

# A Study of Clinical and Laboratory Picture of Acute Tramadol Toxicity in Damietta Governorate

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## ABSTRACT

### KEYWORDS

Tramadol,  
HPLC,  
Seizures,  
Biochemical analysis.

Increased rate of seizures and respiratory complications due to tramadol poisoning have been observed, even with first time of tramadol intake. So, the present work was used to investigate the clinical manifestations and laboratory investigations of acute tramadol toxicity and the correlation between toxic tramadol manifestations and blood tramadol level and laboratory parameters. A study was performed on 100 patients (80 males and 20 females) acutely intoxicated with tramadol, admitted to toxicology unit of Al-Azhar University Hospital (New Damietta) in the period from January to December 2017. Informed consent, urine sample was collected and 10 mL of blood was separated and used for extraction of tramadol residues by using a high-performance liquid chromatography (HPLC) and other blood samples were stored at -8°C for routine investigations. Then a detailed clinical examination was done to all patients. Generally, the frequency of seizures was (46 %) with acute tramadol poisoning. There was no correlation between blood tramadol level and toxic manifestations of tramadol poisoning. So, the frequency of seizures and toxic manifestations are not dosed dependent. Cannabis was the most common co-ingested drugs and adult males were more commonly affected by tramadol poisoning. It is recommended that the drug abuse problem must be treated at the level of community problems in order to minimize medical emergencies related to acute tramadol overdose occurring mostly by addiction and further studies should be proposed to extend our knowledge about relationships between sex and seizures among tramadol intoxicated patients

## Introduction

Tramadol is an opioid used for management of moderate to severe pains. It has been legally used for pain treatment since 1980 in some nations and became the most

prescribed opioid all over the world (Loughrey et al., 2003).

Tramadol exerts its action by weak binding to the  $\mu$ -opioid receptor and inhibiting reuptake of serotonin and norepinephrine (Shadnia et al., 2008).

The mainstream of the pain-killing action of tramadol may be a result of non-opioid characters through central monoaminergic pathways. Oral route is the most frequent route of administration of tramadol (Taghaddo-sinejad et al., 2011).

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Tramadol is addictive and may be abused by young adults. Tramadol therapeutic dose is 50mg orally compared to 50-100mg parentally and 100mg in case of rectal administration, doses of 500-800mg are toxic and estimated lethal dose is between 3-5gm (Chandrasekaran et al., 2007). The most common effects of tramadol toxicity include nausea, vomiting, depression of central nervous system, tachyarrhythmia, cardio-respiratory depression, and convulsions. However, there are some studies reported the likelihood of seizure induction even with therapeutic doses (Derakhshanfar et al., 2012). Overdose of tramadol is one of the most common causes of admissions to the hospital due to tramadol toxicity (Talaie et al., 2009).

Seizures induced convulsions by tramadol were reported to be 15% to 35% (Kroenke et al., 2009).

Accurate mechanism of tramadol-induced seizure is not completely known. Trials indicate that in high concentrations, tramadol produces an inhibitory effect on gamma-aminobutyric acid (GABA) receptors (Rehni et al., 2008).

Inhibition of GABA receptors has been proposed to potentiate severity of convulsions in animal studies (Sun et al., 2007).

Also, inhibition of GABA receptors produced by tramadol can be secondary to its opioid receptor agonist action, and continuing this agonist action on opioid receptor has been confirmed to precipitate convulsions due to inhibition of GABA pathways (Rehni et al., 2008). Tramadol may possibly increase the convulsions risk in patients receiving other medications such as tricyclic anti-depressants, phenothiazines and selective serotonin reuptake inhibitors (Kroenke et al., 2009).

Tramadol - induced convulsions are controlled well by diazepam, but not respond to naloxone, and can be triggered by management

with naloxone, at tramadol overdoses (Raffa and Stone, 2008).

The present study was designed to examine the clinical findings and laboratory tests of acute tramadol toxicity and correlations between toxic tramadol manifestations and plasma tramadol level and other laboratory parameters in toxicology unit, in Al-Azhar University Hospital (New Damietta) from the 1<sup>st</sup> of January 2017 to the 1<sup>st</sup> of December 2017.

### Patients and methods

A cross-sectional study was performed on 100 patients (80 males and 20 females) acutely intoxicated with tramadol, referred and admitted to the toxicology unit of Al-Azhar University Hospital (New Damietta) in the period extending from January to December 2017.

Inclusion criteria included: definite history of tramadol intake alone or in combination with other drugs of abuse including toxicity either taken by subjects themselves or given by their relatives.

Exclusion criteria included: definite history of tramadol intake and negative parameters for qualitative detection of tramadol; history of chronic liver disease to keep away from the affection of liver functions; history of chronic renal disease to keep away from the affection of kidney functions, and pregnancy (Marco, 2007).

An informed consent was taken from every subject before inclusion in the study.

Data were collected from all patients including socio-demographic data (age, sex, occupation, marital status). In addition, clinical examination was done systematically and included vital data (respiratory rate, heart rate,

blood pressure, body temperature and systemic examination according to Epstein et al., (2009) and Talley and O'Connor, (2013) for detection of any systemic abnormalities. Then, 3 milliliters of arterial blood were collected from each patient for measuring arterial blood gases, and 10 milliliters venous blood were collected from each patient for biochemical and toxicological analysis and urine samples were collected for urine toxicological screening of (benzodiazepine, cannabis, barbiturate, opiates, cocaine, and amphetamine).

Tramadol was detected in urine by immunoassay analysis as described by Al-Saffar (2013), by Mgc240 micro genic automated clinical analyzers Tokyo boeki machinery LTD (Japan), while in blood, it was detected by HPLC analysis as described by Halling et al. (2008)

Tramadol (100ml/2ml/ampoules) were obtained from October Company, Cairo, Egypt. Potassium monobasic phosphate, sodium hydroxide, phosphoric acid, ethyl acetate (Analytical grade) and Acetonitrile (HPLC grade), were obtained from Electrosient Company, Cairo, Egypt.

### Statistical Analysis

The collected data were organized, tabulated and statistically analyzed using SPSS software computer package version 16 (SPSS Inc. Chicago, IL). For quantitative data, all the values were expressed as the mean  $\pm$  standard deviation (SD) that the values  $P < 0.05$  were considered statistically significant. For comparison between the two groups, the students (t) test was used. For qualitative data, number and percent distribution were calculated and Chi-square test ( $\chi^2$ ) was used for comparison between two groups. Pearson's correlation coefficient was used to test the

correlation between variables.  $P < 0.05$  was considered to be statistically significant (Campbel and Machin, 2009).

### Results

*Social and demographic data (Table 1)* shows: the mean age for cases in this study was  $26.3 \pm 12.1$  years. Males represented the majority of cases (80%) in comparison to females (20%). Regarding route and mode of poisoning, all cases were intoxicated through the oral route. Tramadol overdose in addicts represented 58% of cases. Attempted suicides were evident in 36% of cases. Accidental ingestions were observed in 6% of cases.

Regarding co-ingested drugs, the most common co-ingested drugs with tramadol in this study were cannabis observed in 54% of cases followed by benzodiazepines detected in 10% of cases followed by opiates detected in 2% of cases.

*Clinical manifestations in studied cases (Table 2):* As regards clinical manifestation, the mean systolic blood pressure was  $120 \pm 17$  mmHg, the mean diastolic blood pressure was  $80 \pm 11$  mmHg, the mean temperature was  $36.12 \pm 1.06$  °C, the mean respiratory rate was  $20.32 \pm 1.06$  rate/min and the mean pulse rate was  $96 \pm 19$  among the studied cases in this study.

As regards the general manifestations, 16% of cases manifested with pallor and 4% of cases manifested with sweating. Concerning gastrointestinal manifestations, 14% of cases complained of vomiting and 4% of cases complained of abdominal pain. Respiratory system revealed that 42% had respiratory failure, 2% had severe hypoxemia and no case manifested with non-cardiogenic pulmonary edema. The neurological manifestations were

46% of cases manifested with seizures, 2% manifested with hallucinations, 6% manifested with agitation, 38% manifested with drowsiness and 8% manifested with coma.

Regarding examination of pupils in cases of this study with respect to size and reactivity to light, normal sized reactive, miotic reactive, dilated fixed, dilated reactive, pinpoint and miotic reactive pupils were present in 94%, 0%, 0%, 2%, 0% and 4% of cases respectively.

There was a non-significant correlation between tramadol blood levels and vital signs either pulse rate, systolic blood pressure, diastolic blood pressure temperature and the respiratory rate among cases in this study (Table 3).

Table (4) showed that blood tramadol levels was ( $614 \pm 223$  ng/ml), arterial blood gases (PH, HCO<sub>3</sub> and PaCO<sub>2</sub>) were ( $7.42 \pm 0.0995$ ,  $23.5 \pm 4.9$  and  $43.3 \pm 7.5$ ) respectively

and within normal range of serum glucose as it was ( $107.2 \pm 45.5$  mg/dL), AST levels were ( $11.7 \pm 7.5$  IU/L), ALT levels were ( $7.6 \pm 5.8$  IU/L) urea levels was ( $26.6 \pm 12.0$  mg/dL), creatinine levels were ( $1.1 \pm 0.4$  mg/dL).

*Correlation between blood tramadol levels and biochemical markers* Table (5) shows that there was no significant correlation between tramadol blood levels and fasting blood sugar, AST, serum creatinine. There was no significant correlation between tramadol blood levels and ALT, blood urea and ABG (blood pH and HCO<sub>3</sub>).

*Correlation between changes in blood tramadol levels and seizures among the studied cases:* Table (6) shows that there was a non-significant correlation between tramadol blood levels and occurrence of seizures among cases in this study.

**Table (1):** Distribution of the demographic and social data in studied cases.

Studied parameters		n (%)
<b>Mode of poisoning</b>	Addict	58 (58.0%)
	Suicidal	36 (36.0%)
	Accidental	6 (6.0%)
	Homicidal	0 (0.0%)
<b>Co-ingested drugs</b>	Absent	40 (40.0%)
	Cannabis	54 (54.0%)
	Benzodiazepines	10 (10.0%)
	Opiates	2 (2.0%)

n: number, %: percentage.

**Table (2):** Clinical manifestations in studied cases (n=100)

Studied Parameters		mean $\pm$ SD
Vital sign	Systolic blood pressure	120 $\pm$ 17 mmHg
	Diastolic blood pressure	80 $\pm$ 11 mmHg
	Temperature (°C)	36.12 $\pm$ 1.06
	Respiratory rate/min	20.32 $\pm$ 1.06
	Heart rate beats/min	96 $\pm$ 19 b/m
Studied parameters		n (%)
General manifestations	Pallor	16 (16.0%)
	Sweating	4 (4.0%)
GIT manifestations	Vomiting	14 (14.0%)
	Abdominal pain	4 (4.0%)
Respiratory manifestations	Respiratory failure	42 (42.0%)
	Severe hypoxemia	2 (2.0%)
	Non cardiogenic pulmonary edema	0 (0.0%)
Central nervous system manifestations	Seizures	46 (46%)
	Hallucinations	2 (2.0%)
	Agitation	6 (6%)
	Drowsiness	38 (38%)
	Coma	8 (8%)
	Normal sized reactive pupils	94 (94.0%)
	Miotic irreactive pupils	0 (0.0%)
	Dilated fixed pupils	0 (0.0%)
	Dilated reactive pupils	2 (2.0%)
	Pin point pupils	0 (0.0%)
Miotic reactive pupils	4(4.0%)	

n: number, %: percentage, SD: standard deviation.

**Table (3):** Correlation between vital signs and blood tramadol levels among the studied cases.

Parameters		Pulse rate	Systolic blood pressure	Diastolic blood pressure	Temperature	Respiratory rate
Tramadol blood level Mean = 614.19 ng/ml	r	0.218	-0.199	-0.1728	-0.1728	0.1728
	p	0.439	0.119	0.615	0.615	0.215
	Mean	95.06	120.1	79.6	79.6	90.6

r: correlation coefficient.

**Table (4):** Laboratory investigations in the studied cases.

Parameter		Mean $\pm$ SD	Range
Tramadol blood levels (ng/ml)		614 $\pm$ 223	102.4-1000
Arterial blood gases	pH	7.42 $\pm$ 0.0995	6.91-7.33
	HCO <sub>3</sub> (mmol/L)	23.5 $\pm$ 4.9	6.4-31.3
	PaCO <sub>2</sub> (mmHg)	43.3 $\pm$ 7.5	29.2-60
Glucose (mg/dl)		107.2 $\pm$ 36.5	63-294
Aspartate aminotransferase AST (IU/L)		11.7 $\pm$ 10.9	4-72
Alanine aminotransferase ALT (IU/L)		7.7 $\pm$ 8.7	3-49
Urea (mg/dl)		26.6 $\pm$ 6.8	10-45
Creatinine (mg/dl)		1.1 $\pm$ .2	0.5-1.7

n: number, SD: standard deviation

**Table (5):** Correlation between blood tramadol levels and biochemical markers.

Parameter		Study group (n=100)	
		r	p
Fasting blood sugar (mg/dL)		0.116	0.21
Liver enzymes	Aspartate aminotransferase ALT (mg/dL)	-0.254	-0.02
	Alanine aminotransferase AST (mg/dL)	0.075	0.884
Kidney enzymes	Creatinine (mg/dL)	0.270	0.058
	Urea (mg/dL)	-0.232	0.105
ABG	Blood PH	-0.158	0.272
	HCO <sub>3</sub> (meq/L)	-0.262	0.066

ABG:arterial blood gases

**Table (6):** Correlation between blood tramadol levels and seizures among the studied cases.

Group of seizures	%	Mean of tramadol blood levels (mean $\pm$ SD)	Mann-Whitney	p-value
Yes	46%	621.6 $\pm$ 170.4	310	0.992
No	54%	607.9 $\pm$ 262.99		

SD: standard deviation

## Discussion

In this study, the mean age of cases was  $26.3 \pm 12.1$  years and this explained that the young people represent the majority of cases. This is in agreement with Afshari et al. (2008) and Ahmad and Reza (2010).

In this study, males represented the majority of cases. Petramfar and Haghghi (2010) justified the high tramadol abuse among males to its alleged improvement of sexual performance.

In this study, all cases were intoxicated by ingestion as it is most prevalent and easily accessible.

According to this study, majority of cases of tramadol overdose were addicts and attempted suicide. This coincides with Marwa (2010). However, in controversy to present study, many researchers reported that the causes for the exposures included mostly suicide attempts (Persson and Sjöberg, 2008, Shadnia et al., 2008).

In this work, the most common co-ingested drugs with tramadol were cannabis followed by benzodiazepines and opiates. The widespread cannabis abuse was documented in previous studies reaching 18% of drivers. It has been explained as well by the WHO, reported that cannabis abusers are found in all age groups and social strata. Special target groups are adult smokers in rural areas of Africa and Eastern Mediterranean (Yassaa et al., 2009). On the other hand, Fariba et al. (2010) noticed that the most common co-ingested drugs were opioids.

Results of blood pressure in the present work were comparable to those observed by Shadnia et al. (2008) and Ahmad and Reza (2010). They that reported tramadol seems to offer advantages due to its minor cardiovascular side effects.

In the current study, as regards the neurological manifestations, most of cases manifested with seizures, followed by drowsiness and coma. On the contrary, Ahmad and Reza (2010) showed that 87% of cases were comatose and 13% were suffering from seizures. Although the typical symptoms of opiates agonist overdose include coma as the expected symptoms of tramadol overdose, yet the presentation with drowsiness in 38%, agitation in 6% and seizures in 46% confirm the multiple actions of tramadol on the CNS. Concerning seizures, nearly different results were obtained by Persson and Sjöberg (2008).

Most of the cases (61.54%) with disturbed conscious levels were found by Shadnia et al. (2008) in coma grade I according to Reed's classification, 23.07% in coma grade II, 11.54% in coma grade III and 3.85% in coma grade IV. This can be explained by the weak-binding capacity of tramadol to  $\mu$ -opioid receptors and its low risk for CNS depression as compared with other traditional opioids.

As regards, coma, seizures, agitation, and hallucination, Marquardt et al. (2005) noticed nearly similar results. Shadnia et al. (2008) noticed seizures in 35.1% who were related this finding to the high doses of tramadol, except in one case, who ingested 300 mg of tramadol.

Seizures in a higher percent in this study (46%) are attributed to the prominent action of tramadol in norepinephrine reuptake inhibition, which is as well responsible for agitation. Mazor et al. (2008) reported unusual neuro-logical presentation in a case of an 8-week-old boy who exhibited an altered mental status and dystonia while the other case of a 10-month-old girl exhibited seizures.

This study revealed that there was no significant correlation between tramadol blood levels and seizures. Petramfar and Haghghi (2010) showed that tramadol provoked seizures not only in supratherapeutic doses but also in the

recommended therapeutic doses even as low as 50 mg. As a matter of fact, in that study, more than 80% of patients had a seizure after ingesting recommended doses of tramadol. Shadnia et al. (2008) in a case report described 2 generalized seizures in a non-epileptic 17-year-old patient following oral intake of 200–250 mg of tramadol.

On the contrary, Talaie et al. (2009) reported that the potential of tramadol to cause seizures seems to be dose-dependent. At clinically relevant doses, tramadol has been shown to slightly suppress the severity of seizures but at relatively higher doses, tramadol has paradoxically been proven to induce seizures.

In this study most of tramadol overdose patients could not be properly recognized due to the inaccessibility to a confident history; the patients being either drowsy, comatose or in a state of seizures with postictal confusion and disorientation/ or coma. Another factor suggesting the poor orientation of dose to the precipitation of seizures seems the co-ingested drugs (like Benzodiazepine) that would abort seizures. The third reason that seems to justify the non-correlation of dose and seizures is the sensitization of the individual to the norepinephrine reuptake inhibition that would provide inter-individual variability.

In the current study, examining the pupils revealed that most of cases were normal sized reactive. Ahmad and Reza (2010) noticed that unlike other opioid overdoses, some patients who were referred with mydriasis are more prone to seizures. Mydriasis, therefore, may be useful as a predictive factor for seizures in tramadol overdose. Also, serotonin syndrome can also cause mydriasis (Radomski et al., 2000). However, Shadnia et al. (2008) observed miosis in 16.8% and mydriasis in 4.4%.

This study revealed that there was no significant correlation between tramadol blood levels and either of serum glucose, AST, ALT, urea or creatinine. This is in accordance with Kung and Ng (2007) who reported normal liver and renal function tests. In contrary to Gheshlaghi et al. (2009) who reported that BUN/Creatinine, blood sodium and potassium, creatinine phosphor-kinase, AST, and ALT were within the normal range. In addition, Daubin et al. (2007) revealed normal laboratory parameters mentioned above except for high serum creatinine, glucose, and creatine kinase. However, in controversy to this study, Ahmad and Reza (2010) showed higher mean levels for serum creatinine and glucose but lower mean levels for serum urea and creatine kinase-total.

In this study, the mean of plasma tramadol levels was  $614 \pm 223$  ng/ml. Lewis et al. (2010) reported that whole blood tramadol concentrations obtained from 11 cases ranged from 81-2720 ng/mL.

## Conclusion

Adult males were more commonly affected by tramadol poisoning. The only route of intoxication was orally and addiction represents the most common mode of poisoning. Cannabis was the most common co-ingested drugs. Seizures were the most common CNS manifestations followed by drowsiness and no correlation between blood levels of tramadol and occurrence of seizures. Normal sized reactive pupils were highly found followed by miotic reactive pupils. No change was found in laboratory parameters with tramadol poisoning and no correlation between the laboratory parameters and blood levels of tramadol.

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## دراسة الصورة الإكلينيكية والمعملية للتسمم الحاد بعقار (الترامادول) في محافظة دمياط

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لقد لوحظ زيادة في معدل حدوث النوبات التشنجية ومضاعفات الجهاز التنفسي نتيجة التسمم بعقار الترامادول مع أشخاص تعاطوا العقار لأول مرة. لذا كان الهدف من هذا الدراسة هو دراسة الصورة الإكلينيكية والفحوصات المعملية الناتجة عن التسمم الحاد بعقار الترامادول وتحديد العلاقة بين مستوى الترامادول في الدم ومظاهر التسمم الإكلينيكية والفحوصات المعملية. تم عمل هذه الدراسة في الفترة من يناير الى ديسمبر ٢٠١٧. وقد شملت هذه الدراسة ١٠٠ حالة (٨٠ ذكور و ٢٠ اناث) ترددت على وحدة السموم بمستشفى الأزهر الجامعي بدمياط الجديدة. تم اخذ الموافقة من الحالات عند وصولهم الى المستشفى. تم اخذ عينة بول و ١٠ مللى دم للكشف عن الترامادول باستخدام "جهاز الاستشراب السائلي الرفيع عالي الأداة" وعينه اخرى تم حفظها في درجة حرارة -٨ درجة مئوية لعمل التحاليل المعملية الروتينية في الدم. كما تم عمل الفحص الإكلينيكي لهم. وقد أسفرت نتائج هذه الدراسة على أن معدل حدوث النوبات الصرعية كان بنسبة ٤٦% نتيجة التسمم بالترامادول، لا يوجد علاقة بين حدوث النوبات الصرعية وجرعة الترامادول فقد تحدثت مع الجرعات العلاجية، كما أنه لا توجد علاقة بين حدوث النوبات الصرعية ومظاهر التسمم الأخرى وبين مستوى الترامادول في الدم، وأن الحشيش كان اكثر المواد تعاطيا مع الترامادول وان الذكور اكثر عرضه للتسمم بالترامادول. وبناءاً على ما سبق نوصى بأنه لا بد من تضافر جهود كافة مؤسسات الدولة ووسائل الاعلام وكافة افراد المجتمع لمواجهة المخاطر الطارئة التي تحدث نتيجة التسمم الحاد بهذا العقار (الترامادول) مع توضيح هذه المخاطر وذلك للحد من تناوله، ولا بد من إيضاح حقيقة هامة وهي ان حدوث التشنجات الناتجة من تناول عقار الترامادول والتي قد تسبب الوفاة قد تحدث مع تناول أول قرص من الترامادول و مزيد من الدراسات المستقبلية حول ارتباط حدوث التشنجات الناتجة عن التسمم بعقار (الترامادول) بالجنس لإيضاح الأسباب المسؤولة عن ذلك.