 40 mg and 80 mg / kg body weight / day respectively for a month followed by 10 days recovery period. Biochemical measurements were carried out every 10 days.

Results: There was significant increase in the levels of serum aminotransferases (ALT,AST), lactate dehydrogenase (LDH), urea nitrogen (BUN), creatinine and lipid peroxide (MDA) in both tramadol groups. In contrast, serum glucose, total cholesterol and triglycerides were significantly reduced. Tramadol significantly reduced serum luteinizing hormone (LH), follicle stimulating hormone (FSH), testosterone and cortisol, but elevated prolactin (PRL) and estradiol (E₂) in male rats specially at 20 and 30 days of treatment. After 10 days recovery, 80 mg tramadol group remained significantly different compared to control one.

Conclusion: The present finding pointed out the risk of increased lipid peroxidation, hepatic and renal damage and sexual dysfunction. Tramadol toxic effects should be kept in mind during long term therapy specially in large doses.

Introduction

Tramadol (Tramal™) is a synthetic, centrally acting analgesic used parenterally and orally for the treatment of moderate to severe pain. 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. Tramadol binds to the μ -opioid receptor, although much more weakly than morphine. It also inhibits the neuronal reuptake of norepinephrine and serotonin as do the antidepressant drugs such as amitriptyline and desimpramine (Raffa *et al.*, 1992; Raffa, 1996; Dayer *et al.*, 1997; Grond and Sablotzki, 2004; Gillman, 2005).

Tramadol has high oral bioavailability in the range of 70- 80%. Peak blood

levels are reached in about 2 hours after an oral dose. The drug is converted in the liver to at least one active metabolite (O-desmethyl-tramadol: ML), which itself is 2 to 4 times more potent than tramadol (Wu *et al.*, 2001; Tao *et al.*, 2002; Janssen-Ortho Inc., 2005). Its opioid activity is greater than the parent compound and could contribute to this component (Lewis and Han, 1997; Grond and Sablotzki, 2004). The parent drug and metabolites are mainly excreted via kidneys (Matthiessen *et al.*, 1998; Janssen- Ortho Inc., 2005).

Tramadol has a dose-dependent analgesic efficacy that lies between that of codeine and morphine, with a parenteral potency comparable to that of pethidine, i.e. about 10- 20 % of the standard morphine

(Wilder- Smith *et al.*, 1999; Pang *et al.*, 2003). The efficacy of tramadol is not associated with the usual serious opioid side effects. Nausea is perhaps the most common side effect and may occur with the same frequency as codeine therapy. Dizziness, constipation and headache have been reported with chronic use (Cossman and Cohnen, 1995). Respiratory depression has not been observed, but large doses of tramadol may increase the respiratory effects of other drugs (Houmes *et al.*, 1992; Tarkkila *et al.*, 1998). Seizures have been reported in patients receiving recommended doses but are more likely associated with abuse of this medication (Jick *et al.*, 1998; Gasse *et al.*, 2000). When seizures do occur, they are commonly of short duration and are easily treatable (Spiller *et al.*, 1997; Tobias, 1997; Gardner *et al.*, 2000).

Unlike nonsteroidal anti-inflammatory drugs, tramadol has no serious adverse gastrointestinal effects such as gut, platelet or renal effects of that drug class (Gibson, 1996; Tolman, 1998).

The incidence of abuse of tramadol is low in all post- marketing surveys; the Food and Drug Administration reported a rate of abuse in the range of 1 in 100,000 patient exposures (FDA, 1998). Rare cases of withdrawal reactions after abrupt discontinuation of tramadol have been reported (Cossman and Cohnen, 1995). But Poison Control data (2002 AAPCC Annual Report) indicated that there were 2,400 exposures of tramadol reported to control centers, of those, 108 resulted in a major medical outcome and 8 resulted in death.

Long- term administration of tramadol for management of pain, as well as its use as an acceptable alternative in persons with drug- seeking behavior is controversial (Drugs and Therapy Bulletin, 2002). Also, long- term effects of tramadol at cellular level, are not clearly understood (Atici, 2005).

So, the present work was conducted to assess the biochemical toxicity profiles of this medication (tramadol HCl) during one month treatment and 10 days recovery period. Liver and kidney functions, some metabolic parameters and sex hormones

activity were studied in male rats (*Rattus norvegicus*).

Materials and Methods

Drug:

Tramal (Tramadol HCl), 50 mg capsules, was obtained from Mina- Pharm, Egypt. Its chemical name is (\pm) cis-2-[(dimethylamino)methyl]-1-(3-m ethoxyphenyl) cyclohexanol hydrochloride.

Experimental Protocol:

110 male rats (*Rattus norvegicus*) weighing 150 ± 5 g were used in the present study. All rats were housed in a quite non-stressful environment for one week before study. They were given normal rat chows *ad libitum* during the experimental period. They were allowed free access to water. Animals were divided into three groups. The first one was comprised 30 rats, served as control and administered oral doses of saline solution for a month. The second and third groups, each comprised 40 rats, were administered oral doses of tramadol HCl suspended in saline solution equal to 40 mg and 80 mg /Kg b. wt. /day for a month respectively. Ten rats from each tramadol group were left ten days more without any additional treatment as a recovery period after one month exposure.

Doses calculated for animals using Paget and Barnes (1964) species interconversion table of dosage.

Control and treated rats were sacrificed at the end of 10, 20, 30, and 40 days respectively. Blood was collected in dry centrifuge tubes. Sera were separated and kept at -20°C until analysis.

Biochemical Analyses:

- Alanine aminotrasferase (ALT) and Aspartate aminotrasferase (AST) activities were measured using the method of Thomas (1998).
- Lactate dehydrogenase (LDH) was measured by the Scandinavian assay (1974).
- Creatinine (Creat.) was determined using the method of Fossati *et al.*(1983).

- Urea (BUN) was measured according to Orsonneau *et al.*(1992).
- Glucose (Glu.) was determined by Trinder (1969) enzymatic method.
- Total Cholesterol (TCh.) was determined according to the method of Flegg (1973).
- Triglycerides (TG.) were measured by the method of Fossati and Prencipe (1982).
- Malondialdehyde (MDA) was measured by the method of Albro *et al.*(1986). The amount of lipid peroxides were calculated as thio- barbituric acid reactive products of lipid peroxidation and reported as nmol of malondialdehyde per ml of serum.
- Luteinizing hormone (LH), follicle stimulating hormone (FSH), prolactin (PRL), testosterone (Tes.), estradiol (E₂) and cortisol (Cor.) were determined using enzyme linked immunosorbant assay (ELISA) kits according to manufacture structure.

Statistical Analysis:

All data were expressed as means \pm standard errors. Data of different groups were compared using Student's t- test. Differences at $p < 0.05$ were considered significant.

Results

Data in Table (1) showed that administration of 40 mg tramadol /Kg b. wt./day significantly increased serum ALT, AST and LDH levels at first, second and third ten days of treatment compared to control group ($p < 0.05$, $p < 0.01$ and $p < 0.01$ respectively). Also, BUN and creatinine were significantly elevated at third ten days of treatment ($p < 0.05$) while, lipid peroxides (MDA) increased gradually and significantly from the first ten days treatment till one month ($p < 0.05$, $p < 0.01$ and $p < 0.01$ respectively). Glucose, total cholesterol and triglycerides were reduced significantly at 20 and 30 days of treatment

($p < 0.05$ and $p < 0.01$). On the other hand, after ten days recovery period ALT, AST, LDH, BUN and creatinine returned to their levels, yet did not reach the corresponding control group, except of glucose, cholesterol, triglycerides and MDA which were significantly different from control group ($p < 0.05$).

Results presented in Table (2) indicated that administration of 80 mg tramadol /Kg b. wt./day was significantly induced the elevation of ALT, AST, LDH and MDA at 10, 20 and 30 days of treatment ($p < 0.01$). BUN and creatinine also increased at 20 and 30 days of treatment ($p < 0.05$ and $p < 0.01$ respectively). But glucose, total cholesterol and triglycerides reduced significantly at 20 and 30 days of treatment ($p < 0.01$) compared to control. The ten days recovery group remained significantly different compared to control group.

Table (3) showed that 40 mg tramadol /Kg b. wt. statistically elevated serum E₂ and PRL secretions with a decrease in testosterone levels at 20 days of treatment, whereas at 30 days LH, FSH, testosterone and cortisol were significantly reduced accompanying with significant increase of E₂ and PRL secretions. After ten days recovery, the measuring parameters reached their normal levels except testosterone and E₂ ($p < 0.05$) which still recorded significant increase compared to control group.

Data in Table (4) revealed that after 20 and 30 days of treatment with 80 mg tramadol /Kg b. wt., there were significant increase in E₂ and PRL ($p < 0.01$) compared to control. Also, there were higher significant reduction in testosterone and cortisol ($p < 0.01$) accompanied by gradual reduction in LH and FSH levels observed at 20 and 30 days ($p < 0.05$ and $p < 0.01$ respectively). The recovery group was noted to be significantly elevated over corresponding control group.

Table (1): Effect of Tramadol (40 mg/kg/day) Administration on Biochemical Profile of Male Rats.

Parameters	Conditions	Treatment (1 month)			Recovery
	Control	10 days	20 days	30 days	10 days
	X±S.E.	X±S.E.	X±S.E.	X±S.E.	X±S.E.
ALT(U/L)	35.2±2.0	43.6±1.1*	48.2±1.0**	55.3±0.9**	40.3±1.1
AST(U/L)	126.4±2.3	143.0±1.4*	188.0±1.2**	203.0±2.6**	130.0±1.2
LDH(U/L)	556.0±3.2	590.0±2.4*	660.0±2.2**	806.0±3.0**	562.0±1.0
BUN(mg/dl)	24.2±1.9	25.8±1.0	28.3±1.1	38.0±1.3*	30.4±1.2
Creat.(mg/dl)	0.4±0.12	0.41±0.1	0.42±0.11	0.56±0.1*	0.43±0.11
Glu.(mg/dl)	205±2.2	200±2.0	189±1.4*	170±1.9**	186±1.5*
TCh. (mg/dl)	83.5±2.0	82.0±1.3	70.0±1.0*	62.0±1.0**	75.3±1.3*
TG. (mg/dl)	92.3±2.2	88.3±1.2	80.0±1.0*	75.0±1.2**	81.5±1.6*
MDA(nmol/ml)	6.3±1.0	11.9±0.9*	18.2±0.8**	26.0±0.66**	9.2±0.32*

*=Significant (p< 0.05)

**= Highly significant (p< 0.01)

Control= The average of the results of control groups were used in the statistical analysis as there is no significant difference between them.

Table (2): Effect of Tramadol (80 mg/kg/day) Administration on Biochemical Profile of Male Rats.

Parameters	Conditions	Treatment(1 month)			Recovery
	Control	10 days	20 days	30 days	10 days
	X±S.E.	X±S.E.	X±S.E.	X±S.E.	X±S.E.
ALT(U/L)	35.2±2.2	53.6±1.4*	64.0±1.6**	69.0±1.3**	49.9±1.3*
AST(U/L)	126.4±2.3	156.0±2.0*	196.0±1.5**	220.0±2.3**	153.0±2.0*
LDH(U/L)	556.0±3.2	686.0±2.4**	803.0±3.0**	930.0±2.9**	708.0±2.0*
BUN(mg/dl)	24.2±1.9	27.0±1.0	39.5±1.0*	50.6±1.3**	32.3±0.9*
Creat.(mg/dl)	0.4±0.10	0.42±0.1	0.58±0.1*	0.65±0.11**	0.50±0.1*
Glu.(mg/dl)	205±2.2	195±1.9	176±2.0**	150±1.1**	183±1.3*
TCh. (mg/dl)	83.5±2.0	80.3±1.3	70.5±1.0**	60.0±1.0**	68.3±1.2*
TG. (mg/dl)	92.3±2.2	86.0±2.0	73.6±1.3**	62.0±1.0**	80.5±1.2*
MDA(nmol/ml)	6.3±1.0	16.3±1.1**	20.5±1.2**	35.0±1.1**	19.6±1.0*

*=Significant (p< 0.05)

**=Highly significant (p< 0.01)

Control= The average of the results of control groups were used in the statistical analysis as there is no significant difference between them.

Table (3): Effect of Tramadol (40 mg/kg/day) Administration on Gonadal Activity of Male Rats.

Parameters	Conditions	Treatment (1 month)			Recovery
	Control	10 days	20 days	30 days	10 days
	X±S.E.	X±S.E.	X±S.E.	X±S.E.	X±S.E.
LH (mlU/ml)	2.25±0.15	2.1±0.11	2.0±0.1	1.4±0.1*	1.9±0.14
FSH(mlU/ml)	2.0±0.11	2.0±0.1	1.9±0.1	1.0±0.1*	1.65±0.12
Tes.(ng/ml)	4.0±0.4	3.7±0.2	2.6±0.1*	2.2±0.1**	3.0±0.1*
E ₂ (pg/ml)	44.2±1.1	46.5±1.2	51.3±1.0*	61.5±1.2**	52.4±1.1*
PRL(ng/ml)	6.6±1.0	8.2±0.9	10.0±0.1*	12.9±0.11*	9.0±0.2
Cor.(ng/ml)	198±2.0	194±1.4	190±1.3	182±1.2*	189.5±1.4

*=Significant (p< 0.05)

**=Highly significant (p< 0.01)

Control= The average of the results of control groups were used in the statistical analysis as there is no significant difference between them.

Table (4): Effect of Tramadol (80 mg/kg/day) Administration on Gonadol Activity of Male Rats.

Parameters	Control	Treatment (1 month)			Recovery
	X±S.E.	10 days X±S.E.	20 days X±S.E.	30 days X±S.E.	10 days X±S.E.
LH (mIU/ml)	2.25±0.15	2.0±0.11	1.3±0.6*	0.92±0.1**	1.4±0.1*
FSH(mIU/ml)	2.0±0.11	1.9±0.1	1.2±0.01*	0.82±0.01**	1.2±0.1*
Tes.(ng/ml)	4.0±0.4	3.5±0.1	2.2±0.1**	1.4±0.1**	2.6±0.11*
E ₂ (pg/ml)	44.2±1.1	48.5±1.2	62.3±1.0**	73.5±1.6**	55.0±2.0*
PRL(ng/ml)	6.6±1.0	8.9±1.2	12.6±1.0**	15.3±1.1**	11.7±0.9*
Cor.(ng/ml)	198±2.0	192±1.6	182±1.3**	177±1.7**	183.0±1.1*

* = Significant (p < 0.05)

** = Highly significant (p < 0.01)

Control = The average of the results of control groups were used in the statistical analysis as there is no significant difference between them.

Discussion

Hepatic metabolism is a mechanism that converts drugs and other compounds into products that are more easily excreted and that usually have a lower pharmacological activity than the parent compound (Tolman, 1998). A metabolite may have higher activity and / or greater toxicity than the original drug. Metabolites of the drugs that are excreted via kidneys may also cause cellular damage leading to kidney dysfunction (Singhal *et al.*, 1998).

The liver and kidney are responsible for tramadol metabolism and excretion. It may cause hepatotoxicity and nephrotoxicity during its metabolism (Wu *et al.*, 2001; Janssen- Ortho Inc., 2005). Borzelleca *et al.* (1994) reported increased in ALT, AST and LDH activities in rats after long- term usage of morphine-like agent levo-alpha-acetylmethadol HCl (LAAM). Also, a significant increase in the levels of ALT, LDH and lipid peroxides was reported among chronic heroin users (Panchenko *et al.*, 1999). Similarly, the present data was found significant increase in the levels of ALT, AST and LDH among rats received both doses of tramadol (40 mg and 80 mg /Kg b. wt.) with a pronounced effect caused by the large dose and the duration of drug administration.

On the other hand, current results indicated a slight increase in BUN and creatinine levels in rats received 40 mg /Kg

tramadol after 30 days treatment but, 80 mg / Kg tramadol exerted moderate effects at 20 and 30 days treatment. These are in accordance with Atici *et al.* (2005) who reported an increase in BUN and creatinine levels in rats receiving morphine for a month and after long- term use of LAAM (Borzelleca *et al.*, 1994).

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 (Lurie *et al.*, 1995). A significant increase in lipid peroxides was reported in rats receiving an acute dose of cocaine (Masini *et al.*, 1997). Similarly, lipid peroxides were found significantly increased among heroin users (Panchenko *et al.*, 1999). 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.

The current data also revealed reduced levels of glucose, total cholesterol and triglycerides in both tramadol groups after 20 and 30 days treatment with more pronounced effect of large dose. These data

supported by a recent study of Cheng *et al.* (2001) which showed that tramadol can decrease glycemia in diabetic rats, via the activation of opioid μ -receptors, suggesting a mechanism possibly related to those of dextro-propoxyphene. Moreover, tramadol acts as serotonin reuptake inhibitor, and hypoglycemia has been described with some serotonin anti-depressants, sertraline (Peyrière *et al.*, 2004). The hypoglycemic effect of Tramacet (tramadol containing product) has been also reported as a metabolic disorder that occurred as an incidence of less than 1 % in clinical trails (Janssen-Ortho Inc., 2005)

The reduction of total cholesterol and triglycerides levels in the present study received evidence from El- Gaafarawi (1990) who observed significant reduction in plasma total cholesterol and triglycerides levels after administration of opioid and non-opioid analgesics in rats. Also, Budzynski *et al.* (2000) reported reduction of serum total cholesterol and triglycerides levels in naltraxone (μ - antagonist) treated patients. In another study using some antiepileptics, Daoud *et al.* (2004) showed similar reduction in serum total cholesterol and triglycerides in addition to glucose levels.

The reduction of serum total cholesterol in the current study supported the reduction of testosterone levels in the same study where, 45% of cholesterol substrate for testosterone and sperm production was derived from plasma (Connor *et al.*, 1997).

Sexual dysfunction as a consequence of drug therapy has been reported with a range of drugs. About 15% of the 200 most commonly prescribed drugs can have adverse effects on male reproduction such as sedatives, tranquilizers, hypnotics, narcotics and cannabis (Chowdhury, 1987), antihypertensives, antipsychotics and antidepressants (Maclean and Lee, 1999). Mckim (2003) stated that opiate use is known to decrease the levels of sex hormones in both sexes and this lowered hormonal level is thought to be responsible for the diminished fertility of both male and female opiate users.

In the present study, gonadal examinations revealed that administration

of tramadol 80 mg /Kg b. wt. for a month influenced sex hormones activity of male rats at 20 and 30 days of treatment compared to control group while, 40 mg / Kg b. wt. tramadol influenced this activity to a lesser extent compared to 80 mg tramadol group and control one.

Previous studies concerned with gonadal activity during drug therapy have been supported the present results. Chowdhury (1987) reported decreased levels of serum LH and testosterone with increased PRL secretion after morphine and methadone administration. Christensen *et al.* (1989) reported reduction of cortisol levels after 3 and 5 weeks treatment with antidepressants and increased PRL after sertraline administration (Broadbear *et al.* 2004). Also, Hezog *et al.* (2004) reported reduced testosterone and elevated E₂ levels while Daoud *et al.* (2004) reported significant reduction in serum testosterone and FSH levels in antiepileptic treated patients and in rats respectively. El-Gaafarawi *et al.*(2005) have been observed in an independent investigation, the reduction of serum levels of LH, FSH, testosterone and the induction of PRL secretion after paroxetine treatment.

On the other hand, the results of 10 days recovery period indicated that most of the measured parameters of 40 mg tramadol group tended to be somewhat higher than the control group, whereas, 80 mg tramadol group remained significantly different compared to control one. This may indicate that tramadol toxic effects induced by therapeutic doses are persisted after drug cessation, and the time of recovery is dependent on the concentration of administered dose.

Conclusion

Tramadol exerts its toxic effect via two distinct and synergistic mechanisms of actions. This may reflect the greater frequency of decreasing hepatic, renal and sexual functions. Physicians should be aware of aforementioned adverse effects and the glycemic disturbances related to tramadol. Dose selection should be cautious.

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السمية الكيميائية الحيوية الناتجة عن تأثير عقار الترامادول في ذكور الجرذان

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يهدف هذا البحث إلى تقييم التأثير السمي الذي قد يصاحب تكرار إعطاء الجرعات العلاجية من عقار الترامادول على بعض الجوانب الكيميائية الحيوية من خلال دراسة وظائف الكبد و الكلى، ونشاط بعض هرمونات الغدة النخامية و بعض هرمونات التناسل، و كذلك بعض معدلات التمثيل الغذائي (الأيض) في ذكور الجرذان البيضاء.

و قد استخدم في ذلك ثلاث مجموعات من ذكور الجرذان، أعطيت الأولى منها (المجموعة الضابطة) محلول ملحي عن طريق الفم، و المجموعة الثانية و الثالثة أعطيت أيضا عن طريق الفم جرعات من الترامادول تعادل 40مجم، 80 مجم / كجم من وزن الجسم يوميا و لمدة شهر على التوالي. و قد تم الاحتفاظ بعدد من جرذان هاتين المجموعتين لمدة عشرة أيام إضافية بدون أى معالجة بالعقار. و قد أجريت القياسات المعملية كل عشرة أيام.

أوضحت النتائج زيادة محتوى مصل الدم من إنزيمات الترانس أميناز و اللكتات دي هيدروجيناز و الكرياتينين، و كذلك زيادة معدلات الأوكسدة الفوقية للدهون زيادة ذو دلالة معنوية لكلتا الجرعتين.

و على العكس، أدى الترامادول إلى نقصان ذو دلالة معنوية في محتوى مصل الدم من السكر و الكوليسترول الكلى و الدهون الثلاثية. أما بالنسبة لنشاط هرمونات التناسل، فقد أدت الجرعتان، إلى تقليل نشاط هرمونات FSH,LH و التستوستيرون و الكورتيزول، في حين زاد إفراز البرولاكتين و الاستراديول في مصل دم الجرذان وخاصة بعد 20، و 30 يوما من المعالجة.

و قد توصلت الدراسة إلى أن استعمال الجرعات العلاجية من عقار الترامادول لمدة طويلة يؤدي إلي مخاطر زيادة الأوكسدة الفوقية للدهون، و خلل في وظائف الكبد و الكلى، و اضطراب في نشاط هرمونات التناسل، كما يؤدي إلى تغيير في بعض عمليات الأيض. و تزداد حدة هذه التأثيرات مع زيادة حجم الجرعة المعطاة، و زيادة فترة المعالجة. و لذا يجب الأخذ في الاعتبار هذه المخاطر عند المعالجة بهذا العقار لفترة طويلة.