ORIGINAL ARTICLE

Acute tramadol poisoning and its clinical and laboratory findings

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Background: Tramadol is a centrally acting analgesic with opioid and nonopioid properties, which extensively used in the relief of mild to moderate pain. Tramadol poisoning is a common cause of acute pharmaceutical poisoning in Iran. There are a few studies about clinical and laboratory findings related to acute tramadol poisoning. Therefore, the aim of this study was to demonstrate the clinical and laboratory findings in tramadol acute poisoning cases. **Materials and Methods:** This was a retrospective descriptive study of patients with acute tramadol poisoning who referred to Loghman Hakim Hospital Poison Center during January to April 2012. Data such as patient's age, sex, time of ingestion, ingested dose, cause of poisoning, mean duration of hospitalization, patient's clinical presentations, laboratory findings, therapeutic measures, and patient's outcome have collected in a predesigned checklist. **Results:** A total of 144 patients including 111 men (77%) and 33 women (23%) with acute tramadol poisoning was included in this study. The mean ingested dose was 1971.2 mg (100-20000 mg). Seizure (47.91%) was the most frequent clinical symptom. Blood gas on admission showed pH (7.3 ± 0.1), PCO_2 (49.7 ± 8.6 mmHg) and HCO_3^- (24.1 ± 3.8 mEq/L), indicating pure acute respiratory acidosis may be occurred in tramadol-intoxicated patients. There were significant differences between tramadol-intoxicated cases with and without a seizure with regard to the time interval between ingestion and admission on hospital, ingested dose and PCO_2. **Conclusion:** Seizure and rise of PCO_2 were the most findings in this study.

Key words: Clinical manifestations, laboratory, poisoning, seizure, tramadol

How to cite this article: Rahimi HR, Soltaninejad K, Shadnia S. Acute tramadol poisoning and its clinical and laboratory findings. J Res Med Sci 2014;19:855-9.

INTRODUCTION

Tramadol is a synthetic, centrally acting analgesic with opioid and nonopioid properties.[1,2] Tramadol has low affinity for μ- and κ-opioid receptors and inhibits the reuptake of both nor-epinephrine and serotonin (5-hydroxytryptamine) neurotransmitters.[2] It stimulates the dopamine (D_2) receptors and also inhibits the gamma amino butyric acid release in central nervous system.[3,4] Furthermore, it has some N-methyl-D-aspartate antagonistic properties.[5,6]

It is available as parenteral and oral pharmaceutical dosage forms. Common therapeutic doses of tramadol are 50 mg orally and 100 mg with parenteral and rectal route of administration up to 400 mg/day.[2,7]

Tramadol has been included in Iran National Drug List since 2003.[8] Recently, tramadol abuse, misuse, and overdose have been increased in Iran.[9-11] The main adverse drug reactions of tramadol are nausea, dizziness, somnolence, drowsiness, increased sweating, vomiting, and dry mouth.[12,13] Seizure and apnea are the most important life-threatening clinical presentations of tramadol in therapeutic and toxic doses.[9,11,14] Liver and kidney dysfunctions have been reported during tramadol chronic use.[15] From this view, evaluation of laboratory findings including plasma electrolytes, kidney and liver function tests, and blood gas analysis have a critical role for patient monitoring.

As there are few studies about laboratory findings in tramadol acute poisoning, we evaluated the clinical and laboratory findings in acute tramadol-intoxicated cases and their role in the prediction of seizure.

METHODS

This was a retrospective study on patients with acute tramadol poisoning who referred to Loghman Hakim Hospital Poison Center, Tehran, Iran from January to April 2012. The exclusion criteria were co-ingestion, intoxication with unknown dose of tramadol, uncertainty about time of tramadol ingestion, onset of a seizure

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Received: 16-04-2014; **Revised:** 08-06-2014; **Accepted:** 11-09-2014

before admission on hospital, the past medical history of epilepsy and history of drug/substance abuse.

Data such as patients' age, sex, time of ingestion, ingested dose, cause of intoxication, respiratory rate, pulse rate, systolic and diastolic blood pressure, temperature, coma grade scale on admission time, and therapeutic interventions and patients' outcome were extracted from the medical records. Laboratory findings including blood sugar, blood urea nitrogen (BUN), creatinin (Cr), sodium (Na^+), potassium (K^+), liver function tests, cell blood count, and blood gas on admission time were retrieved from patients' medical records.

Statistical analyses

The data were expressed as mean ± standard deviation/standard error (SE) for continuous or discrete variables and as frequency and percentage for categorical variables. Chi-square test was used for statistical comparison of qualitative variables. We used the Student's *t*-test and Mann–Whitney U-test for statistical analyses of continuous variables with and without normal distribution, respectively. *P* =0.05 or less were considered statistically significant. Linear correlations between variables were assessed by Spearman and expressed as the Spearman correlation coefficient. Furthermore, we used binary logistic regression analysis to determine the predictor variables. We used SPSS software (version 13, SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 144 patients including 111 men (77%) and 33 (23%) women with the mean age of 23.7 ± 6.9 (range = 15-57) years old included in this study. The average time between ingestion and admission on hospital (mean ± SE) was 292.2 ± 30 min (range = 30-3600 min). Mean duration of hospitalization was 17.9 ± 10.6 h (range = 3.6-80 h). In all of the cases, the route of exposure was oral, and the most drug dosage form was tablet (*n* = 142) and then capsule (*n* = 2). The mean ingested dose (mean ± SE) was 1971.2 ± 233.4 mg (range = 100-20000 mg). In most of the cases (*n* = 99, 68.8%) the cause of intoxication was suicide and then abuse (*n* = 45, 31.2%) [Table 1]. There was no mortality among the patients.

Major cases had stable vital signs on admission and the related data are summarized in Table 2. 128 (88.9%) of patients were conscious, and 16 of them had a decreased level of consciousness. Seizure (47.9%), nausea (29.9%), vomiting (22.2%), drowsiness (20.1%), dizziness (18.1%), lethargy (6.3%), apnea (5.6%), agitation (4.2%), headache (1.4%), blurred vision (1.4%), ataxia (0.7%), anxiety (0.7%), sweating (0.7%), and nystagmus (0.7%) were the most clinical findings in tramadol-intoxicated patients [Table 2]. Laboratory findings on admission time in the intoxicated patients have been summarized in Table 3.

We divided the cases with regard to occurrence of seizure during hospitalization. The results showed that there were significant differences between cases with seizure and cases without seizure according to time interval between tramadol ingestion and hospital admission (TIBTIHA) (mean ± SE) (330.3 ± 53.2 vs. 257.3 ± 30.1 min, *P* = 0.01), ingested dose (mean ± SE) (1395.7 ± 218.3 vs. 2500.7 ± 390.7 mg, *P* = 0.006), with odds ratio 2.7 (1.03-7.09, 95% confidence interval [CI]), dizziness (3 cases vs. 23 cases, *P* = <0.0001), with odds ratio 0.1 (0.29-0.36, 95% CI), PCO_2 (51.2 ± 8.5 vs. 48.4 ± 8.6 mmHg, *P* = 0.03), with odds ratio 0.58 (0.27-1.24, 95% CI), and total bilirubin (0.5 ± 0.2 vs. 0.7 ± 0.4 mg/dL, *P* = 0.002). There was a correlation between ingested dose (*r* = −0.2, *P* = 0.006), PaCO2 (*r* = 0.2, *P* = 0.03), TIBTIHA (*r* = 0.2, *P* = 0.01), total bilirubin (*r* = −0.3, *P* = 0.002), dizziness (*r* = −0.3, *P* = 0.000), and seizure.

DISCUSSION

Tramadol abuse and overdose is one of the most frequent health problems in Iran and worldwide.[9-11,16] In this study, we report clinical and paraclinical findings in 144 cases with pure tramadol poisoning who referred to a referral-poisoning

Table 1: Demographic findings in tramadol-intoxicated patients

Variable	%, mean±SD (range)			*P*
	Total patients (*n*=144)	Patients with seizure (*n*=69)	Patients without seizure (*n*=75)	
Sex				
Male	111 (77)	57 (82.6)	54 (72)	0.16
Female	33 (23)	12 (17.4)	21 (28)	
Age (year)	23.7±6.9 (15-57)	24.2±7.6 (16-57)	23.1±6.1 (15-52)	0.44
TIBTIHA (min)#	292.2±30 (30-3600)¥	330.3±53.2 (30-3600)¥	257.3±30.1 (30-1320)¥	0.01*
Duration of hospitalization (h)	17.9±10.6 (3.6-80)	17.8±8.7 (6.6-43.1)	18.1±12.1 (3.6-80)	0.63
Ingested dose (mg)	1971.2±233.4 (100-20,000)¥	1395.7±218.3 (100-12,000)¥	2500.7±390.7 (100-20,000)¥	0.006*
Cause of poisoning				
Suicide	99 (68.8)	47 (68.1)	52 (69.3)	1
Abuse	45 (31.2)	22 (31.9)	23 (30.7)	

*The difference between two groups is significant at *P<0.05; #Time interval between tramadol ingestion and hospital admission; ¥The data are presented as mean±SE. SE=Standard error; SD=Standard deviation

Table 2: Clinical findings in tramadol-intoxicated patients on admission time

Variable	%, mean±SD (range)			*P*
	Total patients (*n*=144)	Patients with seizure (*n*=69)	Patients without seizure (*n*=75)	
Respiratory rate (16-24 breaths/min)	15.4±2 (6-20)	15.5±2.1 (6-20)	15.4±2 (10-20)	0.61
Pulse rate (60-100/min)	89.9±16.6 (31-150)	91.1±16.4 (64-146)	88.7±16.8 (31-150)	0.58
Systolic blood pressure (□120 mmHg)	121.5±14.3 (90-150)	121.1±14.3 (100-150)	122±14.4 (90-150)	0.58
Diastolic blood pressure (□80 mmHg)	77.2±10.4 (40-100)	77.2±10.9 (40-100)	77.2±9.9 (58-100)	0.98
Level of consciousness				
Conscious	128 (88.9)	61 (88.4)	67 (89.3)	0.36
Nonconscious	16 (11.1)	8 (11.6)	8 (10.7)	
Nausea	43 (29.9)	18 (26.1	25 (33.3)	0.36
Vomiting	32 (22.2)	15 (10.4)	17 (22.7)	1
Drowsiness	29 (20.1)	12 (8.3)	17 (22.7)	0.53
Dizziness	26 (18.1)	3 (4.4)	23 (30.7)	<0.0001
Lethargy	9 (6.3)	2 (2.9)	7 (9.3)	0.17
Apnea	8 (5.6)	3 (4.4)	5 (6.7)	0.72
Agitation	6 (4.2)	2 (2.9)	4 (5.3)	0.68
Headache	2 (1.4)	0	2 (2.7)	0.5
Blurred vision	2 (1.4)	0	2 (2.7)	0.5
Ataxia	3 (2.1)	0	3 (4)	0.25
Anxiety	1 (0.7)	1 (1.5)	0	0.5
Sweating	1 (0.7)	0	1 (1.3)	0.5
Nystagmus	1 (0.7)	0	1 (1.3)	0.5

SD=Standard deviation

Table 3: Laboratory findings in tramadol-intoxicated patients on admission time

Variable	%, mean±SD (range)			*P*
	Total patients (*n*=144)	Patients with seizure (*n*=69)	Patients without seizure (*n*=75)	
pH (7.35-7.45)	7.3±0.1 (7-7.4)	7.3±0.1 (7-7.4)	7.3±0.1 (7.1-7.4)	0.42
PCO_2 (35-45 mmHg)	49.7±8.6 (31.9-87.1)	51.2±8.5 (31.9-77.4)	48.4±8.6 (34.3-87.1)	0.03*
Bicarbonate (18-24 mEq/L)	24.1±3.8 (11.9-34.1)	24.5±3.9 (11.9-32.9)	24±3.7 (14.3-34.1)	0.26
Blood sugar (60-110 mg/dL)	109±41.2 (60-320)	110±44.3 (60-320)	108.2±38.6 (60-254)	0.69
Blood urea nitrogen (7-18 mg/dL)	26.3±7.8 (10-47)	25.7±7.5 (10-44)	26.9±8 (13-47)	0.51
Creatinine (0.6-1.2 mg/dL)	1.1±0.2 (0.7-1.9)	1.1±0.2 (0.7-1.7)	1.2±0.3 (0.7-1.9)	0.30
Sodium (135-145 mEq/L)	142.1±3.5 (130-155)	142.1±3.7 (130-155)	142.1±3.4 (135-150)	0.70
Potassium (3.5-5 mEq/L)	4.1±0.4 (3-5.8)	4±0.4 (3-4.9)	4.1±0.5 (3.1-5.8)	0.08
Aspartate aminotransferase (11-47 IU/L)	30.5±3.6 (10-500)¥	29.5±2.4 (10-120)¥	31.4±6.4 (10-500)¥	0.20
Alanine aminotransferase (7-53 IU/L)	24.2±3.1 (5-418)¥	22.7±2.5 (5-151)¥	25.6±5.6 (8-418)¥	0.63
Lactate dehydrogenase (225-500 U/L)	638.2±93.6 (160-8250)¥	604.6±110.9 (223-7890)¥	669.1±148 (160-8250)¥	0.19
CPK (20-200 U/L)	398±100.5 (30-11,965)¥	528.8±197.2 (40-11,965)¥	277.2±64.6 (30-4600)¥	0.23
Alkaline phosphatase (38-126 IU/L)	198.6±64.6 (13-410)	197.8±61.5 (13-352)	199.4±67.8 (112-410)	0.54
Total bilirubin (0.2-1.3 mg/dL)	0.6±0.3 (0.1-2.4)	0.5±0.2 (0.1-1.2)	0.7±0.4 (0.2-2.4)	0.002*
Direct bilirubin (</0.2 mg/dL)	0.2±0.1 (0.1-0.6)	0.2±0.1 (0.1-0.3)	0.2±0.1 (0.1-0.6)	0.06
White blood cells (4000-10000/m^3)	10642.4±3622.6 (3700-21,400)	11021.7±3922.6 (4700-21,400)	10293.3±3311 (3700-21,400)	0.26
Hemoglobin (12-18 g/dL)	13.6±1.8 (8.6-17.9)	13.6±1.6 (10-17.1)	13.6±1.9 (8.6-17.9)	0.89
Platelet count (150000-400000/m^3)	229104.2±60567.7 (730,00-396,000)	226565.2±63965.6 (730,00-363,000)	231440±57598.9 (101,000-396,000)	0.63

*The difference between two groups is significant at *P<0.05; ¥The data are presented as mean±SE. SE=Standard error; SD=Standard deviation; CPK=Creatine phosphokinase

center in Tehran, Iran. Young male adults were the major patients in our study. This result is in accordance with previous studies.[10,11] Furthermore, the results indicated that oral route is the most common route of exposure, which is similar with the findings of our previous studies.[9,10]

Seizure was the most common symptom among tramadol-intoxicated cases in this study. This result is in concordance with previous studies too.[9,10,17,18] Jovanovic-Cupic *et al*. reported higher seizure frequency (54.4%) in their study.[14] The frequency of other clinical manifestations including lethargy, coma, nausea, vomiting, agitation, and respiratory depression in our study were different with previous studies.[16,19] Tramadol is metabolized by cytochrome P450 (CYP450) enzymes (mainly 2D6 isoenzyme) to its active metabolites

M1 (O-desmethyl tramadol), M2 (N-desmethyl tramadol), M3 (N, N-didesmethyl tramadol), M4 (O, N, N-tridesmethyl tramadol), and M5 (O, N-didesmethyl tramadol). M1 metabolite has more affinity (200 times) for the μ-opioid receptors and also it has more inhibitory effect on biogenic amine reuptake than that of parent drug molecule and may be responsible for tramadol induce analgesia or seizure in intoxicated patients. In this regard, genetic polymorphism in humans may affect the tramadol metabolism and its peak blood concentration resulting to a different frequency of tramadol adverse effects or clinical presentations during therapeutic doses or intoxication.[20,21]

Although the increasing of liver function tests, serum BUN and Cr due to liver and kidney damage have been demonstrated in chronic administration of tramadol in experimental model,[15] but in our study due to acute onset of toxicity we did not observe any increase in liver function tests, BUN and Cr and this is in concordance of the previous study.[11]

Rhabdomyolysis and rise of creatine phosphokinase (CPK) have been reported as a rare and serious complication in tramadol intoxication in the previous studies, which was observed in our study too. Although in the previous studies, prolong immobilization and multiple seizures have been described as one of the reasons for the rise of CPK and rhabdomyolysis,[22,23] but in our study there was no significant difference in level of CPK in the tramadol-intoxicated patients with seizure in comparison to cases without seizure.

Le Berre *et al*., reported tramadol induced hyponatremia which described as a result of inappropriate antidiuretic hormone secretion.[24] In this study, the level of Na, and K was within the normal range.

The PCO_2 level was above normal range which could be attributed to tramadol-induced respiratory depression, which has been reported previously.[25]

In this study, the mean of ingested dose in the seizure group was less than those cases without seizure which is in contrasts with the result of the previous study.[26] One of the explanations is the difference between two groups with regard to TIBTIHA, which was significantly longer in seizure group. Furthermore, as mentioned previously, the other reason could be the genetic polymorphism in patients.

The main limitation of this study is its retrospective design, which should be considered in the interpretation of the results. With this regard, prospective study could be considered.

CONCLUSION

Seizure is the most clinical manifestation in tramadol poisoning. There were significant differences between seizure and nonseizure cases with regard to TIBTIHA, ingested dose, and PCO_2. Furthermore, we showed poor correlation between tramadol ingested dose, TIBTIHA, PCO_2, and seizure in tramadol-intoxicated cases.

ACKNOWLEDGMENT

Our thanks are due to Mr. Atari, who works at archive center of Loghman Hakim hospital for his corporations.

AUTHOR'S CONTRIBUTION

HRR involving in the data collection and data analysis. SS and KSN involving in the study design, conducting of the study and data analysis. The manuscript was drafted by HRR and SS and KSN reviewed the manuscript. Finally, all the authors read and approved the final version of the manuscript.

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Source of Support: Nil, **Conflict of Interest:** None declared.