PATIENTS WITH TRAMADOL INDUCED SEIZURES PRESENTED TO MANSOURA UNIVERSITY EMERGENCY HOSPITAL

BY

Adel M. El-Mansoury; Abdel Aziz A. Ghanem; Mohammad H. Zaghloul;* Osama A. Shabka; Manar Adel

Forensic Medicine & Clinical Toxicology and

Clinical Pathology Departments Faculty of Medicine Mansoura University.*

ABSTRACT

A case control study was conducted among 66 patients presented to Mansoura University Emergency Hospital following tramadol administration to investigate the nature of tramadol induced seizures, its correlation with ingested dose and the relation of drugs of abuse co-administration to seizures occurrence. Patients were divided into two groups: group I were patients presented with seizures and group II were patients presented without seizures. Among studied patients, there wasno significant statistical difference between the two groups in age and sex. Patients were presented with tonic clonic seizures within 30 minutes up to 10 hours post ingestion. The most frequent dose thatcould induce seizures was 500-1000 mg with the lowest reported dose inducing seizures was 225 mg. In addition, patients presented with history of administration of toxic dose (2250 mg) were presented without seizures. On correlating the dose with seizures occurrence, there was moderate positive correlation (p=0.01, r=0.343). The co-administrated drugs of abuse showed that opiates and cannabis co-administration with tramadol increases the risk of tramadol induced seizures three time. In conclusion, although there is positive correlation between seizures occurrence and the ingested dose, tramadol induced seizures is not dose dependent and it can occur on ingestion of therapeutic dose and persons with ingestion of toxic dose can be presented without seizures.

INTRODUCTION

Tramadol hydrochloride, a synthetic opioid, is commonly used as pain reliever. It exerts its analgesic effect mainly through mu (μ) opioid receptor stimulation and increasing noradrenaline and serotonin (5-HT) levels at the nerve endings. Tramadol exerts its monoamine effect through inhibiting both noradrenaline and 5-HT neuronal reuptake, facilitating 5-HT release and stimulating some 5-HT receptors (WHO-2014). Another reported mechanisms of action of tramadol in-

clude weak agonist effect to delta (δ) and kappa (κ) receptors; muscarinic receptor antagonist; opioid-dependent γ aminobuteric acid (GABA) release inhibition; N-methyl-D-aspartate (NMDA) receptor antagonist and blocking transient receptor potential (TRP) cation channels specially TRPV (vanilloid) or TRPA (ankyrin) subtypes (Trescot et al., 2008; Miyanoet al., 2015).

Tramadol is metabolized in the liver through cytochrome P-450 (CYP) 2D6 (CYP2D6), 2B6 (CYP2B6) and 3A4 (CYP3A4) producing O-desmethyltramadol (M1) (ODMT) and N-desmethyltramadol (M2) (Ardakani and Rouini, 2007). In comparison with tramadol, the M1 and M2 metabolites are more (400-fold) and less (0.2-fold) potent μ opioid receptor agonists respectively. While tramadol itself possesses more 5-HT and norepinephrine re-uptake blocking activity. So, the wide variability in the pharmacokinetic and pharmacodynamic properties of tramadol, and hence the wide variability in toxic manifestations of tramadol can partly be ascribed to CYP polymorphism (GrondandSablotzki, 2004; Lynch and Price, 2007; Coller et al, 2012).

Within the first year of tramadol marketing, the Food and Drug Administration (FDA) had received 83 reports of seizures among patients using tramadol even in therapeutic doses and more than 200 reports in the second year (Afshari et al., 2011).

The exact mechanism of tramadol induced seizures remains unclear. Although initially it was thought previously that they are related to 5-HT reuptake inhibition, there is an increasing evidence that it is related to its μ receptor agonist effect. Rehni et al. (2008) found that tramadol induced seizures occur mainly via μ receptors mediated inhibition of GABA inhibitory pathway in mice. In addition, Rehni et al. (2010) explained tramadol-induced seizures in mice via μ receptor mediated histamine receptors (H1) activation. Also, Fujimoto et al. (2015) confirmed the anticonvulsant effect of 5-HT in tramadol induced seizures and reported that rats with low 5-HT level in the brain were predisposed to tramadol-induced seizures.

The aim of the current work was to describe the nature of seizures among patients presented to Mansoura University Emergency Hospital following tramadol administration, its correlation to the ingested dose and the role of drugs of abuse co-administration in its potentiation.

SUBJECTS AND METHODS

Study design:

The study was a case control one among 66 patients presented to the toxi-

cology unit in Mansoura University Emergency Hospital with history of tramadol administration. Based on the investigated disorder, patients were selected and divided into two groups; group I : 33 non-epileptic patients presented to the hospital with seizures or history of seizures within 24 hours after tramadol administration and group II: 33 non-epileptic patients presented to the hospital without seizures or any history of seizures within 24 hours after tramadol administration.

Sample size:

The sample size was calculated by epi-info$^{T.M}$ software program version 7.1.0.6 based on study power 90 and two sided confidence level 99%.

Ethical aspects:

Faculty of medicine, Mansoura University Institutional Review board approved the ethical aspects of the study as a prospective case series with tramadol overdose.

Informed consent:

All participating patients were requested to sign an informed valid consent form indicating their approval to use their clinical data for this research. The consent form contains information regarding the purpose of the study, procedures as well as benefits and confidentiality of the results.

Methods:

For each patient the following was performed:

History: Carful history taking including:

- Demographic data: age, sex.
- Route of tramadol administration; administrated dose; time elapsed since ingestion; history of tramadol addiction and its duration; history of other illicit drug abuse and any other co-ingestion.
- Characters of seizures: type of seizures, interval between tramadol ingestion and seizures and number of seizure attacks.
- Past history of tramadol induced seizures.

Laboratory investigation:

Five ml urine collected on dry polypropylene tube for drugs of abuse testing: tramadol, opiates, benzodiazepines, cannabis (THC), barbiturates and ethanol using MGC 240 autoanalyser in Mansoura Clinical Toxicology Laboratory, Forensic Medicine and Clinical Toxicology Department, Faculty of Medicine, Mansoura University.

Inclusion criteria: Persons above 21 years old.

Exclusion criteria:

- Hepatic patients.
- Renal patients.

• Pregnant female.

• History of administration of CYP2D6 inhibitors: ajmalicine, amitriptyline, amesergide, aprindine, budipine, bufuralol, chloroquine, chlorpromazine, cimetidine, cisthiothixene, citalopram, clomipramine, clozepine, desmethylimipramine, diphenhydramin, flecainide, fluoxamine, fluoxetine, halofantrine, haloperidol, levomepromazine, methadone, meclobemide, olanzapine, oxprenolol, paroxetine, perazine, perphenazine, propofenone, propranolol, quinidine, quinine, qanitidine, reboxetine, resperidone, sertraline, terbinafine, terfenadine, thioridazine, ticlopidine, venlafaxine and yohimbine (Abraham and Adithan, 2001).

• History of administration of drugs reported to potentiate tramadol induced seizures e.g. tricyclic antidepressants, selective serotonin reuptake inhibitors, antipsychotics and lithium (Pothiawala and Ponampalam, 2011).

• Metabolic causes of seizures: alkalosis, hypoglycemia, hyperosmolality (hypernatremia, nonketotic hyperosmolar diabetes mellitus), hyponatremia, hypocalcemia and hypercalcemia (O'Brien, 1998).

Statistical analysis:

Appropriate parametric and non-parametric tests were used for analysis of data using SPSS statistical package version 20 (SPSS, Inc., Chicago, IL, USA).

RESULTS

Group I patients' age ranged between 21-45 years with their mean age ± SD is 31.03 ± 7.47. Patients included were 31 (94%) males and two (6%) females. All patients had history of tonic clonic seizures after tramadol administration before arrival to the hospital. Onset of seizures following tramadol ingestion was highly variable ranging from 30 min up to 10 hours post ingestion with median value 120 min. Number of seizures attacks following tramadol ingestion was single attack in 16 patients (48.5%), two attacks in 14 patients (42.4%), three attacks in one patient(3%) and six attacks in two patients (6.1%). Past history of seizures was positive in 11 patients(33.4%) but all of them were following tramadol ingestion. While in 22 patients (66.6%), it was their first time to experience seizures. Oral route was the only route of exposure to tramadol among all patients. The ingested dose was ranging from 225 mg to 2250 mg with median value 900 mg.

Group II patients' age ranged between 21 - 46 years with their mean age ± SD is 32.69 ± 7.42 years. Patients included were 33 (100 %) males. Oral route was the only route of exposure to tramadol among all patients. The ingested tramadol dose was ranging between (225 – 2250 mg) with median value 450 mg.

Regarding the age and sex difference between studied groups, no significant statistical difference was estimated (p = 0.367, 0.151 respectively). The age and sex distribution in both groups is illustrated in table 1. On correlating the ingested dose with seizures occurrence, moderate positive correlation was detected (p = 0.01 and r= 0.343) (Table 2).

Table 3 and figure 1 show positive cases for drugs of abuse co-administration with tramadol (opiates, benzodiazepines, THC, barbiturates and ethanol) among studied patients. On statistical analysis of the difference between both groups, no significant difference was detected in all drugs. On risk estimation, opiate and cannabis co-administration with tramadol increased the risk of tramadol induced seizures by 3 times (as expressed by odd ratio 3 at 95% confidence interval).

Table (1) : Age and sex distribution among studied patients (n=66) and statistical comparison between studied groups.

		Group I (n=33)	**Group II (n=33)**
Age mean ±SD (minimum-maximum) (years)		31.03±7.47 (21-45)	32.69±7.42 (21-46)
Age groups (years)	**21-30**	17 (51.5%)	15 (45.5%)
	31-40	11 (33.3%)	13 (39.3%)
	41-50	5 (15.2%)	5 (15.2%)
P value		0.367	
Male n (%)		31 (93.9%)	33 (100%)
Female n (%)		2 (6.1%)	0
X^2 **P value**		2.063 0.15	

n: number, p-value is insignificant when > 0.05. Group I (non-epileptic patients presented with seizures following tramadol administration); group II (patients presented without seizures following tramadol administration).

Table (2) : Correlation between ingested dose and seizures occurrence among patients presented following tramadol administration (n=66).

	Ingested dose (mg)	Number of cases (%)	Ingested dose median (minimum-maximum) (mg)	P value	r
Patients presented with seizures (n= 33)	225-500	8 (24.2%)	900 225-2250	0.01*	0.343
	500-1000	13 (39.4%)			
	1000-1500	5 (15.2%)			
	1500-2000	3 (9.1%)			
	2000-2250	4 (12.1%)			
Patients presented without seizures (n=33)	225-500	20 (60.6%)	450 225-2250		
	500-1000	7 (21.2%)			
	1000-1500	2 (6.1%)			
	1500-2000	3 (9.1%)			
	2000-2250	1 (3%)			

n: number, p value ≤ 0.01 is considered significant ; r value: 0 = no relation; 1 = positive correlation; -1= negative correlation; * is significant.

Table (3) : Statistical analysis of difference between group I and II patients regarding drugs of abuse co-administration with tramadol and their risk for potentiation of tramadol induced seizures.

	Group I (n=33) (No & %)	Group II (n=33) (No & %)	p value	Odds ratio (OR)	Confidence interval (CI)[c]
Cannabis	5 (15.2%)	6 (18.2%)	0.74	0.83	0.28-2.46
Benzodiazepines	5 (15.2%)	5 (15.2%)	1	1	0.32-3.31
Cannabis +benzodiazepine	1 (3%)	2 (6.1%)	1	0.5	0. 5-5.25
Cannabis + opiates	3 (9.1)	1 (3%)	0.613	3*	0.33-27.38
benzodiazepine +alcohol	0	1 (3%)	1	-	-
Cannabis + opiates+ alcohol	0	1 (3%)	1	-	-
Cannabis + opiates+ benzodiazepine	2 (6.1%)	2 (6.1%)	1	1	0.15-6.68
Cannabis + opiates+ benzodiazepine + alcohol	1 (3%)	1 (3%)	1	1	0.07-15.33

n: number, p value > 0.05 is insignificant; Odds ratio is considered significant if >1; CI: 95% Confidence interval,* is significant finding. Group I (non-epileptic patients presented with seizures following tramadol administration); group II (patients presented without seizures following tramadol administration).

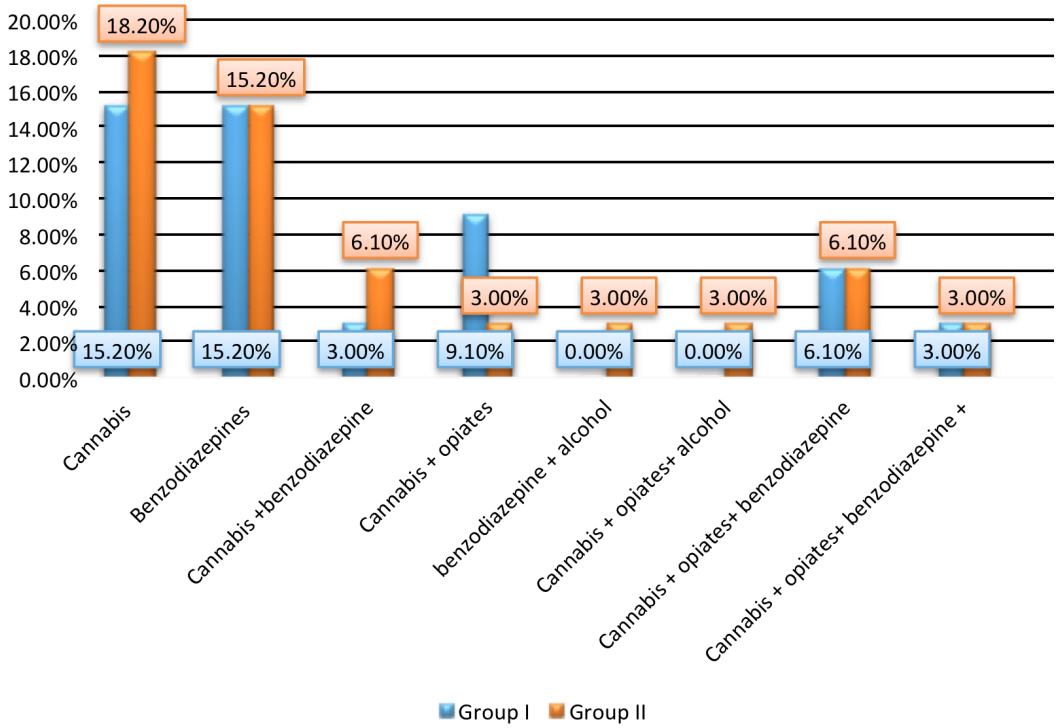

Fig. (1) : Distribution of positive cases of different drug abuse among groups I & II patients. Group I (non-epileptic patients presented with seizures following tramadol administration), group II (patients presented without seizures following tramadol administration).

DISCUSSION

The current work was conducted to investigate the nature of tramadol induced seizures among patients presented to Mansoura University Emergency hospital, its correlation to ingested dose and its relation to drugs of abuse co-administration with tramadol.

Regarding the age, no significant statistical difference between groups I and II patients was observed indicating that tramadol induced seizures is not age related. Age range in 51.5% of cases presented with seizures was 21-30 years old. This finding is similar to Taghaddosinejadet al.(2011)who reported that age range in 50 % of his cases presented with seizures was between 20-30 years. This age predominance can be explained by more consumption and abuse of tramadol in middle-aged persons.

Male predominance was seen among patients presented with tramadol induced seizures (94%) with no significant statistical difference between those presented with seizures and those who did not indicating that tramadol induced seizures are

not sex related. This is consistent with previous studies by Gasse et al. (2000) and Javanovic-cupic et al. (2006) who reported that tramadol induced seizures are more frequently observed in males. This male predominance can be explained by more consumption and abuse of tramadol in males than females.

Ingestion was the only route of tramadol intoxication in all presented patients. This is probably because tablets are widely available in Egyptian market with limited availability of ampoule form. This is consistent with an Iranian study by Taghaddosinejad et al. (2011)who reported that ingestion was the route of intoxication in 100% of their cases.

Interval between ingestion and seizures occurrence was ranging from 30 min to 10 hours with seizures occurring in the first six hours in 93.1% of patients and in 6.1% of them after six hours post ingestion. In accordance with these results, Asadi et al. (2015) and Taghaddosinejad et al. (2011) reported that seizures could occur up to six and 12 hours post ingestion respectively. This range was reported to be the double (up to 24 hours) by Talaie et al. (2009).

Among patients, 48.5% experienced only one attack, and 52.5% experienced more than one attack. This is not consistent with Epstein et al. (2006) and Taghaddosinejad et al. (2011) results in which mostly all patients suffered from only one seizure attack.

From all patients presented with tramadol induced seizures, 66.7% this was their first attack of tramadol-induced seizures and 33.3% had history of previous seizures attacks following tramadol ingestion. Taghaddosinejad et al. (2011) also reported history of previous attacks of tramadol induced seizures in 15% of his studied patients. Thus, past history of seizures especially following tramadol administration can be considered a risk factor for occurrence of seizure and prescribing tramadol for patients with previous history of tramadol poisoning should be performed cautiously.

The range of ingested dose in patients presented without seizures was the same as those presented with seizures (225 - 2250 mg) indicating that seizures can occur after both therapeutic (225mg) and toxic (2250 mg) dose ingestion. In addition, patients ingesting high similar doses can be presented without seizures.

The reported ingested dose in patients presented with seizures (225 - 2250 mg) was very close to that of Javanovic-Cupic et al. (2006) who reported that most cases experienced seizures following exposure to dose range 250-2500mg.

The most frequently observed ingested

dose inducing seizures was between 500-1000 mg (in 39.4% of patients) similar to the dose reported by Talaieet al. (2009). On the other hand, the most frequently observed one in patients presented without seizures was lower ranging between 225-500 mg in 60.6% of patients.

The lowest dose in the current research reported to induce seizure was 225 mg, which is considered a therapeutic dose. This dose is very close to the lowest reported dose in an Egyptian study by Enaba et al. (2015) which was 250 mg; Iranian studies by Taghaddosinejad et al., (2011); Shadnia et al. (2008) and Bozkurt et al. (2015) which were 200, 300, 350 mg respectively. Yet, the lowest reported dose able to induce seizure reported until now is by Asadi et al. (2015) in their Iranian study which was 50 mg.

On analyzing the correlation between the ingested dose and seizure occurrence, it comes out to be moderate positive one. This indicates that tramadol induced seizure is not fully dose dependent and there are factors other than the ingested dose can potentiate it. These findings are consistent with Talaie et al. (2009) and Asadi et al. (2015) who reported thatseizure caused by tramadol is not dose dependent.

However, Taghaddosinejad et al. (2011) reported different results. Among their study, seizures were reported following ingestion of therapeutic dose but it was more frequent in higher reported doses (up to 7000 mg) suggesting seizure as a dose-dependent characteristic of tramadol overdose. This difference between results may be attributed to different sample size and to statistical analysis method used. In their study, they just reported the significance of difference between both groups but they did not assess the strength of the correlation between ingested dose and seizure occurrence.

The wide variability in the onset of seizures following tramadol administration; the difference in the number of seizure attacks between studied patients and in the dose inducing seizures may be attributed to several factors e.g. inaccurate history given by the patients and their relatives, different formulations in the Egyptian market with possibility of different (+) and (-) enantiomers concentrations, difference in drug absorption; genetic difference in the type of metabolism which affect both tramadol and ODMT levels. In addition, associated drug of abuse ingestion may play a role in the nature of these seizures. These factors may also explain the difference between results of the current study and previous studies.

Immunoassay screening was performed among studied patients to analyze the effect of drugs of abuse (opiates, cannabis,

benzodiazepines, alcohol and barbiturates) co-administration with tramadol and whether they increase the risk of tramadol induced seizures or has no effect. On comparing their distribution between both groups, no significant statistical difference was detected. In addition, no increased risk was estimated with all drugs of abuse except for opiates and cannabis co-administration with tramadol that showed odds ratio 3 at 95% confidence interval. Thus, opiate and cannabis co-ingestion with tramadol was found to increase the risk of tramadol induced seizures by three times.

Jick et al. (1998) reported tramadol and opiates co administration and their ability to increase the risk of tramadol-induced seizures. Morphine alone has pro-convulsant effect through stimulation of Mu (μ) and Kappa (κ) receptors (Saboory et al., 2007). In addition, suggested mechanisms of tramadol induced seizures is μ receptors mediated suppression of GABA inhibitory pathway (Rehni et al., 2008) and μ receptor mediated histamine receptors (H1) activation (Rehni et al., 2010). Thus, synergistic effect of both drugs on μ receptors may explain the potentiation of seizures on co-administration.

Controversies are observed in the literature regarding cannabis-related seizures reported in the current work. Similar results were illustrated by Hoyte et al. (2012) and Hamerle et al. (2014) who reported cases presented with seizures following synthetic cannabis consumption. In contrast, seizures are not commonly seen with marijuana use and it is claimed to be protective against new-onset of seizures (Maa and Figi 2014; Devinsky et al., 2014).

There are variable limitations in the current work. Tramadol is a racemic mixture of (+) & (-) enantiomers each has different affinity for the μ receptors and different effects on serotonin and norepinephrine reuptake (GrondandSablotzki, 2004). Therefore, depending upon their ratio, they may affect seizure threshold differently. Thus, the tablets available in the Egyptian market must be analyzed to detect the ratio of different enantiomers in them.

In addition, tramadol absorption from gastrointestinal tract may be affected by many factors such as the nature of food in the stomach or the dose ingested which may affect the rate of absorption and the plasma tramadol level. Thus confirmation by laboratory analysis of tramadol level at the time of seizures must be performed.

Tramadol is metabolized in the liver producing active metabolites (M1), this metabolism is prone to genetic polymorphisms, and this polymorphism will affect peak blood levels of both the parent drug and the metabolites. The relation of difference in the type of metabolism between in-

dividuals, the plasma blood level of the active metabolite M1 and their relation to tramadol induced seizures need to be assessed by further studies.

CONCLUSION AND RECOMMENDATION

Tramadol induced seizures is not dose dependent and can occur in therapeutic dosage, thus initiation of tramadol therapy must be performed gradually. Opiates co-administration with tramadol increase the possibility of seizures, thus it is preferred not to prescribe both of these analgesics in combination.

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التشنجات الناتجة عن الترامادول في مرضي مستشفي الطوارئ جامعة المنصورة

المشتركون فى البحث

أ.د. عادل محمود المنصورى أ.د. عبد العزيز أبو الفتوح غانم
أ.د. محمد حسام الدين زغلول* د. أسامه شبكه
ط. منار عادل

من أقسام الطب الشرعي والسموم الإكلينيكية - الباثولوجيا الإكلينيكية*

كلية الطب - جامعة المنصورة - مصر.

يعد الترامادول (أحد المورفينات الصناعية) من أكثر المسكنات المشاع استخدامها ويقوم بإحداث بمفعوله الطبي عن طريق آلية مزدوجة، أولا: عن طريق تحفيز مستقبلات المور فينات ميو وثانيا: تثبيط إنهاء مفعول السيروتونين والنورأدرينالين في النهايات العصبية. ويهدف البحث إلى دراسة طبيعة التشنجات الناتجة من تناول الترامادول في مرضي مستشفى الطوارئ جامعة المنصورة ومدي علاقته بالجرعة المتناولة وعلاقة تناول الأدوية المخدرة الأخرى مع الترامادول بحدوثها.

تم تقسيم المرضي متناولي الترامادول إلي مجموعتين المجموعة الأولي المرضي الذين عانوا من تشنجات والمجموعة الثانية الذين لم يعانوا من التشنجات. وكان اغلب المرضي من الرجال مع عدم وجود فرق إحصائي في سن وجنس المرضي بين المجموعتين. هذه التشنجات حدثت بعد ٣٠ دقيقة حتى عشر ساعات بعد تناول الترامادول. معظم المرضي عانوا من تشنجات لمرة واحدة فقط. النسبة الأكبر من التشنجات حدثت عند تناول جرعة تتراوح بين ٥٠٠ - ١٠٠٠مليجرام و أصغر جرعة حدث معها التشنجات هي ٢٢٥ مجم. وعلي رغم من ان متوسط الجرعة في المجموعة الأولى مختلف إحصائيا عن المجموعة الثانية. فعند تحليل التناسب بين الجرعة المتناولة وحدوث التشنجات وجد أنها علاقة طردية متوسطة. وعند تحليل تأثير تناول الأدوية المخدرة الأخرى (المورفين، الحشيش، بنزوديازبين، حامض البابيتيورات والايثانول) مع الترامادول وجد أن تناول المورفين والحشيش مع الترامادول يزيد من فرصة حدوث التشنجات. ومن هذه النتائج يتم التأكيد ان التشنجات ليس لها علاقة بالجرعة المتناولة ويمكن ان تحدث عند تناول جرعة علاجية من الترامادول.