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Original Article

Tramadol overdose and apnea in hospitalized children, a review of 20 cases

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Abstract

We aimed to determine the clinical manifestations of tramadol intoxication in children and to find its potential poor prognostic factors. In a retrospective study, from 1363 cases of admitted pediatric poisoning, all tramadol-exposed hospitalized patients younger than 12 years were included in the study. They were hospitalized between March 2010 and April 2012 to the only referral hospital for pediatric poisoned patients in Tehran, Iran. Data including age, weight, gender, ingested dose (determined by history), pupil size, seizure, apnea, treatment interventions, and laboratory results was collected using chart review of the hospitalized intoxicated children. Twenty children with a mean age of 3.7 ± 2.9 years were identified amongst children during this 26-month period of whom, 14 (70%) had a decreased level of consciousness, 3 (15%) experienced apnea, and four (20%) had nausea and vomiting. Witnessed seizure did not occur in any of these patients. All patients were referred to hospital within 10.5 h of the exposure. The mean ingested dose was 9.6 ± 5.5 mg/kg. There was no significant relation between apnea and the estimated toxic dose. Apnea was more common in children who had presented with respiratory acidosis (Relative risk = 3.8, 95% CI = 1.6, 8.7, P = 0.043). All patients survived. Patients with apnea were managed conservatively by naloxone and recovered without need for intubation. Respiratory depression might occur at doses just above the therapeutic dose. We recommend an observation time of 12 h for all asymptomatic children who have ingested any dose greater than the therapeutic one.

Keywords: Tramadol; Intoxication; Overdose; Intensive care units, Pediatric; Apnea

INTRODUCTION

Unintentional ingestion of opioids by children may lead to respiratory or central nervous system (CNS) depression (1,2). Tramadol is a widely used analgesic with a dual mechanism of action: weak agonist at the μ-opioid receptor and inhibition of serotonin and norepinephrine reuptake. Mu receptor agonist may result in respiratory and CNS depression while the other action can cause seizures (3-7).

Tramadol was first marketed in Iran in 2002 (8). Since then, its use has increased dramatically with a 14.6-fold increase over two years (2004 to 2006; 24 million tramadol tablets (100 mg) in 2004 versus 162 million tablets in 2005 and 350 million in 2006) (4).

In contrast to other opioids, there is scant literature on pediatric tramadol intoxication (9-11). Although intravenous or oral form of tramadol has been used as an analgesic with doses of 1-3 mg/kg/day every 4-6 h in children older than four years (12-16), its safety in children younger than 12 years of age has not been confirmed. Currently there are some debates regarding managing moderate pain in children following European advice limiting codeine use and probable substitution of tramadol (17-19).

Non-therapeutic exposures have even been less described in pediatrics. The aim of this

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study was to describe the clinical manifestations of tramadol intoxication in hospitalized children and to determine the potential poor prognostic factors of this toxicity in pediatric population.

PATIENTS AND METHODS

Setting

Loghman-Hakim Hospital Poison Centre (LHHPC) is the only referral hospital for pediatric poisoned patients in Tehran, Iran (a city with 12.5 million permanent and 6.5 million temporary residents). Most paediatric poisonings who require hospital admission are transferred to LHHPC.

Participants

This was an observational, retrospective, single-centre case-series of children younger than 12 years of age with a history of tramadol exposure who had been hospitalized during 26 months (March 2010 to April 2012) at LHHPC. Children with multiple drug exposures other than tramadol were excluded. Cases were identified and reviewed from among all the hospitalized poisoned children using International Classification of Disease Codes (ICD10 codes version 2010). Those with code T40-4 (poisoning chapter; synthetic narcotics (Poisoning by, adverse effect of, and underdoing of other synthetic narcotics)), X42 (accidental poisoning), X62 (intentional self-poisoning), Y12 (poisoning, undetermined intent), and Y45.0 (adverse effects with therapeutic use) were evaluated for possible tramadol exposure.

Tramadol exposure was confirmed by history and qualitative enzyme-linked immunosorbent assay (ELISA, cut-off of 200 ng/ml) urine test which only shows true positive results with this cut-off level (20). Apnea was defined as witnessed, sudden, complete cessation of breathing with cyanosis either in hospital or during ambulance transport by physicians, residents, or paramedics that required medical intervention. Because of the retrospective nature of the study, details on milder forms of respiratory depression were not included. Acidemia and alkalemia were defined as venous blood pH less than 7.32 and greater than 7.42, respectively (21). Respiratory acidosis defined as a pCO2 greater than 52 mmHg and a low pH. Tachycardia and bradycardia were defined as >10th percentile or <10th percentile deviation from the accepted normal range for the age, respectively (22). Central nervous system involvement was graded by the CNS component of the poison severity score (PSS; 0-3 points) (23). This score classifies CNS involvement into none (0; no symptoms or signs), mild (1; i.e. Drowsiness, vertigo, tinnitus, ataxia, and restlessness), moderate (2; i.e. unconsciousness with appropriate response to pain, confusion, agitation, hallucinations, and delirium), or severe (3; i.e. deep coma with inappropriate response to pain or unresponsive to pain and extreme agitation). The score used in this analysis performed by the clinical care team at the time they were treating the patients.

Response to naloxone was considered positive if it improved arousal or reversed respiratory acidosis within 5 min.

Pupils were considered miotic if they were less than 2 mm in diameter and mydriatic if more than 5 mm.

Data including age, weight, gender, maximum possible dose ingested, on-arrival pupil size, on-arrival vital signs, and laboratory data on presentation as well as complications including seizures and apnea (at worst point during presentation and hospitalization) extracted from the medical charts were recorded. Dose was calculated based on the number of pills missing and/or interview with older children and/or parents. Data extraction was performed by three independent trained residents blinded to the study objectives using a specific self-made questionnaire prepared for the study. The quality of data abstraction, “accuracy” and “completeness” was assured by an attending pediatric physician on several occasions.

Statistical analysis was performed using statistical package for social sciences (SPSS) software and application of Mann-Whitney U-test (non-normal distributions according to the Kolmogorov-Smirnov test) for naloxone administration (mg/kg) and hospital stay (hours) or Student's t-test (normal

distributions) for naloxone bolus dose (mg/kg), age (years), pH, pCO_2, HCO_3, and PSS. Pearson's chi-square or Fisher's exact test was used for categorical data. In the variables with normal distribution, we mentioned the means and in those with non-normal distribution, median (inter-quarter range) was given. A *P* value less than 0.05 was considered to be statistically significant. This study was performed in accordance with the declaration of Helsinki and last revision in Hong-Kong (1984). Our institutional review board (IRB) considered this retrospective study and waived the need for formal IRB review.

RESULTS

Of 1363 admissions for poisoning in children younger than 12 years, 20 with tramadol exposure were identified (Table 1), 11 of whom were male (55%). Seventeen (85%) had directly presented to LHHPC and 3 (15%) were referred from other hospitals. All children had ingested immediate-release tramadol (sustained-release form is also available in Iran) at home either provided by their parents as an analgesic or as an unintentional oral exposure. As shown in Table 2, mean ingested dose was 13.1 ± 19.4 mg/kg. Mean age of the patients was 3.7 ± 2.9 years (range; 9 months to 10 years). Fourteen (70%) had decreased level of consciousness, 3 (15%) experienced apnea, and 4 (20%) had nausea and vomiting. On admission, pupils were miotic in 7 (35%), mydriatic in 2 (10%), and normal in the remainder (55%).

All patients had referred to LHHPC within the first 10.5 h of exposure (4.7 ± 2.9 h; range: 1 to 10.5 h). Time elapsed between exposure and presentation was more in the children with apnea (8.5 ± 2.8 vs. 4.2 ± 2.6 h, *P* = 0.044) with a mean difference of 4.32 h (95 % CI = 0.14, 8.50). All 3 children had experienced apnea before hospital admission or on presentation. There was a lower pH (7.28 ± 0.05 vs. 7.35 ± 0.08) and higher pCO2 (46.87 ± 5.58 vs. 37.52 ± 8.84) in initial blood gases in children who developed apnea following respiratory acidosis (Relative risk = 3.8, 95% CI = 1.6, 8.7, *P* = 0.043, Table 2). The minimum dose which led to hospitalization was 3.3 mg/kg (case number 14). Five children without symptoms on presentation remained asymptomatic over observation period and eight developed delayed symptoms after the 4^{th} h of hospital presentation. Of the three with apnea, time of apnea was determined to be 6.5 and 10.5 h after ingestion in two, both of whom were completely asymptomatic at 4 h post-ingestion according to the parent's history and EMS notes. There were no significant electrolyte disturbances in any of the children. Witnessed seizure did not occur in any cases. Table 2 shows demographic and clinical characteristics by the history, clinical manifestations, venous blood gas, and PSS.

All children had received standard dose of activated charcoal (AC; 1 g/kg); gastric washing (GW) via nasogastric tube was performed in one case (5%); AC and milk of magnesium (MOM) were administered to three (15%), and AC + GW + MOM were given to 16 (80%) patients.

Tramadol exposure had been confirmed by urine screen tests in all cases. Bolus (median interquartile range (IQR) dose: 0.03 (0.02-0.12) mg/Kg) or continuous (median (IQR) dose: 0.011 (0.008-0.024) mg/Kg/h) naloxone therapy was used in 17 patients (85% - Table 1). In 14 cases, it was used to reverse respiratory compromise and/or a depressed level of consciousness. In three, it was administered prophylactically. The median (IQR) total dose of naloxone was 0.18 (0.09-0.33) mg/kg (range; 0.05 to 4.00 mg/kg) and was tolerated without complications. The decision for a continuous infusion vs. bolus dose and/or discontinuation of the infusion was based on the physicians' clinical judgment. In most cases, two-thirds of the initial naloxone bolus dose which had reversed opioid effects was used per hours for six hours. It was then titrated every 6 h to achieve a normal consciousness level and preserve adequate respiration.

Two symptomatic children did not respond to bolus naloxone and remained unconscious (0.17 ± 0.23 mg/kg vs. 0.07 ± 0.11 mg/kg, *P* = 0.35). No other drug was detected in screen tests of these two patients and therefore, co-ingestion was unlikely. Not surprisingly, naloxone dose was higher in apneic patients (1.98 mg/kg ± 1.77 mg/kg compared to 0.16 ± 0.09; *P* = 0.001; relative risk = 3.8; 95% CI = 1.6, 8.7).

Table 1. Characteristics of 20 children with unintentional tramadol poisoning during hospitalization.

N	Age (y) & Gender	Elapsed hours (ingestion-admission)	Dose (mg/kg)	Clinical manifestation	Naloxone bolus dose (mg/kg)	Naloxone infusion hours	Total infusion dose (mg/kg)	Response to naloxone / route	Acid-base disturbance	Pupils	Apnea / numbers	PSS	Hospital stay (h)
1	10.0 F	1.0	25.5	Normal	0	12	0.19	-	RES-ALK+MET-ACID	mydriasis	no	1	34
2	2.0 F	1.5	16.4	Agitation, Weakness, Drowsiness	0.01	30	0.26	no	MET-ACID	normal	no	1	140
3	3.0 F*	6.5	10.5	Drowsiness, Ataxia	0.04	18	0.17	Yes / Bolus	RESP-ALK+MET-ACID	miotic	no	1	52
4	1.0 M*	10.5	10.0	Drowsiness, Rhinorhea, Itching, Cyanosis	0.36	30	3.64	Yes / Bolus	mixed-ACID	normal	Yes/2	3	36
5	1.0 M	3.0	9.6	Vomiting, Weakness, Drowsiness	0	0	0	-	normal	normal	no	1	12
6	5.0 M	4.0	9.5	Normal	0.02	12	0.07	Yes / Bolus	RESP-ACID	normal	no	1	36
7	1.0 M	1.0	8.8	Normal	0	12	.06	Yes / infusion	mixed-ACID	normal	no	1	36
8	9.0 F	1.0	8.8	Drowsiness, Headache, Vomitting, Cyanosis	0.02	12	0.16	Yes / Bolus	RESP-ACID	miotic	no	2	50
9	3.0 M	7.5	8.7	Vomiting, Drowsiness	.0	12	0.80	Yes / infusion	mixed-ACID	normal	no	1	24
10	10.0 F	ND	6.7	Cyanosis, Agitation, Vomiting, Vertigo, Diarrhea, Headache, Confusion	0.34	24	0.34	No	RESP-ACID	miotic	Yes/2	3	216

Table 1 (Continued).

N	Age (y) & Gender	Elapsed hours (ingestion-admission)	Dose (mg/kg)	Clinical manifestation	Naloxone bolus dose (mg/kg)	Naloxone infusion hours	Total infusion dose (mg/kg)	Response to naloxone / route	Acid-base disturbance	Pupils	Apnea / numbers	PSS	Hospital stay (h)
11	4.0 F	6.0	6.7	Weakness, Vomiting, Drowsiness	0.03	16	0.11	Yes / infusion	-	normal	no	1	48
12	3.0 M*	4.0	6.3	Normal	0	12	0.40	-	RESP-ALK+ MET-ACID	normal	no	1	26
13	4.0 M	ND	5.9	Normal	0	12	0.09	-	RESP-ALK	normal	no	0	36
14	4.0 F	2.0	3.3	Normal	0	0	0	-	RESP-ALK	normal	no	0	12
15	0.8 M	6.5	ND	Cyanosis, Weakness, Drowsiness, Tackycardia, Agitation,	0.12	18	1.16	Yes / Bolus	mixed-ACID	miotic	Yes/3	3	52
16	2.0 F	6.0	ND	Weakness, Cough, Drowsiness	0	0	0	-	normal	miotic	no	1	50
17	1.0 M	5.0	ND	Drowsiness, Agitation	0.02	12	0.13	Yes / Bolus	MET-ACID	miotic	no	1	24
18	5.0 M	ND	ND	Drowsiness, Bradycardia, Weakness	0.02	18	0.24	Yes / Bolus	normal	mydriasis	no	1	70
19	1.5 F	2.0	ND	Agitation, Vomiting, Vertigo, Ataxia, Drowsiness	0.03	12	0.13	Yes / Bolus	normal	miotic	no	1	24
20	5.0 M	9.0	5.9	Drowsiness	0	6	0.05	Yes / infusion	-	normal	no	1	12

M; male, ACID; acidosis, MET; metabolic, F; female, ND; not determined, RESP; respiratory, ALK; alkalosis, PSS; Poison Severity Score (0-3). *; Referred from other hospitals .

Table 2. Comparison between the children with tramadol induced apnea and the others.

Variable	All	Apnea children	Other patients	*P* value (applied statistical test)
Age (Years)	3.7 (± 2.9)	3.9 (± 5.9)	3.2 (± 2.1)	0.666 (student's *t* test)
Gender (Male/Female)	11/9	2/1	9/8	0.579 (Fisher's exact)
Dose ingested by the history (mg/kg)	13.1 (± 19.40	8.3 (± 2.3)	13.9 (±20.8)	0.372 (student's *t* test)
Clinical manifestations (Positive/Negative)				
Miosis	7/13 (30%)	2/1	5/12	0.270 (Fisher's exact)
Weakness	6/14 (25%)	1/2	5/12	0.681 (Fisher's exact)
Vomiting	6/14 (25%)	1/2	5/12	0.681 (Fisher's exact)
Agitation	5/15 (20%)	2/1	3/14	0.140 (Fisher's exact)
Cyanosis	4/16 (20%)	3/0	1/15	0.004 (Fisher's exact)
Ataxia	3/17 (15%)	0/3	3/14	0.596 (Fisher's exact)
Tachycardia	3/17 (15%)	1/2	2/15	0.404 (Fisher's exact)
Vertigo	2/18 (10%)	1/2	1/16	0.284 (Fisher's exact)
Headache	2/18 (10%)	1/2	1/16	0.284 (Fisher's exact)
Cough	1/19 (5%)	0/3	1/16	0.850 (Fisher's exact)
Itching	1/19 (5%)	1/2	0/17	0.150 (Fisher's exact)
Rhinorrhea	1/19 (5%)	1/2	0/17	0.150 (Fisher's exact)
Bradycardia	1/19 (5%)	0/3	1/16	0.850 (Fisher's exact)
Venous blood gas				
pH	7.34 (± 0.08)	7.28 (± 0.05)	7.35 (± 0.08)	0.103 (student's *t* test)
pCO_2	39.08 (±	46.87 (± 5.58)	37.52 (± 8.84)	0.072 (student's *t* test)
HCO_3	21.02 (±	22.30 (± 1.87)	20.76 (± 2.69)	0.298 (student's *t* test)
Poison Severity Score	1.25 (± 0.85)	3	0.94 (± 0.43)	0.001 (student's *t* test)
Naloxone administration (if any) (mg/kg)	0.48 (± 0.95)	1.98 (± 1.77)	0.16 (± 0.09)	0.001 (MVU)
Hospital Stay (hours)	49.5 (± 48.1)	101.3 (± 2.3)	40.3 (± 30.3)	0.039 (MVU)

Data are presented as mean value (± SD). MWU; Mann-Whitney U test.

Except for CNS poison severity score and cyanosis on presentation, there were no signs or symptoms that predicted respiratory failure (P<0.001 and P = 0.004, respectively, Table 2). None of the children required intubation. All patients were discharged without any complications with a significantly higher length of stay in apneic patients (P = 0.039; Levene's test for equality of variance, P = 0.001; Table2).

DISCUSSION

This observational case-series showed an apnea frequency of 15% in hospitalized pediatric patients with isolated tramadol overdose. Late presentations were more likely to accompany with apnea probably because children with a known history of tramadol ingestion were visited early and rarely became sick, while some apneic children were ultimately found to have unintentional tramadol poisoning.

Although many of the patients had referred too late to undergo GI decontamination, this procedure had been performed for all. Naloxone use was common; this may have prevented apnea in some children. Its use was not standardized but at the discretion of the treating physician.

Tramadol poisoning is a serious problem in the pediatric age group in Iran. In one forensic series, 1.7% (5 cases) of tramadol fatalities had happened in patients younger than 10 years and another 10.5% in those aged 10 to 19 (24). Tramadol was classified as a controlled drug in Iran in April 2007 (14). Tramadol has an agonist effect at μ-opioid receptors as well as noradrenergic and serotonergic systems. Cytochrome P450 (CYP) 2D6 catalyses O-demethylation of tramadol to the more active M_1 (O-desmethyl tramadol) enantiomer that is 200 times more potent than tramadol at the mu receptor. Nine-hour elimination half-life of this active metabolite may cause accumulation with

regular dosing compared to 6 h half-life of tramadol therapeutic dose in adults. Large inter-individual variability in the CYP2D6 activity is reported within a population and between ethnic groups (3,26,27). Analgesic and toxic effects of tramadol may vary more than 30-fold between poor and extensive metabolizers (28). Middle Eastern and Eastern African ethnic groups are more likely to be ultra-rapid metabolizers compared to those from Middle Europe and North America (rate; 21-29% vs. 0.5- 1%, respectively). Accordingly, more opioid effects, sedation, and respiratory depression are expected in them (28-31). This is even more important in pediatric population as it seems that changes in metabolic capacities vary between children and adults (32). Recent works on pediatric and adult ultrarapid metabolizers confirmed higher prevalence of sedation and apnea if tramadol exposure happened in this group of patients (33,34). Our previous data showed the prevalence of apnea to be 3.6% in 525 studied adult tramadol-poisoned patients (35), a percent far less than current 15% rate of apnea in children.

Previous studies in children showed that individual naloxone doses up to 0.4 mg/kg and constant intravenous infusion of 0.16 mg/kg/h had not been associated with adverse effects (36). Our study showed that tramadol overdose necessitated similar doses of naloxone for therapy with no consequent adverse effects.

One of three children with apnea did not respond to naloxone; however, he did not require intubation and mechanical ventilation, either. Use of naloxone resulted in longer hospitalizations due to the need for tapering instead of abrupt cessation. No seizures were observed although unwitnessed seizures might have occurred prior to hospital presentation. According to the available data, children have tolerated 100-300 mg tramadol ingestion (7.35 mg/kg) with only mild sedation, agitation, tachycardia, and no seizures. Administration of a 100 mg suppository to a 6-month-old child resulted in seizures (37). It seems that tramadol induces its convulsive effect via γ-aminobutyric acid inhibitory pathway which can be secondary to its opioid receptor agonist activity or as a result of serotonin and norepinephrine re-uptake inhibition (38).

Spiller and coworkers reported no symptoms in children younger than six years who had ingested a tramadol dose of less than 10 mg/kg. In their study on 15 children, all symptoms occurred within four hours post ingestion (15). Based on this study, Sachdeva and colleagues suggested four hours of emergency department observation in asymptomatic patients who had ingested more than 10 mg/kg of tramadol. A dose less than 3.3 mg/kg was considered non-toxic (1). Current issues regarding toxic dose and observation time are against their recommendations.

These two facts have questioned observation time and dose of toxicity in pediatric group and confirm tramadol narrow therapeutic index. Even more, in the current study, calculated ingested dose was based on the number of ingested tramadol pills. Since many of these patients had vomited before presentation and/ or gastric lavage had been performed for them, the actual absorbed tramadol was even less than the calculated dose based on the history. The minimum estimated oral dose of tramadol that caused apnea in this study was 6.7 mg/kg (Table 1). Regarding risk factors, current study demonstrated that the occurrence of apnea was statistically independent of age, dose, and gender (all p values were not significant). A previous study in adult poisoned patients showed that 3.6% of them experienced apnea and mortality would be higher in apneic patients (35). We did not identify any demographic or clinical features predisposing apnea in this study except for on-arrival respiratory acidosis, subsequent cyanosis, and PSS. In particular, renal impairment was not present in any of the patients who experienced apnea. Interestingly, no witnessed seizure was reported in our cases. Those who did not respond to naloxone despite loss of consciousness might have experienced an unwitnessed seizure before admission.

There are probably limitations to the case ascertainment procedure and low sample size, the retrospective data recording, and the chart abstraction. While pediatric apnea is defined as cessation of respiratory airflow for 20 s or shorter if associated with bradycardia or cyanosis (37), we had to choose those cases with complete cessation of breathing to

increase the accuracy of case selection. In fact, the actual rate of apnea may have been more than 15% in our series.

On the other hand, it is difficult to generalize the results in this group of children to pediatric cases in general including those who were not hospitalized because of their mild nature of toxicity or because they had died before reaching the hospital.

Although tramadol exposure was confirmed by qualitative tests, we could not measure tramadol and most other drug levels by quantitative methods. Doses are therefore estimates based on the history taken from elder children and/or parents and may not be actually correct. On the other hand, even tramadol screen test may encounter false negative results when serum tramadol level is less than 200 ng/ml cut-off point.

Also, the retrospective nature of this study did not let us doing any laboratory investigation for all xenobiotics; but, due to the unintentional nature of poisoning and history, poly-drug consumption is unlikely.

The generalizability of this data to different populations should be considered. Although we recommend more observation period for those who are living in the Middle Eastern and Eastern African countries, this time may be reduced in the Middle Europe and North American regions where patients are less likely to be ultra-rapid metabolizers (29,30). By the way, immigrants live in these areas and genetic maps may be interfered; this complicates the recommendation for reducing observation time.

Due to limited number of cases, we were not able to exclude participants with missing data and perform a complete case analysis, as well.

CONCLUSION

Four- to six hours observation period is not enough for tramadol intoxicated children. Toxicity and further respiratory depression may occur at doses just above the therapeutic dose. All pediatric patients may recover without intubation and mechanical ventilation while the main treatment is naloxone administration and supportive care. Due to the potential for delayed onset of life-threatening symptoms such as apnea, we recommend a 10.5 h period of observation in asymptomatic children rather than the 4 h observation period recommended by Sachdeva and coworkers (1). Further prospective studies are needed to confirm these recommendations.

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