



## Frequency of Tramadol Toxicity in Shahid Mohammadi Hospital in Bandar Abbas

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### Abstract

**Background:** Tramadol is a synthetic drug with central mechanisms which binds to  $\mu$ -opioid receptors. Recently, increased consumption and serious complications have been reported about this drug. Thus, the aim of this study was to determine the frequency of tramadol toxicity in Shahid Mohammadi Hospital in Bandar Abbas.

**Materials and Methods:** This retrospective descriptive study was performed on individuals with tramadol toxicity admitted to Shahid Mohammadi Hospital, Bandar Abbas during 2013-2014. Information was collected through patients' medical files using a checklist including demographic characteristics, toxicity complications, and patients' clinical outcomes. The acquired data were then analyzed using SPSS software.

**Results:** The mean age of 53 patients was  $24.71 \pm 7.76$  years, of which 69.8% were males and 49.1% had a history of drug abuse. In addition, the seizure was observed in 49.1% of them, and 47.2% of cases simultaneously used another drug, along with tramadol. Further, the history of mental disorders was reported in 24.5% of patients. Clinical manifestations included a decreased level of consciousness (49.1%), nausea and/or vomiting (45.3%), and headache (30.2%). Furthermore, the duration of hospital stay was 48 hours in 90.6% of patients. Eventually, a significant correlation was found between seizure and drugs other than tramadol ( $P=0.001$ ), gender ( $P=0.004$ ), and occupation ( $P=0.010$ ).

**Conclusion:** Most cases of tramadol toxicity occur in students and young adults, resulting in complications such as seizure, decreased levels of consciousness, and nausea and/or vomiting. Accordingly, awareness of the complications of tramadol and meticulous observations over its methods of delivery could reduce the associated harms.

**Keywords:** Tramadol, Poisoning, Adverse effects

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### Introduction

Currently, drug toxicity is the most prevalent combinational toxicity since approximately 25 000 people are annually intoxicated with drugs or chemical substances in Tehran. Of these numbers, 12 000, 1200, and at least 120 cases are hospitalized, transferred to the intensive care unit (ICU), and die, respectively. Intoxication with tramadol is one of the most prevalent types of toxicity in Tehran (1-3). In addition, tramadol hydrochloride is a synthetic analgesic agent with the central activity which is used to alleviate moderate to severe pain (4). After the prohibition of injectable diclofenac by the Food and

Drug Administration in 2001, tramadol entered the drug market of Iran as a pain killer. Ever since, many cases of abuse have been reported in this regard (5).

The manifestations of tramadol toxicity are divided into three categories namely, neurotoxicity, cardiotoxicity, and gastrointestinal symptoms including seizure, coma, respiratory depression, tachycardia, mild hypotension, and nausea and/or vomiting. The most prevalent symptom of tramadol neurotoxicity is the seizure and usually occurs as generalized tonic-clonic seizure within the first 24 hours of intoxication. Other presentations are mydriasis, liver failure, the elevation of liver enzymes,

kidney failure through increasing creatinine and blood urea nitrogen, as well as the elevation of creatine phosphokinase, hypoglycemia, pulmonary edema, tremor, serotonin syndrome, and sometimes death (1, 6-8).

Further, the analgesic properties of tramadol are dose-dependent, and the relationship between the serum level of tramadol and its analgesic properties is idiosyncratic. The Iranian Pharmacovigilance Center, which was established in 1998, records adverse drug reactions (ADRs) through spontaneous reporting systems, which are then published in the Razi Journal of Medical Sciences. The analyses of monthly ADR reports show that since its entrance into the market, injectable tramadol has been its most commonly used form (5). Given the above-mentioned discussions, this research aimed to investigate the frequency of tramadol intoxication, its course, complications, and mortality among patients admitted to Shahid Mohammadi Hospital in Bandar Abbas during 2013-2014.

### Materials and Methods

Following the approval of the Ethics Committee of Hormozgan University of Medical Sciences, this retrospective cross-sectional study was carried out based on available information from all patients who were hospitalized from September 2013 to September 2014 in Bandar Abbas Shahid Mohammadi Hospital. The medical files of 53 patients with tramadol toxicity were included based on the aim of the study. The required information including age, gender, occupation, history of addiction, mental disorders, cardiovascular disease, suicide, clinical symptoms, the dosage of the consumed drugs, seizure, and the duration of hospital stay were recorded in a checklist. The SPSS software (version 25) was used for data analysis. Descriptive statistics were presented as the mean, standard deviation, frequency, and percentage, and chi-square and Fisher exact tests were used to compare qualitative data. The  $P < 0.05$  was considered statistically significant.

### Results

Of 53 patients in this study, 69.8% of cases were males and 30.2% of them were females, and the mean age of the patients was  $24.71 \pm 7.76$  years (in the range of 15-52). The demographic characteristics of patients are presented in Table 1, and Table 2 demonstrates the medical history of the study population. Moreover, the frequencies of the clinical manifestations of tramadol toxicity are provided in Table 3.

The results showed that 88.5% (23.26) of patients having seizures were males and 11.5% (3.26) of them were females and the difference was statistically significant ( $P = 0.004$ ). Among the 26 patients who had a history of addiction, 16 (61.5%), 14 (53.8%), 6 (23.1%), and 3 (11.5%) cases had seizures, decreased levels of consciousness, altered

**Table 1.** Distribution of Demographic Characteristics

Individual and Social Characteristics		Number	%
Gender	Male	37	69.8
	Female	16	30.2
Occupation	Housewife	10	18.9
	Unemployed	9	17
	Student	15	28.3
	Self-employed	11	20.8
	Civil servant	8	15.1

**Table 2.** Distribution of the Components of Medical History

Variable	Number	%	
Addiction history	26	49.1	
Previous physical illness history	16	30.2	
Mental illness history	13	24.5	
Suicide history	12	22.6	
History of simultaneous drug use	25	47.2	
The amount of consumed dosage	Unknown	28	52.8
	400-6000 mg	25	47.2
The duration of hospitalization	Less than 24 hours	5	9.4
	More than 24 hours	48	90.6

**Table 3.** Clinical Manifestations of Tramadol Toxicity in the Study Population

Clinical Symptoms	Number	%
Nausea and/or vomiting	29	54.7
Seizure	26	49.1
Headache	16	30.2
Sweating	5	9.4
Decreased level of consciousness	26	49.1
Altered breathing rhythm	11	20.8

breathing rhythms, and sweating, respectively. No significant relationship was found between a history of addiction and the clinical manifestations of tramadol toxicity ( $P > 0.05$ ).

Among the 26 patients who had seizures, 8 (30.8%), 8 (30.8%), and 7 (26.9%) were students, civil servants, and unemployed, respectively, and 1 person (3.8%) was a housewife ( $P = 0.001$ ). Among 29 patients who had nausea and/or vomiting, 10 (34.5%), 8 (27.6%), 5 (17.2%), 3 (10.3%), and 3 (10.3%) were students, housewives, unemployed, civil servants, and self-employed ( $P = 0.106$ ), respectively. Based on the findings, 10 (38.5%), 5 (19.2%), 4 (15.4%), and 3 (11.5%) out of 26 patients who had decreased levels of consciousness were students, civil servants, unemployed, and housewives, respectively ( $P = 0.341$ ). From 25 patients who had used another drug beside tramadol, 6 (24%) cases had a seizure and a significant relationship was observed between seizure and the consumed drug other than tramadol ( $P = 0.001$ ). Furthermore, 17 (68%) and 9 (36%) cases had nausea

and/or vomiting ( $P=0.066$ ) and headache ( $P=0.384$ ), respectively.

## Discussion

Although tramadol is used for the management of moderate to severe pain, (9) it is one of the most commonly used drugs all over the world. In addition, it is a synthetic drug with central effects which is used for treating moderate to severe pain. Toxicity by tramadol causes the severe involvement of the nervous system and can result in nausea and vomiting, confusion, dysphoria, headache, seizure, decreased levels of consciousness, altered breathing rhythms, and coma. It can further lead to long-term hospitalization of approximately 10% in the ICU (5-10).

The number of tramadol intoxicated patients in this research was 53 and their mean age was  $24.71 \pm 7.76$ . In the study by Farzaneh et al, the mean age of tramadol intoxicated patients referring to the emergency department of Ardebil Imam Khomeini Hospital was  $27 \pm 7.2$  years (1). Most tramadol intoxicated patients were men, which is in line with the findings of other studies carried out in Iran and other countries (2, 5, 7).

In our study, 27 out of 53 patients (50.9%) had decreased levels of consciousness. In another study by Shadnia et al, 34% of patients had disturbance of consciousness (2). In addition, the disturbance of consciousness was observed in 27.4% of patients in the study by Marquardt et al (11), which was lower compared to our findings. The difference between studies might result from different consumed doses of tramadol by patients of each study.

The results of this study contradict those of the study by Taghaddosinejad et al (12). Addiction history was one of the main factors of tramadol toxicity in their study while no significant relationship was observed between addiction history and tramadol toxicity in our study. Although the simultaneous consumption of two or more drugs is quite common, this might not always be the case according to our results.

Our findings regarding the most prevalent clinical symptoms are inconsistent with those of other studies. Nausea and/or vomiting were the most prevalent findings among the tramadol intoxicated patients of our study while seizure was reported as the prevalent symptom of tramadol toxicity in other studies. The results revealed that the most frequent presentation of tramadol toxicity in our study was the seizure, followed by decreased levels of consciousness, headache, altered breathing rhythms, and sweating, which is contrary to the results of Rahimi et al.(13) The clinical presentations of tramadol toxicity can be dose-dependent and this can justify the difference between the studies. However, Nasr et al found no association between the toxic manifestations of tramadol overdose and its blood level and further concluded that the frequency of seizure and other symptoms is not dose-dependent (14).

In the current study, 20.8% of patients had altered breathing rhythms. In their study, Shadnia et al reported death due to respiratory arrest after using more than 500 mg of tramadol. (2) Furthermore, respiratory depression was observed in 2% of tramadol intoxicated patients in a study carried out by Spiller et al (15) which is to some extent in line with our findings. Respiratory depression can occur because of cardiogenic pulmonary edema, which happens as a result of an increase in pulmonary vascular permeability in toxicity by opioid compounds (2). This can explain the respiratory disorders that occur in tramadol toxicity.

In the current study, 24.5% of patients had a history of mental disorders, which corroborates with the results of the study by Eizadi-Mood et al (6) Information regarding the history of mental disorders was unavailable in other studies. Approximately 30% of patients in our study had a prior history of diseases while Eizadi-Mood et al reported that only 15% of patients had such history (6).

In the current study, 25 individuals (47.2%) had used a drug other than tramadol. In the study by Marquardt et al (11) 54% of patients had only used tramadol, which is not very different from our study. In another study, Eizadi-Mood et al found that 53.4% (100) of 184 tramadol intoxicated patients had only used tramadol whereas other cases had used other drugs, along with tramadol, which is in accordance with the findings of our study. Based on the findings of the current and previous studies, it appears that most tramadol toxicity patients are likely to commit suicide and use other drugs, along with tramadol.

## Conclusion

In general, most cases of tramadol toxicity occur in students and young adults and can result in complications such as seizure, decreased levels of consciousness, and nausea and/or vomiting. Accordingly, knowing about the complications of tramadol and meticulous observation over its methods of delivery could reduce the associated harms.

## Conflict of Interest Disclosures

The authors declare that they have no conflict of interests.

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## Ethical Statement

The study received the ethics approval from the Ethics Committee of Hormozgan University of Medical Sciences (IR.HUMS. REC.1394.199) and complied with the statements of the Declaration of Helsinki.

## Author's Contributions

Conceptualization: AHA; Study validation and supervision: YK; Data analysis and interpretation: AKHK and AHD; Writing and reviewing: ML.

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**Informed Consent**

Not applicable due to the retrospective design.

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