

Pediatric Toxicoepidemiology of Tramadol Intoxication in Iran: A 5-year Cross-Sectional Study

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INTRODUCTION

Toxicoepidemiology uses a combination of epidemiological methods in medical toxicology to study the patterns and components of poisoning in a population.^[1] Tramadol is an opioid-like analgesic that is used to relieve moderate or severe pain.^[2] Tramadol

ABSTRACT

Objective: We aimed to find the toxicoepidemiological indicators of tramadol poisoning in children and also the relationship of these indicators (such as demographic characteristics, and referral time) with the final therapeutic outcome. **Methods:** In this cross-sectional study with retrospective data collection, we included the records for all the patients under 18 that have been admitted due to tramadol poisoning between 2010 and 2015 to Noor and Ali-Asghar (PBUH) University hospital which serves as the referral medical center for acute poisonings management in the central part of Iran and is located in Isfahan. Demographic characteristics, ingested dose, dosage forms, clinical manifestations, coingested drugs, and the outcome of treatment for all pediatric patients were documented and descriptively analyzed. **Findings:** Demographic and clinical data of a total of 189 patients including 101 male (53.4%) with a mean age of 16.66 ± 2.64 years were abstracted and included in this study. The average time between tramadol ingestion and hospital admission was 3.39 ± 3.23 h. Mean duration of hospitalization was 12.3 ± 10.7 h. In all cases, the route of drug exposure was oral, and the most common form of drug dosage form was 100 mg tablets ($n = 122$) proceeded by 200 mg tablets ($n = 32$). The mean estimated dose of ingested tramadol was 1126 ± 1061 mg (median, 900 range, 50–7000 mg). 43.9% of the poisoned patients were high school students, and 23.3% had a high school diploma. Intentional intoxications were reported in 93.1% cases and 42.9% had coingestions. Activated charcoal (87.3%), gastric lavage (59.3%), oxygen therapy with mask (46.6%), naloxone (11.6%), anticonvulsants (13.2%), and intubation and ventilation (5.3%) were done as first-line therapeutic measures. **Conclusion:** Our results suggest that the trend of acute tramadol poisoning among children is decreasing, mostly accidental in adolescents and commonly intentional among young children. Proper education to improve emotional intelligence for young adults and to keep drugs out of reach of the children and safer packaging is recommended to reduce tramadol poisoning incidence in the pediatric population.

KEYWORDS: Acute poisoning, children, Iran, pediatric toxicoepidemiology, Tramadol

intoxication can lead to prolonged hospitalization in about 10% of poisoned patients in intensive care

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units.^[3] The safety of prescription and use of this drug in children has not been satisfactorily documented yet^[4] and toxic doses are merely determined according to the case reports.

Two retrospective studies have been conducted on tramadol poisoning in Iran. A study was conducted on symptoms of tramadol poisoning in cases referred to the emergency department of Noor and Ali Asghar Hospitals in 2007, that the number of hospitalized patients due to tramadol poisoning in 1 year was 184 cases and also two death cases were reported.^[5] Another study was carried out on 114 patients poisoned with tramadol referred to poisoning center of Luqman Hospital in Tehran that the clinical symptoms of them included nausea, vomiting, loss of consciousness, tachycardia, and seizures.^[6] Also, in this study, tramadol intake was reported as the most common cause of drug poisoning in cases with substance abuse or mental disorders.^[6]

Since there is no specific study on tramadol intoxication in Iranian children, and Given the serious side effects of tramadol, especially seizures that occur even with low doses in children, it seems that further and more precise studies on the causes and effective factors of this kind of poisoning on the population of children are needed.

The purpose of this study was to document and descriptively analyze the toxicoepidemiological indicators of tramadol poisoning in children and also the relationship of these indicators (such as demographic characteristics, and referral time) with the final therapeutic outcomes in the Iranian pediatric population.

METHODS

In this retrospective descriptive-analytic study, which was carried out in Isfahan (Iran), epidemiological data of tramadol poisoned pediatric patients aged <18-year-old for a 5-year period (2010–2015) were abstracted and analyzed. These data were gathered via in-patients' medical charts of Noor and Ali Asghar (PBUH) University hospital (affiliated with the Isfahan University of Medical Sciences), which is the referral medical center for poisoning emergencies at the central part of Iran. According to a previous study in Isfahan, at least 77% of drug and nondrug poisonings are referred to poisonings center of Noor and Ali Asghar Medical Center.^[7] At the same time, more than half of the remaining 23% that was directly referred to other healthcare facilities, patients were re-referred to this center after initial stabilization.^[7]

The study protocol was approved by the institutional board of human studies at Isfahan University of Medical Sciences and was in accordance with Tehran's code of

ethics for human researches. All patient information was protected and kept confidential.

Data of all patients aged <18 years old who were admitted and hospitalized for tramadol poisoning during March 2010–September 2015 were abstracted. Therefore, the sample size calculation was not needed.^[8]

To determine the type of needed data, a focus group consisting of 5 experts in the fields of medical toxicology, biostatistics, and pharmacoepidemiology was setup, and the indicators with toxicoepidemiological importance for the objectives of this study were recognized and identified. Then the primary topics of interest together with the main purpose and essential objectives of the project were sent via E-mail to 5 external clinical toxicology experts and also to 5 external epidemiologists who were not employed at the institute. Twenty five items were finally selected for providing the toxicoepidemiological aspect of tramadol poisoning in hospitalized children in Isfahan, using a Delphi method.^[9]

Exclusion criteria included missing data in more than 25% of the collected data from patients' charts.^[10]

Collected data has been reported using descriptive statistical analysis, and possible correlations between epidemiological indicators and the outcomes of the treatment have been analyzed and statistically modeled. All statistical analysis was done by SPSS software (IBM Corp., Released 2013. IBM SPSS Statistics for Windows, Version 22.0, Armonk, NY, USA: IBM Corp.) A $P < 0.05$ considered as statistically significant.

RESULTS

Demographic and clinical data of a total of 189 patients, including 101 males (53.4%) with a mean age of 16.66 ± 2.64 (range, 3–18) years, were abstracted and included in this study. Of all intoxicated patients, 44.4% were residents of east and north east of Isfahan. The divided frequency of tramadol intoxication in each year is presented in Table 1.

The average time between tramadol ingestion and hospital admission (mean \pm standard deviation [SD])

Table 1: Frequency of tramadol intoxication in pediatrics of Isfahan, Iran (2010–2015)

Year	Number of children hospitalized with tramadol intoxication
2010	47
2011	37
2012	29
2013	34
2014	28
2015 (until September)	14

was 3.39 ± 3.23 h (range, 0.5–24 h). The mean duration of hospitalization was 12.3 ± 10.7 h (median, 10 range, 1–336 h). In all cases, the route of drug exposure was oral, and the most common form of drug dosage form was 100 mg tablets ($n = 122$) proceeded by 200 mg tablets ($n = 32$). The mean estimated dose of ingested tramadol (mean \pm SD) was 1126 ± 1061 mg (median, 900 range, 50–7000 mg). About 44% of the poisoned patients were high school students, and 23.3% had a high school diploma. Intentional intoxications were reported in 93.1% cases, and 42.9% had coingestions. The most frequent coingested drug in 24 patients was clonazepam, followed by alprazolam (14 patients) and alcohol (11 patients). Of all patients, 24.3% had a positive history of addiction, of which 4.8% were tramadol abusers. Furthermore, 22 patients (11.6%) had a history of mental disorders. Clinical manifestations and patients' symptoms are presented in Table 2.

Activated charcoal (87.3%), gastric lavage (59.3%), oxygen therapy with mask (46.6%), naloxone (11.6%), anticonvulsants (13.2%), and intubation and ventilation (5.3%) were done as first-line therapeutic measures. Despite all of the supportive medical care, two (1.1%) patients died (aged 18 and 15 years).

Table 2: Symptoms of Tramadol intoxication in pediatrics of Isfahan, Iran (2010-2015)

Symptom	Frequency (%)
Nervous system	
CNS depression	113 (59.8)
Vertigo	38 (20)
Seizure	35 (18.5)
Headache	17 (9)
Coma	4 (2.1)
Ataxia	4 (2.1)
Motor dysfunction	2 (1.1)
Blurred vision	1 (0.5)
Cardiovascular system	
Tachycardia	51 (27)
Bradycardia	2 (1.1)
Hypotension	14 (7.4)
Hypertension	4 (2.1)
Respiratory system	
Tachypnea	41 (21.7)
Bradypnea/apnea	7 (3.7)
Digestive system	
Vomiting	31 (16.4)
Nausea	10 (5.3)
Stomachache	15 (7.9)
Miscellaneous	
Itching	13 (6.9)
Sweating	10 (5.3)
Rash	2 (1.1)
Fever	1 (0.5)

CNS=Central nervous system

Linear regression statistical analysis of our data showed a significant association between tramadol dose, dosage form, and the time elapsed from tramadol ingestion to hospital admission, with a duration of hospitalization ($P < 0.001$, 0.01, and <0.001 , respectively).

DISCUSSION

Combined with results of another study which was performed in the same medical center (Noor Hospital) on epidemiological characteristics of poisoning in vulnerable groups, we can epidemiologically say that poisoning with tramadol includes about 15% of poisoning cases in children and adolescents in Isfahan, Iran.^[11]

Tramadol poisoning has had a downward trend from 2011 to 2015, which seems to fit with the overall decline in poisoning admissions to this center. Furthermore, reduced distribution amount of tramadol among distributing companies and applying stricter rules on pharmacies for nondelivery of tramadol to patients without a prescription could be as effective factors in this regard.

In Iran, tramadol is also included in the red list of controlled drug products, which by law must be delivered to patients only with a physician's prescription, and in redelivery, the previous prescription must be received from the patient. Only certain companies have the license for tramadol distribution. However, according to the results of the study, it is clear that in spite of these provisions, the clients and even their children have relatively easy access to these drugs. Thus, developing more intelligent measures and the need to monitor the implementation of laws belonging to this class of drugs by pharmacies and supervising bodies appear to be crucial.

Almost all the patients in this study were in the age range of 12–18. Only six patients poisoned by tramadol were under 6 years, which seems to be logical due to the commonly available tramadol form (tablets and capsules) and the relatively large size of tablets and capsules.

In a study conducted in 2013 on the pattern of poisoning in children in Turkey, most of the poisoning cases had occurred in the final months of the year (January–February), while the lowest rate had been in November.^[12] In a study published in 2014 in Zahedan, Iran, most of the poisoning cases had occurred in the fall.^[13] In another study in Isfahan carried out on poisoning in the population of children younger than 10 years, the highest rate of poisoning cases had occurred in September, while the lowest had occurred in November.^[14] It seems

that the seasonal density of poisonings varies due to geographical conditions and the cultural background of each region. The highest rate of poisonings in the periods of our study had happened in May (11.6%), and in general, the poisoning rate was higher in the first half of the solar year (52.6%). The lowest rate of poisoning had also happened in December (5.8%). Given that the most important causes of suicide in youth and adolescents are social failures, educational difficulties, and deficiencies and problems with parents,^[15] a higher frequency of poisoning in this month may be due to simultaneity with the examinations in schools.

In this study, the majority of patients were high school students or had a high school diploma. Also, 27 patients (14.2%) had educations lower than their age that 11 of them were of Afghan nationality.

In this study, the number of males (53.4%) was slightly more than females. This pattern was the same in other studies on tramadol as well.^[6,16] In this study, in males, 84.1% of poisoning cases were with the intent to commit suicide, and 15.9% were done for abuse. All of the females had taken tramadol to commit suicide. In other studies, performed in neighboring countries, the suicide rates in females have been more than males.^[17,18] In general, based on previous research by these authors, poisoning has been reported as the most common nonfatal method of suicide leading to debilitating complications in women.^[19]

In this study, 44.4% of the total poisoning cases with tramadol in children admitted were related to the eastern region of Isfahan alone, which has a population growth and density higher than the average population of the city. The rate of the illiterate population over 6 years and the immigrant population are more in these two areas than the rest of the Isfahan regions. Therefore, this area seems to be a good option in case of the need to establish a new MMT Center or development of the toxicological health department.

Based on our results in this study, the majority of poisoning cases were intentional (93.1%), which seems reasonable given the age range of the patients that were often teenagers.

The majority of patients (57.1%) had used tramadol only, which was the same in other studies. However, combined drug intoxication was also relatively common, suggesting the surplus pharmaceuticals in households' drug basket.

A study conducted on deaths caused by opioids use in the U. S. from 1999 to 2011 showed that in 31% of deaths caused by opioids, benzodiazepines had been used as the associated medications.^[20] Benzodiazepines have been the

most common drugs used together with tramadol in most studies carried out on tramadol.^[20] In this study, among the patients taken another medicine together with tramadol, the greatest rate was related to clonazepam (24 patients), alprazolam (14 patients) and alcohol (11 patients), which are all the prescription or illegal drugs. Thus, it seems that further and more stringent measures are required to control the activities of pharmacies.

According to 62.4% of patients, tramadol has been already available in their home, which can indicate the possibility of the parents' addiction to tramadol or using it as a pain reliever. Also, 36.5% of patients had purchased tramadol from a pharmacy without a prescription. Given the directive of the distribution and consumption of narcotic drugs, this reaffirms the need for greater oversight of pharmacies.

The average amount of the drug used by patients in this study was equal to 1126 mg (approximately 12 of 100 mg tablets). In previous studies in Iran— based on the adult population—the maximum doses used had also been reported up to 20 grams.^[6,21] The average dose used in most studies has been between 1000 and 10,000 mg.

The most common form of the drug used by patients was the 100 mg tablet. There was a significant difference among the use of distribution of drug forms in different years. Thus, since the beginning of 2015, no poisoning with the 100-mg capsules has been seen, which would be due to reduced or stopped production of this form of the drug or its reduced distribution to pharmacies by the manufacturing companies.

The mean interval between the estimated poisoning time and the patient's admission to the hospital was equal to 3.39 h. According to the results, 90.8% of patients had been brought to the hospital before the end of 6 h of the poisoning. In a study conducted in 2009 in Tehran on the adult population, the average period time accounted for 6.1 h (Min: 0.5 h; Max: 24 h).^[6] A comparison of these results with the results of studies on adults shows that due to further attention of parents to their children, probably they notice the occurrence of poisoning sooner and bring them to medical centers faster.

The main symptom in the majority of patients on admission has been central nervous system depression (drowsiness, stuporous, or coma), which was the same way in most studies as well.^[5,6,21] Dizziness, nausea, vomiting and headache were all lower than the rates reported in previous studies.^[5,6,21] Thus, it seems that tramadol poisoning is relatively well tolerated by children.

Of all patients, 77.8% were discharged without particular problems, and 2 patients (1.1%) died. In an earlier study

in Isfahan on the adult population, two patients also had died (1.1%).^[5]

The mean duration of patients' hospitalization was 12.3 h (at least 1 h and the maximum up to 336 h-the mid of 10 h). The duration of hospitalization was dependent on the dose of the drug used, dosage form, the interval between exposure and acceptance, patient's blood glucose level on admission, level of consciousness on the time of admission, and incidence of seizure. In previous studies, a relationship between the duration of hospital stay and the dose of tramadol use was found.^[5]

Since a high percentage of patients in this study had received tramadol from a pharmacy without a prescription and given that tramadol is on the red list of controlled substances and medicines, the need for greater oversight of the pharmacies in this area seems to be necessary.

The results show that most of the poisoning cases in children and adolescents over 12 years have been intentional. Perhaps, strengthening emotional intelligence and training appropriate problem-solving methods instead of taking drugs could be put on the agenda of schools and their advisers. Furthermore, special attention should be paid to the mental health of parents as a model for teenagers.

In children with younger age, the poisoning cases were often unintentional. Thus, measures such as reducing children's access to these medicines, putting medications in a locked closet or at higher levels of the reach of children and use of children proof packaging can be important in the prevention of their poisoning.

Our results also suggest that the trend of acute tramadol poisoning among children is decreasing, mostly accidental in adolescents and commonly intentional among young children. Proper education to improve emotional intelligence for young adults and to keep drugs out of reach of the children and safer packaging is recommended to reduce tramadol poisoning incidence in the pediatric population.

Incomplete details of the studied patients' records, especially about demographic characteristics, family history, and history of diseases, was one of the limitations for our study.

AUTHORS' CONTRIBUTION

Ali Mohammad Sabzghabae and Nastaran Eizadi-Mood conceptualized the idea and Marjan Mansourian and AMS proposed and managed the study design and the research protocol respectively. Mohaddeseh Hedayati Goudarzi recruited the patients and gathered the data and drafted the manuscript. Nastaran Eizadi-Mood, Soroush

Mohammadi-Jouabadi and Payam Peymani analyzed the data and all authors have contributed for corrections and modifications of the manuscript and are accountable for the originality and validity of the data.

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Conflicts of interest

There are no conflicts of interest.

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