

Tramadol intoxication in infants: experience at a tertiary care hospital in Dhaka, Bangladesh

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ABSTRACT

Background: Tramadol is a widely used opioid analgesic for different types of pain. Very few cases of acute tramadol intoxication in infants have been reported where respiratory and central nervous system depression are frequent. The aim of this study was to evaluate the clinical manifestation, treatment and outcome of tramadol intoxication in infants.

Methods: This was a retrospective observational study of hospitalized infants in the Department of Neonatology and Paediatrics in BIRDEM General Hospital, Dhaka, Bangladesh from February 2014 to November 2019. Ten infants with history of administration of tramadol suppository were included in this study. Data regarding clinical features, cause of the “incident dose and route of administration” of tramadol, effects of naloxone and outcomes were recorded and analyzed.

Results: Of 10 infants, 6 were male and 4 were female. The mean age was 5.1 ± 3.0 months and the mean weight was 6.1 ± 1.8 kg. The mean time of onset of symptoms after drug administration was 2.6 ± 1.0 hours with a mean dose of 17.9 ± 6.4 mg/kg body weight. The main clinical features were decreased level of consciousness (100%), seizure (80%), meiosis (80%) and apnoea (50%). In each 50% (5) of cases, tramadol was given erroneously instead of glycerine and paracetamol suppository. Among them 2 (20%) infants received tramadol suppository as an over-the-counter (OTC) drug. All infants were treated with naloxone without any side effect. In addition, three infants needed mechanical ventilation. The average duration of hospital stay was 89.3 ± 47.4 hours. Nine infants were discharged and one (10%) died.

Conclusions: Our study suggested that tramadol intoxication among infants is predominantly accidental. Early identification and prompt initiation of treatment are essential. The creation of public awareness about the safe storage of drugs at home and avoidance of OTC drugs can prevent tramadol intoxication in children.

Key words: Infants, tramadol suppository, tramadol intoxication, naloxone, mechanical ventilation.

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INTRODUCTION

Tramadol is a centrally acting synthetic opioid analgesic. It acts on the μ receptor as an agonist and inhibits the reuptake of serotonin and norepinephrine in the central nervous system (CNS).¹ Tramadol is widely used in adults to treat both acute and chronic pain of moderate to severe intensity.¹ But the Food and Drug Administration (FDA) did not approve the use of tramadol in children less than 12 years of age.² However, this drug is used in children over 1-3 years of age in Europe.³ It can be administered orally, sublingually, rectally, sustained/immediate release and in solution for intravenous (IV)/intramuscular (IM) administration. The absorption of oral and rectal tramadol is almost the same.^{3,4} Peak plasma concentrations after oral and rectal administrations are reached in 1-2 hours and 3 hours respectively.^{1,3} It is extensively metabolized in the liver, mostly by CYP2D6 to O-desmethyltramadol which is 200-300 times more potent than tramadol at μ receptor.^{5,6} Severity of toxicity depends on weight, age, sex, dose, route of administration and gene polymorphisms of metabolizing enzymes.^{3,5,7} Classic features of intoxication are bradypnea or apnea, CNS depression and meiosis.⁸ Others include seizures, dizziness, confusion, nausea, vomiting, constipation, haemodynamic instability, headache and dry mouth.^{3,9-12} Blood glucose abnormality, hepatic injury and anaphylaxis are also evidenced.¹²⁻¹⁴ Toxicity can be reversed by naloxone without significant adverse effects. But there is evidence of seizure after naloxone.^{15,16}

Tramadol intoxication is rare in younger children and this occurs mostly accidentally.¹⁷⁻²⁰ A retrospective study was done in Tehran among hospitalized poisoned patients from 2006 to 2007, where paediatric tramadol intoxication was found in 15% of cases but all of them were more than 12 years of age.²¹ In our country only one single centre study was found on accidental tramadol intoxication in children. So, we did this study to explore the sign-symptoms, treatment and outcome as well as to create awareness.

METHODS

This was a retrospective observational study on infants who had a history of giving tramadol suppository. Ten infants were enrolled from February 2014 to November 2019 in the Department of Neonatology and Paediatrics, BIRDEM General Hospital. Extracted data: age, sex, weight, route and dose, time of onset of symptoms, elapsed time before hospitalization and cause of incident were recorded. Level of consciousness, pupil size, respiratory depression, apnoea, seizure, bradycardia/

tachycardia, hypotension/hypertension and vomiting were documented at admission and during the hospital stay. Arterial blood gas (ABG), serum creatinine, serum glutamic pyruvic transaminase (SGPT) and blood glucose reports were collected from hospital data. Overdose of tramadol was defined when the dose exceeded 8 mg/kg/day and intoxication was considered when infants developed features of toxicity following overdose. Due to unavailability, we did not measure the blood level of tramadol. Supportive care and naloxone were provided to all infants. Injection naloxone was given as IV bolus /continuous infusion at a dose of 0.1 to 0.2 mg/kg and 0.16 mg/kg/hour respectively. Response to naloxone was considered positive when consciousness level improved and respiratory depression reversed within 5 minutes. Infants who had prolonged apnoea or severe respiratory depression needed intubation and mechanical ventilation. Adverse effects of naloxone, duration of hospital stay and outcome were also recorded. All data were analyzed by frequency distribution with the help of SPSS version 21.

RESULTS

Among ten infants 6 (60%) were male and 4 (40%) were female. The mean age was 5.1 \pm 3.0 months and the mean weight was 6.1 \pm 1.8 kg. The mean time of onset of symptoms after drug administration was 2.6 \pm 1.0 hours with a mean dose of 17.9 \pm 6.4 mg/kg body weight (all infants got 100 mg tramadol suppository). The mean elapsed time before hospitalization was 3.9 \pm 2.0 hours.

At presentation, all (100%) infants had decreased level of consciousness with meiosis in 80% of cases (Table I). Besides eight infants (80%) had a history of seizure on one occasion.

Table I Clinical manifestations of tramadol intoxication (N=10)

Clinical manifestations	No of cases (Percentage)
Decreased level of consciousness	10 (100)
Seizure	8 (80)
Meiosis	8 (80)
Apnoea	5 (50)
Hypotension	4 (40)
Tachycardia	4 (40)
Bradycardia	1 (10)
Vomiting	1 (10)

** Infants had more than one symptoms at a time

Infants were managed with supportive care and antidote naloxone. Three infants needed mechanical ventilation and two infants got anticonvulsants. Six (60 %) infants received injection naloxone as continuous infusion and another 4 (40%) got as IV bolus on two occasions. No adverse reaction was noted after naloxone.

The average duration of hospital stay was 89.3 ± 47.4 hours. Nine infants (90%) were discharged and one (10 %) died who came 8 hours after tramadol exposure.

Out of 10 infants, 5 (50%) got tramadol suppository instead of glycerine for constipation and 3 (30%) infants got this drug instead of paracetamol suppository for fever mistakenly. Tramadol suppository was given to another 2 (20%) cases for fever as an over-the-counter medicine. In all cases suppository was given by the parents unintentionally. Tramadol suppository was kept at home for adults as analgesics.

DISCUSSION

We have summarized 10 cases with tramadol intoxication, a centrally acting synthetic analgesic. Tramadol was patented in 1963 and launched in 1977 by a West German pharmaceutical company. In the mid-1990s it was approved by the FDA in the United States and also approved in the United Kingdom.^{1,2} The recommended therapeutic dose in children is 1-2 mg/kg every 6 hours.¹⁸ Tramadol is almost completely absorbed (>90%) after oral, rectal and intramuscular administration. The average bioavailability is 70%.¹ It is subsequently eliminated by the kidney with an excretion half-life of 6 hours in children.^{18,20} The serum therapeutic levels are 0.2 to 0.8 mg/l and toxicity is considered when above 1mg/l.^{18,23}

In infants, few cases of acute tramadol poisoning have been reported, mostly occurred after oral and parenteral administration.^{8,18-20,24-26} Zamani et al described 228 infants and 82 toddlers with acute tramadol poisoning where only 1 patient got per rectal tramadol.⁸ Besides this one, very few cases were found who developed intoxication after per-rectal administration of tramadol.^{22,25,26}

In our study, decreased level of consciousness was found in all cases after tramadol exposure which was accompanied by meiosis in 80% of cases and apnoea in 50% of cases. Although the prevalence of these symptoms varies in different studies, these are the classic triad of opioid intoxication.^{8,9,11,19}

Seizure seems to occur in the first hours following a high dose of tramadol. It occurs often as an isolated event or with other features of tramadol poisoning.^{3,8,9,27} Spiller et al. studied 87 patients with tramadol poisoning and described seizures in 8% of cases.²⁸ Zamani et al found 10.3%, Talaie et al found 46.2% and Rahman et al found 18% seizure episode in children following tramadol intoxication.^{8,22,29} The frequency of seizure (80%) in our study is remarkably higher.

Other clinical features we experienced in our study were tachycardia and hypotension in 4 (40%) cases and bradycardia in 1 (10%) cases. A few cases of cardiogenic shock and haemodynamic instability have been reported in the literature.^{10,17}

Another symptom of tramadol intoxication described in different studies is vomiting, which was 10% of cases in this study. Walton et al described nausea and vomiting in 75% of cases following tramadol poisoning where Hossein et al found only 20% of children experienced vomiting after intoxication with tramadol.^{11,19}

Tramadol exposure was confirmed by the history from parents, we could not measure the blood level of tramadol. According to the available data, children tolerates 7.35 mg/kg tramadol with only mild sedation, agitation, tachycardia and no seizures.^{3,10,19} In our study the mean administered dose of tramadol was 17.9 ± 6.4 mg/kg. Hossein et al described the mean administered dose of tramadol in which children showed features of intoxication was 9.6 ± 5.5 mg/kg and Walton et al found 14.8 mg/kg which signifies that our patients got a much higher dose of tramadol.^{11,19}

We found the meantime of onset of symptoms was 2.6 ± 1.0 hours which was similar to another study.¹¹ On the contrary with this study Rahman et al described 5.2 hours and Hossein et al found 4.7 ± 2.9 hours needed to developed features of tramadol intoxication.^{19,22}

There is controversy over the use of naloxone in tramadol intoxication. But it accelerates recovery in case of CNS depression and hypoventilation.²⁰ Grosek et al. showed naloxone improved CNS depression in seven out of eight patients.¹⁶ Another multicentre study showed naloxone was immediately beneficial for apnoea and drowsiness in 4 out of 8 patients but also caused seizure immediately following administration of naloxone in one patient.²⁷ Though the seizure could be the residual effect of tramadol.^{27,30} However, other studies

showed bolus dose of naloxone up to 0.4 mg/kg and continuous IV infusion of 0.16 mg/kg/hour in children had not been associated with significant adverse effects.^{15,16,30} In our study naloxone was given to all infants without any side effects. So, despite lots of dilemma regarding the use of naloxone, it could be useful as diagnosis and/or treatment of tramadol intoxication with close monitoring.

Nine infants were discharged with an average duration of hospital stay of 89.3±47.4 hours. This result does not correspond with Hossein et al and Rahman et al, who narrated less duration of hospital stay in case of tramadol intoxication.^{19,22}

Though fatality in the case of paediatric tramadol intoxication is rare but may cause death if handled too late or in case of aspiration or cardiac toxicity.^{10,17,18} Zamani et al stated that no children died after tramadol poisoning among 310 patients aged less than 2 years.⁸ Sruthi et al described two infants who died after tramadol intoxication on the way to the hospital due to a delay in recognizing symptoms by parents.¹⁸ In our study, one infant died who reached hospital 8 hours after tramadol exposure with severe CNS and respiratory depression.

Maternal anxiety, similarities of tramadol with paracetamol and glycerine suppository and easy availability of tramadol are the main cause of accidental intoxication in our study which was similar to another study.²² But family drug addiction, unintentional therapeutic overdose, accidental and parental poisoning/Munchausen syndrome by proxy were also reported in different studies as a cause of tramadol intoxication in children.^{18,20}

Conclusions

Our study found that the most important symptoms following tramadol intoxication were decreased level of consciousness, seizure, meiosis and respiratory depression. The occurrence of intoxication was mostly accidental. Though tramadol intoxication is rare but can lead to death. Parenteral and public alertness about the use of drug and avoidance of non-prescription medicine can prevent this kind of incident.

Author contribution: JB, NB, NI designed the research; JB, NB analyzed data, drafted manuscript, TB reviewed manuscript, All authors read and approved the final manuscript.

Conflicts of interest: Nothing to declare

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