Severe Adverse Effects Associated with Tramadol Over Dose

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Abstract

Introduction:

Severe complications have been reported for tramadol overdose; however, few large-scale studies have investigated this issue. Therefore, this study aimed to explore the manifestations and complications associated with tramadol overdose in patients admitted to an intoxication referral center in northwestern Iran.

Methods and Materials:

Patients with tramadol overdose admitting to Sina Teaching-Hospital of Tabriz during 2013-2017 were included. For each patient the following data were collected: demographics, previous drug or medication overdose, being in period of quitting drugs, ingested dose of tramadol and co-ingestants, Glasgow Coma Scale (GCS) and clinical symptoms of patients at time of admission, and admission characteristics. Serotonin toxicity was diagnosed if the patients fulfilled the Hunter's criteria. Multiple logistic regression was performed seeking the associated variables with the incidence of severe effects of tramadol overdose.

Results:

512 cases of tramadol overdose were evaluated, of which 359 patients were included that had a median age of 41 (16-69) years old and median tramadol dose of 1500 (500-4000) mg. The most frequent complications associated with tramadol overdose were hypertension (38.4%), tachycardia (24.8%) and seizure (14.5%). No serotonin toxicity was detected in patients. Having a GCS <15, being poisoned with a tramadol dose of >1000 mg, being in the period of quitting drugs, being 30-49 years old and being a male were significantly related to the incidence of severe effects of tramadol overdose.

Conclusion: Although seizure was prevalent among Iranian patients with tramadol poisoning, serotonin toxicity and cardiac shock were rare findings.

Keywords: tramadol, serotonin toxicity, overdose, complications

Introduction:

Tramadol is one of the most widely used opioid drugs in medicine, mainly prescribed as a centrally acting analgesic for patients suffering moderate to severe pain (1). Tramadol is a synthetic 4-phenyl-piperidine analog of codeine and its opioid effects are due to interacting with μ receptors and affecting noradrenergic and serotonergic systems respectively through norepinephrine and serotonin reuptake inhibition in Central Nervous System (CNS) (2); Moreover, it results in GABAergic manifestations through increases the level of GABA's mediator in CNS (3). Tramadol poisoning causes some mild to severe impairments in CNS which clinically get revealed as dizziness, nausea, vomiting, facial anesthesia, agitation, headache, ataxia, seizure, impaired consciousness or coma (4). The impaired consciousness can lead to hospitalization in about 10 percent of tramadol poisoned patients and their longer stay in intensive care units (5). Previous studies assumed that the manifestations of tramadol poisoning are mostly due to the inhibitory effects of tramadol on reuptake of catecholamine and serotonin in CNS (6, 7). It has been postulated by some case reports that tramadol is also associated with serotonin toxicity in therapeutic range (8, 9). Serotonin toxicity is described as a series of conditions including neuromuscular excitement (e.g. hyperreflexia, clonus, and rigidity), autonomic effects (e.g. tremor, tachycardia, diaphoresis, flushing, and hyperthermia) and altered mental status (e.g. agitation, confusion, and anxiety) (10). Moreover, a cardiogenic shock has also been reported as a consequence of tramadol overdose (11). There is a large number of patients admitting with tramadol poisoning to toxicology unit of Sina Teaching-hospital, annually. Therefore, we aimed to investigate the first manifestations of patients with tramadol poisoning (coma, seizure, serotonin toxicity, etc.) admitted to the toxicology unit to shed some more light on its possible complications even the rare ones.

Materials and methods:

In this cross-sectional study, all patients with tramadol overdose (with doses greater than the maximum recommended dose of 400 mg) admitted to Sina Teaching-Hospital of Tabriz city, during January 2013 to December 2017 were included. Patient demographics, previous history of overdose with any drugs or medications, being in the period of quitting drugs and admission data including the Glasgow Coma Scale (GCS), ingested dose of tramadol and co-ingestants, clinical symptoms and special complications of patients (such as coma, seizure, serotonin toxicity,

cardiovascular events, respiratory depression and fatality) in time of admission, Length Of Stay (LOS), admitted wards or units, and administration of mechanical ventilation were recorded using a pre-prepared checklist. Data gathering was performed by trained staffs who were blinded to the results of the study. Tramadol ingestion and ingested dose were confirmed through the patient's medical history and the patient's information taken by EMS and emergency staffs. Informed consent was waived by each patient included.

Hunter criteria (12) which includes the conditions of clonus (inducible, spontaneous or ocular), agitation or diaphoresis, tremor, hyperreflexia, hypertonia, and temperature more than 38 ℃, was considered for serotonin toxicity diagnosis. Patients were excluded in case of uncertainty about tramadol ingestion and/or its dose, also if the dose of ingested tramadol was below 400 mg. The patients were also excluded if they had any previous convulsive disorder or concomitantly ingested other drugs with tramadol.

Data analysis was performed using SPSS version 22. Data were reported as means and standard deviation if they were normally distributed, otherwise, the median and range were reported. For normally distributed data, means were compared through Student t-test, otherwise, they were analyzed through the Mann – Whitney U test. For investigating the relationship of study variables with the incidence of severe effects of tramadol overdose, through computing adjusted Odds Ratio (ORs) and their 95% confidence intervals (an initial analysis presented a least value of 1.12 for ORs in investigating the relationship), a multiple logistic regression was performed on data from 214 samples who presented seizure, respiratory depression or tachycardia following tramadol overdose. For this mean, a backward elimination multiple logistic regression was occupied to find the set of best predictors of the incidence of severe effects of tramadol overdose including GCS score, consumed tramadol dosage, having a previous history of overdose with any drugs or medications, being in the period of quitting drugs, age and sex. P-values<0.05 considered to be as significant.

Results:

512 cases of tramadol overdose were admitted to the toxicology unit during the study period. 153 cases were excluded due to the following reasons: in 16 patients the dosage was unclear, in 25 dosages were below 400 mg. Moreover, 94 cases had concomitantly ingested other drugs including benzodiazepines, tricyclic –antidepressants (TCA), other opiates and etc. 18 patients

had previous unprovoked seizures. Finally, the remaining 359 patients were included in the study and their data were meticulously recorded. The majority of patients (91%) were males. Only 15 (2.9%) patients had a previous history of overdosing, while 162 (31.6%) were in the period of quitting drugs in time of admission. The median age of patients was 41 (16-69) years old. The median dose of tramadol was 1500 (500-4000) mg (Table 1). The seizure occurred in 52 patients (14.48%) while they had evidence for generalized tonic-clonic seizures. Seizures occurred in 80.1% of cases in less than 24 hours after tramadol intake (Table 2).

The median dose in patients presenting with seizure was 2700 (1300-4000) mg, which was significantly higher than the median dose in patients without a seizure (P-value=0.001). Seizures also occurred in 7 out of 25 patients whose doses were unclear. The ingestion to seizure time was unknown for 12 patients, however, the median time among the other 40 patients was 7.7 (0.5-19.5) hours.

In none of the patients, serotonin toxicity was detected according to Hunter criteria. GCS in 108 (30.1%) cases was below fifteen and in 23 (6.4%) patients, it was below nine; The median dose in patients with GCS of less than nine was 3100 (2850-3750) mg, that was significantly higher than that in patients with GCS > 9 (P-value=0.012). Ingestion of 1100 to 4000 mg of tramadol in 73 patients had resulted in respiratory depression; The median dose in these patients was 2750 (2350-4000) mg, which was also significantly higher than the median dose in patients without respiratory depression (P-value=0.034).

192 (53.48%) patients presented only nausea and/or vomiting. 101 (28.13%) patients presented cardiovascular complications, of which, 89 (4.79%) cases had tachycardia, 138 (38.44%) had mild hypertension and 19 (5.29%) had arrhythmia. However, no cardiogenic shock occurred among patients.

Seven patients were transferred to ICU due to respiratory depression. LOS in patients admitted to toxicology ward was 28 (12-136) hours, while the patients who were transferred to ICU had significantly longer LOS (P-value=0.01). Three patients died but the dose of tramadol in them was unknown. Naloxone was administered in 76 (21.16%) cases with a median dose of 4.2 (0.8–8.4) mg. Naloxone could help to recovery of 19 patients from respiratory depression and improved consciousness in 21 patients. However, no significant effect of naloxone was seen in 36 other patients. No seizure occurred in patients who received naloxone.

Based on the results of backward logistic regression model for variables associated with incidence of severe effects of tramadol overdose, having a GCS score of below 15 (especially below 9), being poisoned with a tramadol dosage of above 1000 mg (especially above 2000 mg), being in the period of quitting drugs, being 30-49 years old (especially 40-49) and being a male were significantly related to incidence of severe effects of tramadol overdose (All P<0.05). (table 3)

Discussion:

The most significant complications of tramadol overdose in our study were seizure, respiratory depression, and impaired consciousness. Regarding the rarity of fatal consequences of tramadol overdose in literature (13), we encountered a few cases of mortality but the dose of tramadol in those cases was unknown. Despite the previous reports of serotonin toxicity in tramadol overdose, no such case of tramadol poisoning was found in our study, this could be due to considering serotonin toxicity as a consequence of tramadol overdose - based on HUNTER's criteria - when tramadol was concomitantly ingested with other drugs especially TCA in those reports (15, 16); however, we had excluded such patients from our study to see the unadulterated effects of tramadol.

Other common side effects, including nausea and vomiting, as well as tachycardia and increased blood pressure (SBP> 160mmHg) occurred in the majority of patients which were assumed to be due to noradrenergic reuptake effects of tramadol (6). Some of the symptoms of tramadol poisoning were similar to that reported previously for other synthetic opioids which have oral forms including methadone and dextromethorphan. Gastrointestinal symptoms were comparable to those reported for methadone poisoning by one previous Iranian study; however, respiratory depression was lower in tramadol poisoning. Hypotension was reported in methadone poisoning but we did not encounter any in our study in tramadol-poisoned patients (14). The prevalence of tachycardia in our patients was similar to that in dextromethorphan-poisoned patients reported by a large study in the USA; however, the rate of hypertension in tramadol-poisoned patients in the current study was higher than that in dextromethorphan-poisoned patients (15).

Previous studies in Iran on tramadol poisoning also reported that majority of patients were male with a similar range of age to our study including the studies of Taghaddosinejad et al. (14 – 50

years), Goodarzi et al. (17–45 years), and Shadnia et al. (16–54 years) (16-18). Regarding the dose of tramadol to induce seizure, previous studies in Iran have reported similar doses. Talaie et al. reported that the mean dose of tramadol was 2186.00 (±280.80) (19). Also, Taghaddosinejad, et al. reported a similar dose of tramadol that was 1511 (±1353) (17). However, Petramfar et al. reported a very lower dose than our study (363.2 ± 303.1 mg) and Goodarzi et al. reported higher dose than our study (3248 ± 2515) (20, 21). The discrepancy could be due to ambiguity about the number of ingested tablets and their dosage under the psychological stress of confronting a tonic-clonic seizure in included patients in these studies. Also, some of the studies have not reported a clear policy for confirming the occurrence of seizure and its dosage (20, 21).

We observed that intentional overdose was the most common manner of tramadol poisoning. Young males were involved more frequently than females in tramadol overdose, which is in agreement with other studies in Iran and other countries (18,19,6). Being 30-49 years old (especially 40-49) was significantly related to the incidence of severe effects of tramadol overdose. People aged the 40s and 50s experience more persistent pains compared to younger ages due to physical weakness. High usage of tramadol in people of 40-50 years old may reflect their persuasive request for overcoming physical pains (1,2).

In the present study, the time of seizure varied from 30 min to 12 h post-ingestion; however, 80% of seizures occurred in the first 24 h after ingestion, which is in agreement with studies conducted by Marquardt et al. (24), Jovanović-Cupić et al. (26), and Talaie et al. (19). Single seizure was the most frequent one that happened in 84.3% of cases while multiple seizures were seen in 15.7% of cases, which is similar to other studies (27).

The results of our study demonstrated that the prevalence of seizure was 14.48 percent. This was similar to the finding of previous studies on tramadol overdose. A national pharmacovigilance study in France reported that seizure occurred in 6.7 percent of patients with tramadol poisoning (22). Correspondingly, other investigations reported similar results such as 8 percent by Spiller et al. (6), 11 percent by Ryan et al. (23), and 16 percent by Maraquaradt et al. (24).

Naloxone was effective for 39 out of 76 patients in recovering from respiratory depression or loss of consciousness. Although the seizurogenic effect of naloxone was reported previously (25), we did not encounter such complications among our patients.

The discrepancy of tramadol ingested doses causing seizure in our study showed that seizure was more unlikely to be dose-dependent. Consequently, the determination of a lower limit of

dangerous dose for tramadol resulting in seizure was not feasible. The study of Talaei et al. also demonstrated that seizure was not dose-dependent (19). However, some studies postulated that seizure seemed to be dose-dependent, however, these studies covered only a small number of tramadol patients with seizure (17, 22, 26). Therefore, it is conceivable that those patients who presented seizure with lower doses in our study may remain unnoticed in those studies. So that, future studies evaluating the complications of tramadol based on its serum concentrations can put more reliable information on it.

We acknowledge some limitations within our study. Although the researchers tried to report the most accurate ingested dose of tramadol, the possibility of imprecise claims was of particular concern. Moreover, excluding patients with concurrent use of other drugs with tramadol could impose the risk of missing some potential patients of tramadol overdose.

Conclusion:

We found some severe complications of tramadol overdose could be loss of concessions, seizure, and respiratory depression. However, cardiac shock and serotonin toxicity were rare findings. Also, our results demonstrated that seizure due to tramadol was not a dose-dependent complication occurring in a variety of doses. Naloxone was effective in most patients with some severe complications and did not induce seizure in any of them. Also, several variables including sex, age, GCS score, consumed tramadol dosage and quitting drugs were associated with the incidence of severe effects of tramadol overdose.

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Table 1 patients demographics and clinical finding	
Total number of patients	359
Gender (M/F)	9/350
Age, y Median Range	 41 16-69
Dose, mg Median range	 1500 500-4000
Seizures, *n* (%)	52 (14.48)
Seizure Tramadol Dose, mg Median range	 2700 1300-4000
No Seizure Tramadol Dose, mg Median range	 1450 500-3250
Serotonin Toxicity *n* (%)	0
Gastrointestinal Symptoms *n* (%)	192 (53.48)
ICU, *n* (%)	7 (1.94)
Respiratory depression *n* (%)	73 (18.48)
Intubated/Ventilated *n* (%)	11 (3.6)
LOS, h Median Range	 28 12-136
Max HR, bpm Median range	 100 88-140
Max Sys BP Median range	 135 100-160

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Table 2 Characteristics of seizures	
	n (%)
Generalized tonic-clonic seizures	52 (100)
single	41(78.8)
multiple	11(21.15)
Time of occurrence	
<24 hours after tramadol intake	42(80.1)
>24 hours after tramadol intake	10(19.2)

Table 3. The association between study variables and incidence of severe effects of tramadol over dose based on a backward logistic regression model				
	OR	Lower	Upper	P-Value
GCS Score				
<9	3.80	2.00	4.00	<0.001
9-15	2.00	0.15	2.45	0.024
>15	Referent	-	-	-
Tramadol Dosage				
>2000 mg	3.55	2.37	4.73	<0.001
1000-2000 mg	1.34	0.02	2.66	0.039
<1000 mg	Referent	-	-	-
A Quitting Addictive				
Yes	2.99	1.22	3.75	<0.001
No	Referent	-	-	-
Age				
30-39	2.23	1.26	3.38	0.013
40-49	3.23	1.17	4.28	<0.001
>65	Referent	-	-	-
Sex				
Male	4.21	2.09	5.48	<0.001
Female	Referent	-	-	-
OR: Odds ratio Lower: Lower Bound for 95% C.I. for OR Upper: Upper Bound for 95%C.I. for OR Logistic regression showed an acceptable amounts for model fit (LR chi2(4)= 4.463, P-value = 0.043)				

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