ASSESSMENT OF TRAMADOL BLOOD CONCENTRATION IN CASES OF ACUTE TRAMADOL OVERDOSE

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ABSTRACT

Background: Tramadol is a synthetic analgesic drug that has been used for acute and chronic pain. It has a potential risk of addiction and overdoses due to its common illegal abuse. The analgesic effect of tramadol is dose dependent and in medical literature no study evaluates its blood concentrations in overdose and its relation to outcome. **Objective**: the aim of this study was to evaluate the relation between tramadol blood Level and the different severity grade and outcome in tramadol overdose. **Methodology**: this study included patients admitted to poisoning control centre Ain Shams University hospitals with tramadol overdose from January 2016 to July 2016. All patients subjected to demographic, clinical, and laboratory evaluation including estimation of tramadol blood level at admission. **Results**: 91patients included in the study, 67% were due to drug abuse, 39 % of the patients had minor manifestation, 21% had moderate manifestation and 32% had major manifestation. The mortality rate was 8% and all died patients were male and due to abuse. Statistical analysis revealed no relation between tramadol blood Level and severity grade or mortality. **Conclusion**: the study concluded that tramadol blood level is not a marker for evaluation of severity or the outcome of tramadol overdose and no role for assessment of tramadol blood Level in tramadol overdose.

Keywords: tramadol, coma, mortality, abuse, seizure, ventilation.

INTRODUCTION

Tramadol is a central synthetic morphine-like drug free of several side effects of opioid. Tramadol has less effect on μ- and κ-opioid receptors and inhibits the reuptake of nor-adrenaline and serotonin **(Grond and Sablotzki, 2004).** It has stimulating effect on dopamine receptors and suppressing effect on the gamma amino butyric acid (GABA) release **(Rehni et al., 2008).** It is completely absorbed after oral administration and the therapeutic blood concentration achieved in 2 - 3 hours. It is then metabolized by the cytochrome P450 enzymes to O-desmethyl tramadol (M1) and N-desmethyl tramadol (M2) **(Ardakani et al., 2008).** Its half- live is 6.3 hours, the plasma protein binding is 20%, Sixty percent is excreted in urine as metabolites and the rest is eliminated as unchanged drug. The therapeutic blood levels range from 0.1–0.8 mg/L, toxic level ranges between 1–2mg/L and the fatal concentration is higher than 2mg/L **(Clarot et al., 2003).** Tolerance to tramadol can occur after prolonged use, and this result in increasing the dose to get desired effect **(Pothiawala**

and Ponampalam, 211).The clinical symptoms and signs of the overdose include vomiting, tachycardia, confusion, convulsion, coma and respiratory failure **(Ryan and Isbister, 2015)**. Hepatic and renal abnormalities have been reported during tramadol chronic use **(Atici et al., 2005).** The tramadol related Seizure could be recurrent and not respond to naloxone while it can be precipitated by its usage **(Raffa and Stone, 2008).**The seizures usually controlled by benzodiazepines which by several researches suggest that it increase the morbidity and mortality **(Clarot et al., 2003).**Also tramadol intoxication can present with picture of serotonin syndrome which include neuromuscular irritability, agitation, tachycardia, hyperpyrexia and confusion due to the Serotonin-Norepinephrine reuptake suppression**(Chandrasekaran et al., 2007).**The control of tramadol on pain depend on the ingested dose and the relation between the blood level and analgesic effect varies between individuals **(Clarot et al., 2003).** In clinical research, less record had studied the tramadol blood level in tramadol overdose and its relation to mortality or different grades of severity **(Taghaddosinejad et al., 2011).**

OBJECTIVE

The objective of this study was to evaluate the relation between tramadol blood Level and the different severity grade and outcome in tramadol overdose.

PATIENTS AND METHODS

This was a prospective observational study. Patients whom admitted to the Poisoning Control Centre Ain Shams University hospitals (PCCA), Cairo, Egypt with a history of tramadol overdose from January 2016 to July 2016 were included in the study. Data such as patients' age, sex, delay time until presentation to the hospital, ingested dose and cause of intoxication were collected from the patients or relative. Clinical data such as vomiting, conscious level, seizure, apnea, therapeutic interventions e.g. (naloxone and mechanical ventilation) and patients' outcome were recorded. Laboratory finding including, renal function tests, liver function tests, arterial blood gas and tramadol blood level were collected at admission. Grade of severity were coded as: (No effect, Minor, Moderate, Major, and Death) according to the American Association of Poison Centres National Poison Data System (NPDS) outcome criteria **(Bronstein et al., 2008)**. The exclusion criteria in this study were patients with no effect, history of head trauma, epilepsy, hypoglycaemia, hypo- and hypernatremia, hypocalcaemia, liver impairment, renal impairment, or toxicity from other drugs. One milliliter (ml) of arterial blood collected in heparinized syringe for blood gases analysis using (Gem Premier Blood Gas Analyser). Five ml venous blood samples were taken in heparinized tubes on admission and centrifugation at 4000 × g for 10 min, plasma samples were obtained and analysis of liver enzymes, urea and createnine were done using (COBAS C311 automated chem. Analyzer, ROCH), and rest of the sample were stored at −70 °C for later analysis of tramadol blood level by using Gas chromatography (GC master (Dani company), with flame ionization detector, capillary column Econo-cap 100% Dimethyl-polysioxane 10m x 0.53mm I.D.x 0,25mm film thickness. Oven: 220 °C ramp to 245 °C /min. then ramp to 275 °C by 3 °C/min. Injector: 295 °C, Detector: 300 °C flame ionization detector carrier gas: Helium. Flow pressure: 2 psi. It is a one-step extraction procedure with dichloromethane at pH 11.15. The recoveries of tramadol and meperidine (internal standard) were greater than 88%. Standard curves from 100 to 10,000 ng/mL concentration were used to estimate plasma tramadol levels. The specificity of this assay was checked with two major metabolites of tramadol (M: O-demethyltramadol; M: N-demethyltramadol) **(Shung et al., 1999).**

Statistical analyses:

The data were expressed as mean ± standard deviation for continuous variables and as frequency and percentage for categorical variables. We used the Student's t-test for statistical analyses of continuous variables, Chi-square test was used for comparison of categorical values and Anova test was used for comparison of more than two continuous variables. P equal to or less than 0.05 was considered statistically significant. We used SPSS software (version 13, SPSS Inc., Chicago, IL, USA).

RESULTS

Ninety-one patients met our inclusion criteria and included in the study. The mean ages of the patients were 28±12 years old, 77% were male, and the mean time delay between ingestion and admission to hospital was 6.3 ± 3.3 hours. The mean ingested dose of tramadol was 1.4 ± 0.7gm and the cause of intoxication was abuse in 71% of the patients, suicidal in 21%and accidental in 8%of the patients. The most clinical findings were coma (54%), apnea (33%), seizure (18%), agitation (15%) and vomiting (10%). As regarded the Laboratory findings, respiratory acidosis was found in (33%) of the cases, metabolic acidosis in (24%), renal impairment in (6%), liver impairment in (6%) and the mean tramadol blood level was 1.8±2.5 mg/L. As regarded the emergency management did for the patients, 34% received naloxone and 20% received mechanical ventilation (Table 1). Thirty nine percent of the patients had minor manifestation, 21% had moderate manifestation, 32% had major manifestation and 8% died (Table 2). Statistical analysis revealed no significant differences between the minor, moderate, major and death groups as regard age, sex, mode of poisoning, dose of tramadol ingested and the tramadol blood level, while there were significant increases in delay time to presentation to hospital in the minor group (Table 3). All died patients were male and was due to abuse. Also, Statistical analysis revealed no significant differences between the survived and non-survived patients as regard age, sex, mode of poisoning, delay time to presentation to hospital, dose of tramadol ingested, tramadol blood level and number of cases received naloxone (Table 4). Moreover (Table 5) revealed no significant differences between the seizure and non-seizure patients as regard age, sex, mode of poisoning, delay time to presentation to hospital, dose of tramadol ingested and tramadol blood level. While there was significant increase in number of cases received naloxone in the non-seizure group

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Table (1): Demographic, Clinical and Laboratory findings in 91 tramadol-intoxicated Patients

Variables	**Mean**	**Standard deviation**
age / years	28	±12
delay / hours	6.3	±3.3
dose of tramadol ingested /gm	1.4	±0.7
Tramadol blood Level/ mg/L	1.8	±2.5
	No=91	%
Sex		
Male	70	77%
Female	21	23%
Mode of poisoning		
Accidental	7	8%
Suicide	19	21%
Abuse	65	71%
Clinical Signs		
Coma	49	54%
Apnea	30	33%
Seizure	16	18%
Agitation	14	15%
Vomiting	9	10%
Laboratory		
Respiratory acidosis	30	33%
Metabolic acidosis	22	24%
Abnormal liver function test	5	6%
Abnormal renal function test	5	6%
Treatment		
Naloxone/ no of cases received	31	34%
Mechanical ventilation / no of cases received	18	20%

Table (2): Grade of severity of the 91 tramadol- intoxicated patients

Grade of severity	**Minor**	**Moderate**	**Major**	**Death**	**Total**
Number	36	19	29	7	91
Percent	39%	21%	32%	8 %	100 %

Table (3): Statistical analysis of the different grading groups of the tramadol intoxicated patients.

Variables	Minor No =36	Moderate No =19	Major No = 29	Death No = 7	f-ratio	P
Age / years	29±12	26±15	26±10	31±11	0.7	0.6
Delay time / hours	7.6±3.9	5.2±1.8	5.6±3	5±1.9	3.8	0.01*
Dose of tramadol ingested / gm	1.4±0.6	1.2±0.8	1.5±0.7	1.8±0.6	1.1	0.3
Tramadol blood Level / mg/L	1.7±2.2	2±1.9	1.3±1.7	2.8±2.8	1.2	0.3
Sex	**no (%)**	**no (%)**	**no (%)**	**no (%)**	**Chi-square X2**	**P**
Male	26(72%)	14(74%)	23(79%)	7(100%)	2.7	0.4
Female	10(27%)	5(26%)	6(21%)	0		
Mode of poisoning						
accidental	2(6%)	3(16%)	2(7%)	0	6	0.4
Suicide	10(28%)	4(21%)	5(17%)	0		
Abuse	24(66%)	12(63%)	22(76%)	7(100%)		

Table (4): Statistical analysis of the survived and non-survived tramadol intoxicated patients.

Variables	Survived No = 84	Non survived No = 7	T	P
Age / years	28±12	31±11	0.7	0.5
Delay time/ hours	6.4 ±3.3	5±2	1.1	0.3
Dose of tramadol ingested/ gm	1.3±0.7	1.8±0.6	1.8	0.08
Tramadol blood Level / mg/L	1.6±1.9	2.8±2.8	1.5	0.1
Sex	**no (%)**	**no (%)**	**Chi-square X2**	**P**
Male	63(75%)	7(100%)	2.3	0.1
Female	21(25%)	0		
Mode of poisoning				
Accidental	7(8%)	0	3	0.2
Suicide	19(23%)	0		
Abuse	58(69%)	7(100%)		
Naloxone/ no of cases received	29(35%)	2 (29%)	0.1	0.7

Table (5): Statistical analysis of the seizure and non-seizure tramadol intoxicated patients.

Variables	Seizure No = 16	Non seizure No = 75	T	P
Age / years	28±11	28±12	0.2	0.8
Delay time / hours	5±2.6	6.5±3.4	1.7	0.09
Dose of tramadol ingested/ gm	1.4±0.7	1.3±0.7	0.4	0.7
Tramadol blood Level / mg/L	1.3±1.9	1.8±2.1	0.9	0.4
Sex	**No (%)**	**No (%)**	**Chi-square X2**	**P**
male	13(81%)	57(76%)	0.2	0.7
female	3(19%)	18(24%)		
Mode of poisoning				
Accidental	1(6%)	6(8%)	0.1	0.9
Suicide	3(19%)	16(21%)		
Abuse	12(75%)	53(71%)		
Naloxone/ no of cases received	2 (13%)	29(39%)	4.02	0.04*

DISCUSSION

The abuse of tramadol has increased in the last years; with increase in the number of people admitted to emergency departments with tramadol toxicity has been observed **(Afshari et al., 2008)**. Due to its opioid effects, it is abused by opium addict which is a problem of general concern worldwide. Tramadol overdose is reported as 4.4% (1042/23680) of all poisoning cases presented to PCCA during year 2016.

Our study revealed that 77% of the patients were male with mean age was 28±12 years, mean time delay until arrival to hospital was 6.3±3.3 hours and the mean ingested dose of tramadol was 1.4±0.7gm. Most of overdoses were due to abuse 71%, while suicidal represent 21%, accidental was 8% of the patients and the mortality rate was (8%). Similarly, **Taghaddosinejad et al. (2011)** in their study of 135 patients with tramadol overdose found that 83 % of the patients were men and the mean age was 22.9 years; the mean reported dose was 1.5 ±1.4 gm and the delay time was 5.2 ±3.1 hours. Moreover **Shadnia et al. (2012)** in their study of 100 patients with tramadol overdose found that 82% were male, with mean age was 23.3 ± 7.7 years, the mean ingested dose was 1.2 ± 0.9 gm, the average delay time was 4.7 ± 3.3 hours. While in contrast they found that 93% were suicidal intent, and did not have any deaths in their study. Also,**Rahimi et al. (2014)** studied 144 patients with tramadol overdose and found higher mean ingested dose 2 ± 2.3 gm and higher rate of suicide 68.8%, while abuse was 31.2% and there was no mortality among the patients. Also in contrast **Ryan and Isbister (2015)** found in their study of 71 patients with acute tramadol poisoning that median age was higher 41 years with increasing percent of female 61% and there were no deaths.

Clinically our results revealed that 54% of the patients presented with coma, 33% had

apnea, 18 % had seizure, 15 % had agitation, 10% had vomiting and 34% of the patients received naloxone. Similarly, **Shadnia et al. (2012)** in their study of 100 patients with tramadol overdose found that 33% of their patients had coma. Moreover, **Henry** (**2009)** found that Symptoms reported with tramadol overdose were: lethargy 30%, vomiting 14%, agitation 10%, while they found lesser presentation with 8% had seizures, 5% had disturbed conscious level, and 2% had respiratory failure. Other results reported by **Marquardt et al. (2005)** where they found that the main symptoms observed were nausea and vomiting21%, seizures 14%, agitation 5%, coma 2% and apnea in 0.5%. Also **Ryan and Isbister (2015)** found that seizures occurred in 11% of cases and Naloxone was given to 13% of the patients. In contrast **Taghaddosinejad et al. (2011)** in their study of 135 patients with tramadol overdose found higher percent of seizures (30%) and lesser percent of coma (3.5%).

Our results revealed that (39%) had minor manifestation, (21%) had moderate manifestation, (32%) had major manifestation and (8%) died. Nearly similar results obtained by **Marquardt et al. (2005)** in their study of 190 patients with tramadol overdose where they found 36.3% had no effect, 43.7% had minor effects, 19.5% had moderate effects and in contrast 0.5% had major effects and no deaths.

Our statistical analysis revealed no significant differences between different grade of severity, survived and non-survived patients and patients whom had seizures and those whom don't had seizures as regard age, sex, mode of poisoning, delay time to presentation to hospital, dose of tramadol ingested and tramadol blood level. While there was significant increase in number of cases received naloxone in the non-seizure group and this can be attributed to that we usually give naloxone to patients with bradypnea and respiratory acidosis to save them from mechanical ventilation and not giving for patients with agitation or history of seizure and this result denies the accusations that naloxone induced seizures in tramadol overdose. Moreover, the delay time was significantly increased in minor grade patients which could be explained by that the time of ingestion informed was not completely reliable and these patients had minor symptoms and were reluctant in presentation to hospital. Similarly, **Taghaddosinejad et al. (2011)** in their study of 135 patients with tramadol overdose found that no significant difference between males and females as regard age, tramadol dose, time elapsed between ingestion and arrival, seizure, and coma.Also, they found weak correlation between convulsions and tramadol plasma level and not correlated to delay time, age, sex, history of abuse, and coma. Also, **Behzadnia (2018)** found that high tramadol blood level is not necessarily associated with convulsions. Moreover **Shadnia et al. (2008)** found that seizures were not depending on dose and all patients with tramadol overdosed should be considered to be at risk. In contrast **Ahmadimanesh et al. (2018)** found that tramadol blood levels were significantly related to the amount of ingested tramadol and there were reverse correlations between tramadol blood level of and delay time, also they found that Seizure was significantly related to the tramadol blood Level, and by increasing level, the risk of seizure increased significantly.

Our results revealed that the mean tramadol blood Level in died patients were 2.8±2.8mg/L which was higher than the survived patients but not statistically significant. Similarly, **Loughrey et al. (2003)** reported that mortality due tramadol overdose occurred at a blood tramadol level of 3.7 mg/L. Moreover, lower results were reported by **Baselt (2004)** where he found 6 deaths occurs at tramadol blood level of average 1.1mg/L. In contrast **Musshoff and Madea (2001)** reported a fatal case of tramadol

intoxication with a blood tramadol concentration of 9.6mg/L. So, we can conclude that there was inter-subject variability in the metabolism of tramadol with variation in some individual and some patients might developcertain degree of tolerance to the drug after chronic ingestion. Therefore, it was difficult to find a relation between the plasma concentrations and the grade of severity or outcomes.

CONCLUSION

Tramadol blood level is not a marker for evaluation of severity or the outcome of tramadol overdose and no role for assessment of tramadol blood Level in tramadol overdose.

RECOMMENDATION

•Tramadol is fatal in acute overdose and must be written cautiously by treating doctors especially in abusers

• Consider any tramadol overdose as an emergency situation irrespective to the tramadol blood level

• Re-assessment of the role of naloxone in tramadol overdose and put guidelines for its usage in certain circumstances in tramadol overdose.

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الملخص العربي

تقييم تركيز الترامادول بالدم فى حالات الجرعة الزائدة من الترامادول

الترامادول هو دواء مسكن صناعي يستخدم لعلاج الالم الحاد والمزمن.وهو لديه خطر محتمل من الإدمان والجرعات الزائدة بسبب تعاطية الشائع و غير المشروع .التأثير المسكن للترامادول يعتمد على الجرعة و لا تقيم أي دراسة طبية تركيز الترامادول بالدم في الجرعة الزائدة وعلاقتها بالنتائج .**الهدف** :كان الهدف من هذه الدراسة هو تقييم العلاقة بين مستوى الترامادول فى الدم ودرجات الشدة المختلفة والنتائج في الجرعة الزائدة من الترامادول .**المنهجية** :شملت هذه الدراسة مرضى تم قبولهم في مركزالسموم بمستشفيات جامعة عين شمس نتيجة جرعة زائدة من الترامادول من يناير 2016 إلى يوليو 2016جميع المرضى خضعوا للتقييم الديموغرافي والسريري والمختبري بما في ذلك تقدير مستوى الترامادول فى الدم عند الدخول .**النتائج** :اشتملت الدراسة على 91 مريضا ، 67٪ كانوا بسبب تعاطي المخدرات ، 39٪ من المرضى كان لديهم درجة شدة بسيطة، 21٪ كان لديهم درجة شدة متوسطة و 32٪ كان لديهم درجة شدة كبيرة .وكان معدل الوفيات 8٪ وجميع المرضى الذين ماتوا كانوا من الذكور بسبب الادمان .كشف التحليل الإحصائي عدم وجود علاقة بين مستوى الترامادول بالدم ودرجة الشدة أو الوفيات .**الخلاصة** :خلصت الدراسة إلى أن مستوى الترامادول بالدم ليس علامة لتقييم الشدة أو النتائج لتناول جرعة زائدة من الترامادول وليس هناك دور لتقييم مستوى الترامادول بالدم في الجرعة الزائدة من الترامادول.