

## Clinical and Laboratory Findings in Patients with Tramadol Intoxication Referred to Razi Hospital During 2005-06

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### ABSTRACT

**Introduction:** Frequency of Tramadol intoxication is increasing as a result of its use as a drug for suppression of withdrawal symptoms by opioids abusers and its wide accessibility of this drug. Tramadol intoxication can lead to death and, therefore, early identification of its clinical manifestations is crucial since early detection of the intoxication and its treatment could improve patients' survival. This study investigated the frequency of clinical and laboratory findings in Tramadol intoxication.

**Methods:** In this cross-sectional study, patients with Tramadol intoxication who referred to Razi Hospital in Rasht, Iran, during 2005-06 were examined. Their medical records were surveyed for demographic data, past medical history, neurological examination, and routine laboratory tests. All data were statistically analyzed by SPSS software version 14.

**Result:** The majority of the 306 patients (83.3% male) were in the age range of 20-40 years and 68.6% of them had been educated up to high school. The mean dose of ingested Tramadol was  $746 \pm 453$ mg (mean  $\pm$  SD). Agitation (25.2%) and seizure (20.3%) were the most frequent reported symptoms. Among laboratory abnormalities, the most common findings were prolonged PT (18.3%) and increased ALT (5.6%).

**Conclusion:** The most common clinical presentation was agitation and the most common laboratory finding was prolonged PT. Of all the patients, 3 cases were admitted to ICU. Although Tramadol poisoning might lead to death, there was only one death after Tramadol poisoning in the current study.

**Key words:** Intoxication, Rasht, Tramadol.

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### INTRODUCTION

Tramadol hydrochloride is a synthetic, centrally acting analgesic used both parenterally and orally for the treatment of moderate to severe pain. It has dual mechanism of action; weak agonistic effect at the  $\mu$ -opioid receptor, as well as inhibition of monoamine (serotonin, norepinephrine) re-uptake (1). Tramadol is distributed in the body, with a mean distribution half-life of 1.7 hours. The high total distribution volume of 306 liters (L) after oral administration indicates its high

tissue affinity. The plasma protein binding of this drug is reported about 20% (2).

This compound is rapidly and extensively metabolized in the liver by two principal pathways: O-demethylation to O-desmethyltramadol (M1) by CYP2D6 and N-demethylation to N-desmethyltramadol (M2) by CYP2B6 and CYP3A4 (3). Biliary excretion of Tramadol and its metabolites are negligible and from a quantitative point of view all metabolites as well as intact tramadol are almost completely excreted via the kidneys (4).

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Nowadays tramadol is widely used for the treatment of different pain disorders. But there is limited data available about its side effects and manifestations in over dose cases (5). Lethargy, nausea, tachycardia, agitation, seizure, coma, hypertension and respiratory distress are the more frequently reported symptoms and they are mostly attributable to the monoamine reuptake inhibition rather than its opioid effects (5,6). Nausea, vomiting, Central Nervous System (CNS) depression, tachycardia, and seizure are the most common findings in this kind of poisoning. Cardiopulmonary arrest was found as the cause of death in cases who had ingested more than 5000 mg tramadol (7). Tramadol overdose frequently cause CNS depression, respiratory depression, tachycardia, hypertension, and seizure. these symptoms could be from both effects of tramadol either on mu receptor or inhibition of monoamine reuptake (5). Despite of the general attitude about its safety, several fatal incidents by tramadol have drawn attention toward its underestimated toxicity (8). In recent years, under the false shadow of safety, the rate of tramadol abuse is becoming disastrous (9).

It has been reported that tramadol overdose is one of the most frequent causes of drug poisoning in Iran, especially among young male adults, with a history of substance abuse and mental disorder (1). Tramadol intoxication can cause death

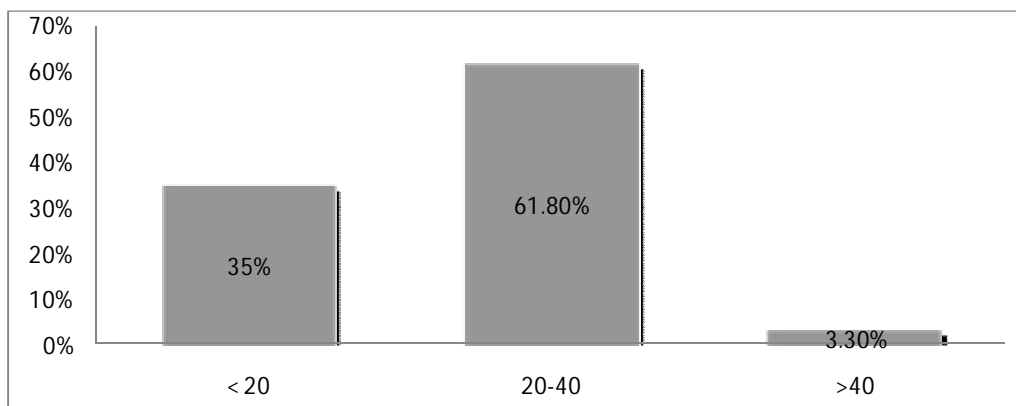
Therefore, the identification of clinical manifestations is important; so, early detection and early treatment could save patient's lives. In this study, we decided to explore the tramadol intoxication clinical signs and symptoms and laboratory data in the Razi emergency room visitors between 2005-06.

## MATERIALS AND METHODS

All patients with tramadol intoxication referred to Razi hospital, Rasht, Iran from 2005 through 2006, were studied. The study was cross sectional and retrospective. The aim of the study was to assess the frequency of various clinical and laboratory findings. Demographic data including age, gender, educational grading, duration of tramadol use and the last dose of ingested tramadol were inquired from the patients or their relatives. Signs and symptoms (agitation, hypotension, midriasis, seizure and apnea) and laboratory findings (PT, PTT, ALT, AST, BUN, and Cr) were documented by a questionnaire. All descriptive statistical analyses were achieved using SPSS software (SPSS version 18, USA).

## RESULTS

Three hundred and six patients were studied. intoxication with tramadol was more common in men than women (83.3% were male). The most patients were 20-40 years old (61.8%) (Figure. 1) and 68.6% of them studied till high school.



**Figure 1.** Distribution of percentage frequency of age groups in intoxication Tramadol patients

All cases admitted with suspected Tramadol overdose. The average dose of tramadol had ingested was  $745.87 \pm 453.05$  mg. The most symptom among them was Agitation (25.2%). Beside, seizure (20.3%), hypotension (10.5%), midriasis (8.2%) and apnea (2.3%) were seen among patients. Contrary of other opioids, miosis did not detect in the poisoning patients. 10 patients had apnea that three of them had transmitted to ICU and one of them death because of cardiopulmonary arrest. Two Others patients with apnea survived with supportive care. among patients had been hospitalized with seizure, all of them had new onset seizures, provoked by tramadol; Their seizure controlled by Diazepam and they did not have any seizure before that within their hospitalization time. The most Laboratory disorder was PT that increased but there aren't any symptoms of ecchymosis or hemorrhage. (Table. 1)

## DISCUSSION

In this study, we reported a series of 306 patients with tramadol intoxication during 2005-06. Tramadol intoxication is more common in young male patients (83.3% were male). Out of our subject, 61.8% were between 20-40 years old. Some other studies showed that Tramadol intoxication was more in male than female. In a study has carried out on 520 Tramadol intoxication patients during 2008-09 in kermanshah, the results showed that male was predominantly more than female (93.7% male and 6.3% female).

Also, The mean age for seizure was 32.5 year old for those with seizure during consumption and 16.7 year old for the other group (10). The similar findings were obtained in Eizadi's study has done on 184 patients in Isfahan (11). It may happened because of addict to Tramadol was more in male than female.

Most of the subjects (68.6%) studied till high school. Also, in the study was done in Kermanshah most of the participants studied till high school (31.7%) or holder of diploma (38.3%) (10).

Petramfar F, et al. studied on 106 patients with tramadol intoxication in 2006-08. 81% of patients abused tramadol and others consumption tramadol for therapeutic purposes. They ingested 50-1500mg tramadol (1). Although, in our study the average dose of tramadol that used was  $746 \pm 453$  mg that was less than early study. In other studies the average of the dosage resulting to seizure was about 650 mg, although it was seen in a few cases in dosage 50mg to 2500mg (11).

Tramadol poisoning may causes sudden death (3), certainly in patients with high dose consumption or use tramadol with other drugs. In a study has done in Isfahan, a 19 years old man ingested one hundred tablets (each one is 100mg) of tramadol was reported. He experienced with confusion, ataxia, and agitation. Finally, he went toward seizure and apnea. So, he was transferred to ICU, and then he died (3).

**Table 1.** Relative frequency of Laboratory Data in intoxication Tramadol patients

Frequency Alternation in Laboratory Data	Number	Percentage
	Increased BUN	7
Increased Cr	7	2.3
Increased ALT	23	7.5
Increased AST	17	5.6
Increased PT	56	18.3
Increased PTT	9	2.9

Michaud, et al. recounted a death as a result of tramadol overdose in combination with alprazolam (12). Also we reported one case died; He was 35 years old. He had used different opioids and was addicted. Tramadol was prescribed for him in order to cessation opioids and suppression of withdrawal symptoms. But at the end, he arrested and died.

seizure was survived in some study as The first symptom that patients admitted with it. Mehrpour.M.reported two cases with tramadol induced seizure in recommended dose.First case was a 21 years old girl; Because of her headache,she received intravenous injection of tramadol (100 mg). Another case was 18 years old boy for whom tramadol had been prescribed because of his headache, too. He had received tramadol 100 mg intravenously which caused seizure just after injection (13).

In one study Seizure occurred more frequently in patients with tramadol use only and midriasis on admission (14).

In the current study, agitation and seizure are the most common symptoms. Similar findings were received in the other studies; aresearch was done in Isfahan on 184 patients.The most common chief complaint was central nervous system (CNS) depression (57%) followed by seizure (25%) (11).

## CONCLUSION

In our study The most clinical presentations was agitation and the most laboratory findings was prolonged PT. among our patients, 3 cases were admitted in ICU. Contrary to previous beliefs, tramadol poisoning might lead to death. In the current study there was one death.

In Iran, tramadol is easily available for patients without prescription. According to annual reports of Iranian ministry of health, 24 million tramadol tablets (100 mg) were sold from 21 March 2004 through 20 March 2005. It was increased to 162 million in the next year

and 350 million in 2006-07, demonstrate 14.6-fold increase during 2 years .So, it is essential for health care centers to Increase people's information about tramadol side effects and limitation of Tramadol usage, as low as possible.

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