Incidence and Factors Influencing Acute Tramadol Toxicity-Inducing Seizures in Damietta Governorate

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ABSTRACT

An increased rate of seizures due to tramadol poisoning has been observed. However, the actual incidence and related factors are not well-studied. The purpose of this work was to investigate the relationship between the incidence of seizures and plasma tramadol level in patients with tramadol-inducing seizures. In addition, we reported the pattern of tramadol overdoses in selected patients. The study was conducted from 1st January 2017 to 28th February 2018. It involved 102 cases who recruited from toxicological units of Al-Azhar University Hospital (New Damietta). After free informed consent to contribute in this study and within one hour after arrival to a toxicological unit, 10 mL of blood were separated and the serum was used for extraction of tramadol residues by using a high-performance liquid chromatography (HPLC) and other blood samples were stored at – 8°C for the following assays to all patients; fasting blood sugar, hemoglobin levels, serum urea, serum creatinine and liver enzymes. Then clinical examination to all patients included vital signs with a special attention to central nervous system (CNS) manifestations, gastrointestinal (GIT) manifestation. The frequency of seizures (27.4%) with acute tramadol poisoning in humans is not dose dependent and seizures occurred with therapeutic doses and there were no relation between blood tramadol level and seizures. We concluded that risk of seizures increase in cases took other drugs with tramadol as alcohol and heroin. The frequency of seizures is not dose dependent; seizures occurred with therapeutic doses.

Introduction

Tramadol is an opioid used for treating moderate to severe pains. It has been lawfully used for pain management since 1980 in some countries and become the most prescribed opioid worldwide (Elmorsy et al., 2015).

Tramadol is acting through weak binding to the μ-opioid receptor and also inhibits reuptake of monoamines such as serotonin and norepinephrine (Shadnia et al., 2008).

Tramadol is addictive and may be abused by the young adults. Nausea, vomiting, central nervous system depression, tachycardia, cardio-respiratory arrest, and seizures are among the side effects of tramadol poisoning. However, there are reports indicated the probability of seizures induction even with therapeutic doses of this drug (Derakhshanfar et al., 2012).

An increased rate of seizures due to tramadol toxicity has been observed. The prevalence of tramadol overdose-inducing seizures was reported to be 15% to 35% (Kroenke et al., 2009).

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The accurate mechanism of tramadol in induction of seizures is not completely understood. Studies indicated that in high concentrations tramadol exerts an inhibitory action on gamma-amino butyric acid (GABA) receptors. In addition, GABA receptor inhibition induced by tramadol can be secondary to its opioid receptor agonist activity, and continuing this agonist activity on opioid receptor has been confirmed to induction of seizures because of inhibition of GABA pathways (Rehni et al., 2008).

The risk of tramadol induced seizures may increase in patients receiving other drugs like tricyclic antidepressants, phenothiazines, and selective serotonin reuptake inhibitors (Kroenke et al., 2009).

Tramadol-related seizures would be controlled well by diazepam, but not responsive to naloxone, and moreover these seizures can be precipitated by management with naloxone, at tramadol overdoses (Raffa and Stone, 2008).

The present study was designed to investigate the relationship between the incidence of seizures and plasma tramadol concentrations in patients with tramadol overdoses-inducing seizures. In addition, we were reporting the pattern of tramadol overdoses in patients admitted in toxicology units, in Al-Azhar University Hospital (New Damietta) from 1st January 2017 to 28th February 2018.

Patients and Methods

This is an observational cross-sectional study that included 102 cases admitted to Poisoning Treatment Center at Al-Azhar University hospital (New Damietta) in the period from 1st January 2017 to 28th February 2018.

Patients' Inclusion Criteria:

Definite history of tramadol intake, patients without previous history of epilepsy, both sexes (male and female), and multi-drugs of abuse intoxicated patients (tramadol and other substances of abuse toxicity).

Patients' Exclusion Criteria:

Patients without history of tramadol intake and negative laboratory parameter for qualitative detection of tramadol, any patient with history of chronic liver disease, renal disease and patients with pseudo-seizures.

Consent:

An informed written consent was taken from every patient before history taking and sample collection.

Clinical Data:

a) History:

Dose of tramadol, delay time (time passed between ingestion and admission to hospital), route of exposure, manner of toxicity and co-ingested substance were recorded. Socio-demographic Data: age, sex, occupation, special habits (including smoking), past history of seizures were recorded. The duration of hospital stay and outcome (whether survival or death) were recorded.

b) Physical examination on admission:

1. General examination: pulse, respiratory rate, blood pressure, temperature and pupillary examination (normal, dilated, constricted, and reactive to light reflex or not).

2. Systemic Examination: neuropsychiatric, cardiovascular, respiratory and gastro-intestinal examination, the degree of consciousness was estimated according to Glasgow Coma Scale.

Investigations:

a) Routine investigations:

Complete blood picture (CBC), arterial blood gas (ABG) liver and kidney functions analysis, random blood sugar determination.

b) Specific investigations:

1. Tramadol detection in urine:

Ten ml urine were collected and stored it in the deep freeze at -20°C till immunoassay analysis. Microgenic Automated Clinical Analyzer MGC 240 Tokyo Boeki machinery LTD (Japan) for immunoanalysis.

2. Tramadol detection in plasma:

Drugs and reagents:

Tramadol (1.0 mg/ 2ml/ ampoule), potassium monobase phosphate, sodium hydroxide, phosphoric acid, ethyl acetate (analytical grade) and acetonitrile (HPLC grade), were purchased from Elctrosient Company, Cairo, Egypt.

A sample of 10 ml blood was collected in Ethylenediaminetetraacetic acid (EDTA) tube. The samples were centrifuged for 5 minutes at 3500 rpm, and plasma was isolated and stored at -20˚C awaiting HPLC analysis. A high-performance liquid chromatographic method using UV detection was used for determination of tramadol concentration in human plasma according to (Chandra et al., 2012).

HPLC chromatographic condition:

A high-performance liquid chromatographic system equipped with a pump was used; the auto sampler was used. The eluent was detected with Agilent 1200 UV detector at a wavelength of 225 nm. Hypersil column with (4.6 x 250mm), particle size 5 µm was employed. The mobile phase consisted of 0.05 M KH_2PO_4 aqueous solution (adjusted to pH 3.5 with H_3PO_4) and acetonitrile in a ratio of 80:20 (v/v). The flow-rate was set at 1.0 ml/min., and injection vol. 50 µl.

Steps:

The pH of plasma samples was adjusted to 12 with 0.1 M NaOH, followed by thorough vortexing. Six milliliters of organic solvents chloroform were added for extraction. The mixture was then shaked and centrifuged at 3000 rpm (1000 g) for 15 min. The supernatant was transferred to a clean glass tube and the organic solvent was evaporated with nitrogen gas at room temperature until the tube was dry. The extract was reconstituted with 200 ml of the mobile phase, and vortexed again for several seconds till totally dissolved. One hundred microliters of this solution was injected into the HPLC for analysis (Chandra et al., 2012).

Calibration:

The concentration of the unknown tramadol concentrations in plasma samples was calculated using this formula CS/CA= (Peak Area) S/ (Peak Area) A, CS: concentration of the standard, CA: concentration of the unknown (Peak Area) S: peak area of the standard (Peak

Area) A: peak area of the unknown (Kucuk and Kadioglu, 2005).

Treatment:

Regarding the lines of treatment, the following were recorded:

1. Gastric decontamination by emesis and gastric lavage and charcoal administration.
2. Supportive treatment with oxygen and fluid administration.
3. Specific treatment with diazepam if seizures occurred and Narcan administration as an antidote, endotracheal intubation and mechanical ventilation if comatose.

Statistical Analysis

The collected data was statistically analyzed using SPSS software computer package version 22. For quantitative data, all the values were expressed as mean ± standard deviation (SD). P values < 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 (X2) was used (Campbel and Machin, 2009).

Results

Social and Demographic Data:

Age ranged from 5 to 55 years with a mean of 26.24 ± 9.50 years in cases without seizures and in cases with seizures it ranged from 5 to 30 years with a mean of 20.78 ± 5.9 years. Regarding sex in cases without seizures 62 of cases (83.8%) were males and 12 cases (6.2%) were females and in cases with seizures 26 cases (92.9%) were males and 2 cases (7.1%) were females.

Regarding occupation in studied cases, drivers were the most common 30 cases (29.4%), carpenters were 14 cases (13.7%), students were 14 cases (13.7%), mechanics were 12 cases (11.8%), housewives were 8 cases (7.8%), farmers were 6 cases (5.9%), painters were 4 cases (3.9%), metal makers were 4 cases (3.9%), chefs were 2 cases (2.0%), upholsters were 2 cases (2.0%), fish sellers were 2 cases (2.0%), and no-workers were in 4 cases (3.9%) (Table 1).

The route of toxicity was oral in all cases. As regard mode of toxicity in cases without seizures it was addiction in 56 cases (75.7%), then accidental in 10 cases (13.5%) and suicidal in 8 cases (10.8%) also in cases with seizures it was addiction 24 cases (85.7%), then accidental 2 cases (7.1%) and suicidal 2 cases (7.1%) (Table 2).

Table (1): Occupation in studied cases (n = 102).

	Cases with seizures (n=28)	Cases without seizures (n=74)	χ^2	p value
Drivers	8(28.6%)	22(29.7%)	12.7	0.31
Painters	4(14.3%)	4(3.9%)		
Carpenters	4(14.3%)	10(13.5%)		
Mechanics	4(14.3%)	8(10.8%)		
Students	4(14.3%)	10(13.5%)		
Steel makers	0(0.0%)	4(5.4%)		
Chefs	2(7.1%)	2(2.0%)		
Upholsters	0(0.0%)	2(2.7%)		
Farmers	0(0.0%)	6(8.1%)		
Fish sellers	0(0.0%)	2(2.7%)		
Housewives	0(0.0%)	8(10.8%)		
Unemployment	2(7.1%)	2(2.7%)		

χ^2= chi square test. n: number

The mean dose of tramadol in studied cases without seizures was 481.08 ± 292.3 mg (100 – 1500 mg) and the mean dose of tramadol in cases with seizures was 685.7 ± 318.3 mg (300-1500 mg) (Table 2).

The route of toxicity in all cases was oral route. In cases with seizures there were 26 cases were smoking cigarettes and 2 cases were not smoking but in cases without seizures there were 60 cases were smoking cigarettes and 14 cases were not smoking. Regarding delay time in cases without seizures it was 3.7 hours (2-5 hours), in cases with seizures was 4.0 hours (2-5 hours) (Table 2).

Table (2): Mode of toxicity, dose of tramadol, delay time of studied cases (n = 102).

		Cases with seizures (n= 28)	Cases without seizures (n= 74)	Test	p value
Mode of toxicity	Addiction (n=80)	24 (85.7%)	56 (75.7%)	0.620#	0.733
	Accidental (n=12)	2 (7.1%)	10 (13.5%)		
	Suicidal (n=10)	2 (7.1%)	8 (10.8%)		
Dose of tramadol	Mean ± SD	685.7 ± 318.3	481.08 ± 292.3	2.17$	0.034
	Minimum	300.00	100.00		
	Maximum	1500.00	1500.00		
Delay time	Mean ± SD	4.0 ±1.07	3.7 ±0.85	1.00$	0.32
	Minimum	2.00	2.00		
	Maximum	5.00	5.00		

= chi square test. $=t test, n:number, SD: standard deviation.

As regard co-ingested drugs in cases without seizures cannabis was co-ingested in 20 cases (27.0%), sildenafile in 8 cases (10.8%) paracetamol in 6 cases (8.1%), NSAIDS in 6 cases (8.1%), heroine in 6 cases (8.1%) and propranolol in 2 cases (2.7%) but in cases with seizures cannabis was co-ingested in 6 cases (21.4%), alcohol in 6 cases (21.4%), heroine in 4 cases (14.3%), methanol in 4 cases (14.3%), paracetamol in 2 cases (7.1%), NSAIDS in 2 cases (7.1%) (Table 3).

Table (3): Co-ingested substances in studied cases (n= 102)**.**

	Cases with seizures (n=28)	**Cases without seizures (n=74)**	χ^2	**p value**
Cannabis	6(21.4%)	20(27.0%)	17.152	0.029
Alcohol	6(21.4%)	0(0.0%)		
Methanol	4(14.3%)	0(0.0%)		
Heroine	4(14.3%)	6(8.1%)		
Paracetamol	2(7.1%)	6(8.1%)		
NSAIDS	2(7.1%)	6(8.1%)		
Sildenafile	0(0.0%)	8(10.8%)		
Propranolol	0(0.0%)	2(2.7%)		
No	4(14.3%)	26(35.1%)		

χ^2= chi square test, n: number.

Clinical Data:

As regard clinical presentation of studied cases there were 28 cases (27.4%) presented with seizures, 24 cases (23.5%) with coma, 2 cases (2%) with lethargy, 10 cases (9.8%) with drawsiness, 26 cases (25.5%) with dyspnea, 2 cases with blurring of vision (2%), 8 cases with vomiting (7.8%) and 2 cases with anxiety (2%) (Table 4).

Table (4): Clinical presentation of studied cases (n =102).

Clinical presentation	**n**	**%**
Seizures	28	27.4%
Dyspnea	26	25.5%
Coma	24	23.5%
Drowsiness	10	9.8%
Vomiting	8	7.8%
Lethargy	2	2.0%
Blurring of vision	2	2.0%
Anxiety	2	2.0%

n: number.

The mean pulse rate in studied cases was 94.1 ± 30.9 beats per minute (40-60 bpm). The mean systolic blood pressure in studied cases was 110.1 ± 20.3 mm/Hg (70-150 mm/Hg). The mean diastolic blood pressure in studied cases was 69.6± 15.3 mm/Hg (40-100 mm/Hg). The mean respiratory rate in studied cases was 13.3 breath/minute (6-30 breath/minutes).

As regard examination of pupil in cases without seizures it was pin pointed pupil in 30 cases (40.5%), dilated responsive pupil in 2 cases (2.7%), constricted pupil in 4 cases (5.4%), dilated unresponsive in 2 cases (2.7%) and normal pupil in 18 cases (48.6%) but in cases with seizures it was pin pointed pupil in 20 cases (71.4%), dilated responsive pupil in 4 cases (13.3%) and normal pupil in 4 cases (14.3%).

Regarding degree of coma in cases without seizures, it was estimated by Glasgow Coma Scale and there were 6 cases (8.1%) with a scale < 8 GCS, another 22 cases (29.7%) with a scale from 9 to 11 GCS and 46 cases (62.2%) with a scale from 12 to 15 GCS.

Investigation:

The mean hemoglobin concentration was 10.7 g/dl with minimum 8 g/dl and maximum 13 g/dl. There were metabolic acidosis in 14 cases (18.9%), respiratory acidosis in 10 cases (13.5%) and respiratory alkalosis in 4 cases (5.4%), meanwhile normal ABG in 46 cases (62.2%) but in cases with seizures there were metabolic acidosis in 18 cases (64.3%), respiratory acidosis 4 cases (14.3%) and respiratory alkalosis in 2 cases (7.1%) while normal ABG only in 4 cases (14.3%). Liver and kidney functions tests were normal in all cases. Tramadol detection in urine in all cases was positive.

The mean *O*-desmethyltramadol plasma level in cases with seizures was 891.4 ng/ml (250-1900 ng/ml) and in cases without seizures, it was 447.9ng/ml (120-1700 ng/ml) (Table 5).

Table (5): Plasma tramadol levels in studied cases (n=102).

		Cases with seizures (n=28)	Cases without seizures (n=74)	Test	p value
Plasma *O*-desmethyltramadol levels	Mean	891.4	447.9	37.6 $	0.57
	Minimum	250	120		
	Maximum	1900	1700		
Arterial blood gases	Metabolic acidosis	18 (64.3%)	14 (18.9%)	11.46 #	0.09
	Respiratory acidosis	4 (14.3%)	10 (13.5%)		
	Respiratory alkalosis	2 (7.1%)	4 (5.4%)		
	Normal	4 (14.3%)	46 (62.2%)		

$= t test. #= chi square test, n: number.

Treatment:

Decontamination was done in the form of gastric lavage and activated charcoal in 30 cases (29.4%) and emesis plus activated charcoal was done in 20 cases (19.6%). supportive treatment in the form of oxygen and IV fluids were given to 56 cases (54.9%) and antibiotic was given to 56 cases (54.9%) and Na bicarbonate was given 46 cases (45.09%) with metabolic acidosis and respiratory acidosis. Specific treatment in the form of diazepam was given to 28 cases (27.5%). Antidote narcan was given to 36 cases (35.3%) and narcan and ethanol were given to 4 cases (3.9%). The emergency measures in the form of endotracheal intubation and mechanical ventilation were done in 14 cases (13.7%).

Time staying in hospital and outcome:

The mean time staying in hospital of cases without seizures was 2.67 days, minimum time staying was one day and the maximum time staying was 9 days but in cases with seizures the mean time staying was 6.21 days, minimum time staying was 2 days and the maximum time staying was 12 days. As regard outcome of cases without seizures recovery was the most common in 70 cases (94.6%), death in 4 cases (5.4%) but in cases with seizures recovery was occurred in 24 cases (85.7%) and death in 4 cases (14.3%) (Table 6).

Table (6): Duration of stay in hospital and outcome in studied cases (n=102).

		Cases with seizures (n=28)	Cases without seizures (n=74)	Test	p value
Time staying in hospital	Minimum	2.00	1.00	4.58$	< 0.001
	Maximum	12.00	9.00		
	Mean ± SD	6.21 ± 2.88	2.67 ± 2.28		
Outcome	Recovery (n=94)	24 (85.7%)	70 (94.6%)	1.10 #	0.292
	Died (n=8)	4 (14.3%)	4 (5.4%)		

$= t test. #= chi square test, n: number, SD: standard deviation.

Discussion

Regarding age distribution ranged from 5 years to 55 years with mean age for patients was 24.74 ± 9.50 years. This result is in agreement with Petramfar and Haghighi (2010), who reported that mean age of the patients was 26.7± 6.9 years. This age represents age of youth who is one of the most vulnerable stages of life.

In this study male patients were more common (88 patients, 86.3%) than female patients (14 patients, 13.7%). This result is in agreement with Petramfar and Haghighi (2010) who had reported (102 male patients, 96.2%) and (4 female patients, 3.8%).

As regard occupation in the present study, drivers were the most common representing 29.4%. Tramadol use may also happen among professional drivers who drive long distances that is related to fatigue and muscle aches (United States National Highway Traffic Safety Administration Report, 2007). Hence, tramadol with its properties as a pain reliever and a mood elevating drug became their drug of choice.

In the present study, the mode of poisoning addiction was the most common as it was reported in 80 patients (78.1%), then accidental in 12 patients (11.8%) and suicidal in 10 patients (9.8%). These findings are in agreement with Talaie et al. (2009) who reported that tramadol intake had been shown to be due to drug abuse, therapeutic purpose, intentional overdose and as a replacement for opioid agents. However, in controversy to this study, many authors showed that the reasons for the exposures included mostly suicide attempts (Marquardt et al., 2005).

As regard delay time in all patients the mean delay time was 3.86 hours (2-5 hours). This finding is in agreement with Shadnia et al. (2008) who noted that the time elabsed between ingestion and admission ranged from 0.5 to 24 hours with average of 6.12 hours. This can be attributed to the fact that the peak plasma concentration following orally administered tramadol is reached in 1-3 hours for regular release preparations and in 5 hours for sustained release products (Ardakani and Rouini, 2007).

The mean dose of tramadol in patients without seizures was 481.08mg (100- 1500mg). It is known that the maximum therapeutic dose per day shouldn't exceed 400 mg/day (Michelon et al, 2016). Tramadol mean dose is higher between patients referred to poisoning units reaching 2186 mg/day (Talaie et al., 2009). Regarding dose of tramadol the mean dose ingested in patients with acute tramadol inducing seizures was 685.7 mg (300-1500mg). Jovanović-Cupić et al. (2006) reported that the mean dose of tramadol was 765 mg/day in 31 tramadol abusers with seizures.

As regard co-ingested drugs in cases without seizures cannabis was co-ingested in 20 cases (27.0%), sildenafile in 8 cases (10.8%) paracetamol in 6 cases (8.1%), NSAIDS in 6 cases (8.1%), heroine in 6 cases (8.1%) and propranolol in 2 cases (2.7%). This may be explained as well by WHO which reported that cannabis abusers are found in all age groups and social status (Yassaa et al., 2009). On the contrary, with the finding of Shadnia et al. (2008) who revealed that benzodiazepines were the most common co-ingested drugs.

In patients with seizures cannabis was co-ingested in 6 patients (25%), alcohol in 6 patients (25%), heroin in 4 patients (16.7%), methanol in 4 patients (16.7%), paracetamol in 2 patient (8.3%), NSAIDS in 2 patient (8.3%). Helander et al. (2014) found that seizures which happened in 26% of patients were taking marijuana and tramadol among 123 young drug abusers.

Regarding respiratory rate, 40 patients (39.21%) presented with bradypnea, 54 patients (52.94%) were normal and 8 patients (7.84 %) were tachypnea. skin temperature was normal in all cases. This goes hand in hand with Persson and Sjöberg (2008) who showed that respiratory depression was observed at high doses and frequently with ethanol. Marquardt et al. (2005) observed respiratory depression in 0.5% and 2% of cases respectively.

Pupil examination in cases with seizures was pin point pupils in 20 cases (71.4%), dilated responsive pupils in 4 cases (13.3%) and normal pupils in 4 cases (14.3%). Examination of the pupils by Tashakori and Afshari (2010) revealed that 32% of patients were presented with miosis, 56% with midsize and 12% with mydriasis.

Seizures were in 28 cases (27.4%), coma in 24 cases (23.5%), agitation in 4 cases (3.9%) and drowsiness in 8 cases (7.8%) and this on the contrary with Ahmad and Reza, (2010) showed

that 87% of cases were comatose and 15% presented with seizures.

The mean *O*-desmethyltramadol plasma level in cases without seizures was 447.9 ng/ml (120-1700 ng/ml). This agrees with Abd Elwahab (2012) who reported that the mean of tramadol level in plasma for cases was 614 ± 223 ng/ml and not in agreement with (Taghaddosinejad et al., 2011) mean blood tramadol concentration was 3.843 (3.715 ± 269 ng/mL).

Arterial blood gases (ABG) of patients in cases without seizures were metabolic acidosis in 14 patients (18.9%), respiratory acidosis in 10 patients (13.5%), respiratory alkalosis in 4 patients (5.4%) and normal ABG in 46 patients (62.2%). Respiratory acidosis can be explained by Hoffman (2006) who recognized that opioid agonists decrease ventilation by diminishing the sensitivity of the medullary chemoreceptors to hypercapnia, as well as the loss of hypercarbic stimulation; opioids also depress the ventilatory response to hypoxia. The combined loss of hypercarbic and hypoxic drive leaves virtually no stimulus to breathe and apnea might follow.

In this study cases with acute tramadol poisoning antidote narcan was given to 60 patients (58.8%). This is in agreement with Tashakori and Afshari (2010) they showed that 24% of patients with acute tramadol poisoning were managed with narcan. As well Marquardt et al. (2005) observed administration of narcan in 5.8% of patients.

The mean time staying in studied patients was 3.6 days (1-12 days). This unlike Shadnia et al. (2008) admission period that ranged between 1 and 21 days with average of 2.75 days.

Regarding outcome, the recovery rate in cases without seizures was 70 patients (94.6%), death was 4 patients (5.4%). Tashakori and Afshari (2010) reported that mortality rates was (1.75%) and (0.7%) respectively.

Conclusion

Adult young males were the most frequently affected with tramadol intoxication than females. Drivers were the most commonly affected with tramadol poisoning. Seizures increases in cases took other substance with tramadol as alcohol, heroin, cannabis and methanol. The frequency of seizures with acute tramadol poisoning in humans is not dose dependent. Seizures were occurred with therapeutic doses and there is no relation between blood tramadol level and seizures.

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معدل الانتشار والعوامل المؤثرة في احداث النوبات التشنجية نتيجة التسمم الحاد بعقار الترامادول فى محافظة دمياط

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لقد لوحظ ازدياد معدل حدوث نوبات تشنجية نتيجة التسمم بعقار الترامادول ولكن العوامل المؤثرة لم تتم دراستها بشكل جيد. الهدف من العمل: هو تحديد العلاقة بين حدوث نوبات تشنجية ومستوى الترامادول بالبلازما فى الحالات التى تعانى من نوبات تشنجية نتيجة التسمم الحاد بالترامادول، بالاضافة لذلك وصف الحالات التى تأتى الى وحدة السموم نتيجة التسمم الحاد بالترامادول. تم عمل هذه الدراسة فى الفترة من ١ يناير ٢٠١٧ الى ٢٨ فبراير ٢٠١٨. تشمل الدراسة ١٠٢ حالة من الذين أتو الى وحدة السموم بمستشفى الازهر الجامعى بدمياط الجديدة. تم اخذ الاذن من الحالات الذين أتوا الى المستشفى فى خلال ساعة من وصولهم الى المستشفى . تم سحب ١٠ مللى دم ثم تم فصلهم وتم اخذ مصل الدم ليتم استخراج بقايا الترامادول بواسطة جهاز" الفصل الكروماتوجرافى السائلي عالي الجودة". عينات الدم الاخرى تم حفظها عند درجة حرارة - ٨ درجة مئوية: تم عمل تحليل سكر عشوائى بالدم، وقياس مستوى الكرياتينين بالدم وعمل غازات بالدم، وتم قياس مستوى انزيمات الكبد بالدم، ونسبة الهيمجلوبين بالدم. تم عمل فحص طبى لكل الحالات التى أتت الى المستشفى من علامات حيوية وفحص الجهاز العصبى المركزى والجهاز الهضمى. وكانت النتيجة ان معدل حدوث النوبات التشنجية كان بنسبة ٢٧,٤% نتيجة التسمم بالترامادول، ولا يوجد علاقة بين حدوث النوبات التشنجية وجرعة الترامادول، أومستوى الترامادول بالدم. تم استنتاج ان معدل حدوث النوبات التشنجية يزداد نتيجة تعاطى الترامادول مع الكحول او الحشيش أو الهيروين، و ان حدوث النوبات التشنجية لا يعتمد على جرعة الترامادول.