

## Severe Tramadol Overdoses in Children: A Case Series Admitted to Paediatric Intensive Care Unit

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### Abstract

Tramadol misuse can lead to severe intoxication in which respiratory failure and seizures are frequent. We reviewed 7 paediatric cases of patients hospitalized in the Intensive Care Unit. We reported unusual hypertonia and chest rigidity leading to ventilator difficulties. None of the children were suspected to be ultra-rapid metabolizers, and one case led to death.

Overdoses can lead to death and must maintain practitioners on alert because of the increasing use of tramadol in the paediatric population. The handling of the bottles should be explained to families and Naloxone could be efficient when opioids signs.

**Keywords:** Tramadol; Paediatric; Rigid chest; Intensive care units; Intoxication; Overdose

### Introduction

Tramadol ( $\pm$ cis-2-[(dimethylamino) methyl]-1-(3-methoxyphenyl)- cyclohexanol hydrochloride) is a common painkiller used for the management of mild to moderately severe acute pain. It is a central analgesic that works through two mechanisms according to its two enantiomers, being effective on  $\mu$ -opiate receptors agonists but also on serotonin and norepinephrine reuptake inhibition [1,2].

This painkiller is metabolized in the liver through the P450 cytochrome, cytochrome P450 CYP2D6 being the main metabolizer conducting in the O-demethylation. The pharmacodynamic active metabolite seems to have a 200-300 higher affinity for  $\mu$ -opiate receptors than tramadol [3]. The genetic polymorphism of those cytochromes explains the inter-individual variability of tramadol pharmacokinetics.

In California, Tramadol is the fourth cause of drug poisoning in adults, and seizures are frequently reported [4]. Due to O-desmethyltramadol's affinity for the  $\mu$ -opiate receptors, an overdose can cause systemic symptoms such as nausea, vomiting, and respiratory or neurologic depression [5]. Other clinical presentations include serotonergic syndromes or tonico-clonic seizures [5-7].

Intoxication is rare in the paediatric population and few cases are reported [3,5,6,8-11]. We report 7 paediatric cases of Tramadol poisoning (voluntary or accidental) for patients admitted in our Paediatric Intensive Care Unit (PICU). Among clinical symptoms, chest rigidity was unusually documented. We did not suspect ultra-rapid metabolisms in our patients.

### Patients and Methods

This was an observational, retrospective, single-center case-series of children hospitalized in PICU from November 2008 to June 2016. Cases were identified and reviewed from among all the hospitalized poisoned children for which Tramadol overdose was confirmed. We defined as overdose an excessive dose taken by the child. The usual dose is 1 to 2 mg/kg every 6 hours, not to exceed 8 mg/kg/24 hours with a maximum dose of 400 mg/day if the child's weight exceeds 50 kg. Intoxication was confirmed by quantitative blood sample and questioning the child and/or parents. Informed consent was waived according to French law.

Cases were identified combining PICU database with International Classification of Disease Codes (ICD10 codes version 2010) with T40 codes (Poisoning by narcotics and psychodysleptics [hallucinogens]): T40.2 (Other opioids, Codeine Morphine), T40.4 (Other synthetic narcotics Pethidine), T40.6 (Other and unspecified narcotics) and T40.9 (Other and unspecified psychodysleptics [hallucinogens]). Patient data were extracted from the medical charts and recorded from informatics medical records and hospital reports.

The review of the medical literature was made by using PubMed key concepts: children/paediatric tramadol intoxication / overdose.

### Results

**Case Reports:** All 7 cases are reported in Table 1

#### Case 1

A 15.5 year-old girl was admitted in PICU following 2 general convulsive seizures with persistent post-critical confusion. She received 1 dose of Diazepam after each seizure. She didn't present hemodynamic failure and was intubated because of persistent

drowsiness. Pupils were middle and reactive. Since a febrile headache was reported, the patient received antibiotics and an antiviral treatment. Infectious, metabolic and traumatic causes were excluded. She presented a moderate hepatic cytolysis. Cerebral imaging (scanner and Magnetic Resonance Imaging) and an electro-encephalography (EEG) were not conclusive. A toxicological blood screening showed Tramadol levels of 5.51 mg/L (the therapeutic window ranging from 0.2 mg/L to 0.8 mg/L). After extubation, she explained the act as a voluntary intoxication. Apneas were still observed and she received Naloxone. 48 hours after intoxication, Tramadol levels were of 0.075 mg/L. She was discharged without sequelae on day 4.

#### Case 2

A one year-old boy was examined at home when consciousness disturbances quickly appeared. Following a child care investigation, drug intoxication was suspected. The Paediatric Glasgow Coma Scale score was of 9 and the boy exhibited hypoventilation (apneas and bradypneas) with bilateral myosis. A Naloxone injection led to rapid improvement. The toxicological screening showed Tramadol levels of 0.96 mg/L. The boy quickly returned to a proper level of consciousness. He was not intubated and was discharged after 1 day in the Intensive Care Unit. This was considered to be the accidental intoxication of a child at home due to negligence.

#### Case 3

A one month-old girl was admitted to the Emergency Unit (EU) with tonico-clonic seizures. She was pale and hypotonic but didn't present hemodynamic failure. She first displayed hypoventilation at a very slow frequency (10-15/min) and ample respiratory movements. Her pupils were in symmetric and reactive myosis. She was drowsy, did not completely wake up after stimulation, and presented abnormal diffuse clonic movements.

The computed tomography of the brain, the chest radiography and the cardiac and abdominal ultrasonography's were normal; an electro-encephalography (EEG) was not available. She was given 0.3 mg/Kg of Diazepam and 15 mg/Kg of Phenobarbital to treat epileptic episodes, but these did not improve her neurological status. Management was symptomatic and required invasive respiratory support after an attempt at non-invasive ventilation support failed because of chest wall rigidity. The toxicology analysis revealed a high level of Tramadol in blood samples (0.78 mg/L) and traces of Zolpidem (0.016 mg/L, normal therapeutic range: 0.1-0.2 mg/L). The evolution was spontaneously favorable with complete neurological recovery in the first 24 hours. Tramadol was still present in blood samples one day after admission (0.07 mg/L) with traces of Zolpidem. No injections of Naloxone were performed. She was quickly extubated and discharged from the PICU on day 3. We subsequently learned that the poisoning might have happened through the mother.

#### Case 4

A 13.5 year-old girl was admitted in PICU after a suicide attempt. She seemed to have swallowed Tramadol, Lanzoprazole (a proton-pump inhibitor), Ebastine (an antihistaminic) and Paracetamol. She presented a convulsive tonico-clonic seizure and was intubated. Her initial paediatric Glasgow Coma Scale score was of 8. The toxicology analysis revealed a high level of Tramadol in blood samples (4.68 mg/L). Flumucil was promptly administered and recovery was

prompt. The extubation was possible at hour 6 and the patient was discharged from the PICU 1 day after being admitted.

#### Case 5

A 4 year-old girl was prescribed Tramadol after thigh abscess surgery. Tramadol was used before each daily dressing. One month after the surgery, she was found unconscious at home. The medical care at home found a Glasgow Scale Score of 3 with no hemodynamic failure. The state of consciousness improved after stimulation. The transfer could occur without an intubation. In the PICU, we noticed that there was generalized hypertonia with a paediatric Glasgow Coma Scale Score that was still of 3. Clonazepam was administered because the hypertonia was considered to be a convulsion. Clonazepam was ineffective. The patient was intubated due to low chest compliance and respiratory arrest. The computed tomography of the brain, the transcranial Doppler, the lumbar puncture and the biology were normal. The EEG was uninterpretable under sedation. The chest radiography tended towards right aspiration pneumonia. The toxicology analysis revealed a high level of Tramadol in the blood samples (4.16 mg/L). An empty bottle was later found on the couch in the family's home. Because of simultaneous vaginal bleeding, a court reporting was conducted. Our patient was extubated on day 2 and was discharged of PICU on day 4 with right aspiration pneumonia as the only sequela.

#### Case 6

A 3 year-old and formerly premature boy with asthma had been examined at the EU during the day for a herpetic gingivostomatitis and fever. Tramadol and Paracetamol had been prescribed. In the evening, after 1 administration, he was described as unstable when standing and with moderate breathing difficulties, which led to the administration of Ventolin. Loss of contact with eye revulsion and staring occurred. Limbs were described as being in hypertension but no abnormal movements were observed. When the medical home-care team arrived, the patient's Paediatric Glasgow Coma Scale score was of 5 with generalized hypertonia, high blood pressure and tachycardia. Diazepam was ineffective. The patient was then intubated because of apneas, at which time he inhaled. He presented a first cardiac arrest while he was being medically transported (about 5 hours after taking Tramadol), and recovered a heartbeat after 8 minutes reanimation but kept a refractory hypoxia post inhalation.

The clinical presentation was immediately severe when he was admitted in the PICU; a second cardiac arrest occurred in the EU and was fatal after 53 minutes of resuscitation maneuvers.

Post-mortem explorations detected moderate hepatic cytolysis but the lumbar puncture and biological samples were normal. The whole-body scanner only showed post-reanimation bilateral pulmonary condensation. The toxic screening found Tramadol levels of 3.49 mg/L. When exploring Tramadol metabolizer cytochromes, an ultra-rapid metabolism was not detected. The family was informed of the diagnosis and couldn't give an explanation. It seems that the boy had received a single administration of Tramadol. Upon examination of the Tramadol bottle, it was revealed that 340 mg were missing (10 times the prescribed dose).

#### Case 7

A 17 month-old healthy boy presented a seizure at home when he was found to be sleepy, with a hoarse voice, eye rolling and with clonic contractions of the mouth. A package of sustained-release Tramadol of

150 mg was found near him. At the EU, he presented hypoventilation and two generalized tonico-clonic seizures. The first seizure stopped spontaneously, the second one stopped with a 10 µg/kg Naloxone injection. Naloxone was kept at 10 µg/kg/h. A normal resumption of consciousness was progressively observed, with a persistent state of agitation. Seven hours after absorption, the Tramadol dosage was of 5

mg/L and Naloxone was maintained for less than 10 hours due to clinical improvement. The patient was discharged after 24 hours of surveillance. Parental questionnaires revealed that the family was moving from one house to another and that the pharmacy box was therefore within reach of the child.

Case	Age (years, months)	Gender (F/M)	Voluntary intoxication	Blood level (mg/L)	Co-intoxication (molecule)	Neurological		Respiratory depression	Intubation	Hemodynamic	Pediatric Intensive Care Unit Stay (day)	Antidote	Death
						Number of Seizures	Level of Consciousness						
1	15 y 6 m	F	Child voluntary intoxication	5.51	No	2	Drowsy	Apneas	Yes – 1 day	stable	4	Naloxone	No
2	1 y	M	Child accidental intoxication	0.96	No	0	GSCS 9-10	Apneas, hypoventilation, bradypnea	No	stable	2	Naloxone	No
3	1 m	F	Probable parental voluntary intoxication	0.78	Yes (Zolpidem)	1	Drowsy	Apneas	Yes – 1 day	stable	4	No	No
4	13 y 5 m	F	Child voluntary intoxication	4.68	Yes (Paracetamol)	1	GCS 8	No	Yes – 1 day	stable	1	N-acetylcysteine	No
5	4 y 2 m	F	Child accidental intoxication	4.16	No	0	GCS 3	Hypoventilation low chest expansion then respiratory failure	Yes – 2 days	stable	4	No	No
6	3 y	M	Parental accidental intoxication or parental voluntary intoxication	3.49	No	1	GCS 5	Apneas and hypoventilation, likely aspiration pneumonia	Yes – 1 day	cardiac arrest	1	No	Yes
7	17 m	M	Child accidental intoxication	5	No	3	Drowsy	Hypoventilation	No	stable	1	Naloxone	No

y: Years; m: Months; F: Female; M: Male; GCS: Glasgow Coma Scale

**Table 1:** Epidemiology of 7 cases.

## Discussion

We describe 7 various paediatric cases of Tramadol intoxication, a centrally acting, synthetic analgesic agent. Although its metabolite has some affinities for µ-opiate receptors, it exerts its analgesic effect by inhibiting the re-uptake of norepinephrine and serotonin and by increasing their respective release or secretion. This process depends on ontogeny, postmenstrual age-dependent CYP2D6 activity and polymorphisms [12].

The recommended therapeutic dose in children is of 1-2 mg/kg every 6 hours. The peak serum level is attained in 30 minutes and it is subsequently eliminated by the renal route with an excretion half-life of 6 hours in children. The serum therapeutic levels are of 0.2 to 0.8 mg/L, and toxicity is considered when above 1 mg/L [2,13].

In adults, overdose symptoms include hypotonia with hypoventilation and, sometimes, seizures. Patients present generalized and tonico-clonic seizures in 84% cases, a single seizure in 45% and multiple seizures in 55% of cases. Most seizures (85%) occur in the first 24 hours and mainly concern young adults between 20 and 30 years old [4,5,7,14].

An EEG sometimes reveals epileptiform patterns. Frequently, patients present a central nervous system depression linked to the opioid effects of Tramadol, but real serotonergic syndromes involving tachycardia, hyperthermia, hypertension, hyper reflexia and clonus have been described [6,15]. Srinivas et al. confirmed respiratory depression and seizures as an effect of Tramadol central action [16]. In our cases, we can notice the appearance of chest rigidity with initial transient difficulties to ventilate. In case n°3, this symptom made it

possible to evoke an opioid intoxication. Truncal rigidity can be seen in severe serotonin syndrome [7] and can lead to respiratory failure.

These symptoms can be linked to global or limb hypertonia as seen in those intoxications, as described by Mazor et al. [5]. In addition to fentanyl intoxication, ventilation difficulties or abnormal rigid-chest syndromes should also make us think of serotonin syndrome and/or tramadol intoxication. Seizures seem to occur in the first hours following Tramadol ingestion and are often isolated. Only 7% of patients have more than one seizure, and prophylactic anticonvulsant therapy seems unnecessary [17,18]. Benzodiazepines seem to be the first line treatment even though they are not very effective for chemically induced seizures [8] and there is evidence that patients with most of the fatal cases of tramadol intoxications congested benzodiazepines [19].

Only very few cases of acute Tramadol poisoning in infants have been reported [11], which can be daily treatment overdoses [8], accidental [6,9,10] or parental poisoning/Munchausen syndrome by proxy [5].

They mostly presented short generalized tonico-clonic seizures [8-10], with serotonergic syndromes or with symptoms of opioid overdose, as some of our cases attested. To our knowledge, there are no other reported cases of chest wall rigidity observed with Tramadol. However, a case of rigid chest syndrome has already been described in a one month-old infant following an accidental methadone overdose, and in two infants exposed to low-doses of fentanyl [20,21]. In our case, we did not note any serotonergic symptoms.

In our case n°3, non-invasive ventilation failed because of rigid chest syndrome but, in the context of intubation, the symptoms fade quickly, especially with the use of a neuromuscular blockade. Central nervous system depression and hypoventilation can be treated with Naloxone which accelerates recovery [9] if used early.

Most patients spontaneously recovered a normal neurological condition within the first 24 hours without an antidote treatment. Faced with acute neurological deficiency in an infant who has no fever or no known metabolic diseases, the toxicology analysis is crucial to diagnose poisoning and an appropriate antidote treatment can be initiated if it is considered necessary. As shown in Table 1, some symptoms are suggestive of intoxication.

Unfortunately, Tramadol intoxication can be fatal if handled too late. Factors that could explain this fatal evolution are:

- A delay in recognizing symptoms by parents;
- Pulmonary inhalation during prehospital management;
- Potential cardiogenic failure as described in the literature with a high plasma level [9];
- Admission in PICU after prolonged cardiac arrest.

Central nervous system depression and hypoventilation can be treated with Naloxone, which accelerates recovery [22]. Some cases of children intoxicated report the use of Naloxone as a diagnosis and treatment with success [10]. In a multicentre study, Spiller et al. [23] reported that the use of Naloxone as an antidote was immediately beneficial for apneas and drowsiness in 4 out of 8 patients. This study also reported a case of seizure in one patient, immediately after administering naloxone, although the seizure could be the residual effect of Tramadol. In Saidi et al. [22], 43 out of 47 patients over 16 years of age had clinical Cerebral State Monitor benefits after a Naloxone injection. Side effects were minor in this study. The use of

Naloxone could be useful as a diagnosis and/or a treatment for Tramadol intoxication but should be used carefully due to the lack of available data for the paediatric population.

A few cases of ultra-rapid metabolizers can be found in the literature, both for the paediatric population [3] and for adults [24,25]. In 6 of our cases, we had a history of drug overdose but in one case (case n°6), no clear explanation was found after parental questioning. In this context, we analysed the CYP2D6 genotype to eliminate an ultra-rapid metabolizer that may produce more active opioid metabolites resulting in life-threatening adverse effects. We therefore highly suspected a voluntary or involuntary administration when examining the container bottles. An etiologic exploration did not detect underlying diseases or a rapid metabolizer (normal cytochrome CYP2D6 exploration). Those cases are due to an increased blood concentration of O-demethyl Tramadol and lead to the same clinical symptoms as an intermediate metabolizer. The proportion of ultra-rapid metabolizers is estimated to be 5.5% of the population in Western Europe [24].

Most patients are quickly discharged from PICU without any neurological or respiratory sequelae. Fatal reports following Tramadol poisoning and overdoses have not often been reported even in the adult population. Moreover, all reported fatal tramadol poisonings have been reported in conjunction with the detection of other drugs. One of our patients died of a mono-intoxication with a post-mortem diagnosis, which is unusual.

## Conclusion

Tramadol overdose can present opioid-like intoxication symptoms, serotonergic syndrome and/or seizures. Our study found that the most important symptoms following tramadol overdose were seizures, a decreased level of consciousness and respiratory depression. We can observe cases of rigid chest syndromes as described with others opioids. Paediatric fatal tramadol poisonings are rare, but high doses of tramadol may have cardiac toxicity. Moreover tramadol overdoses can lead to death in any situation and must maintain practitioners on alert.

Because of the increasing use of tramadol in the paediatric population, practitioners should be aware of its side effects and lethal potential, even without an ultra-rapid metabolism which may affect up to 5.5% of the Western European population [26]. The handling of the bottles should be explained to families in order not to exceed the prescribed dose. Emergency physicians must be aware that when faced with acute neurological deficiency in an infant without fever, drug poisoning is possible and a toxicological analysis is to be recommended. Naloxone can be efficient when with opioids signs are predominant. Paediatric fatal tramadol poisonings are rare, but high doses of tramadol may have cardiac toxicity.

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## References

1. Beakley BD, Kaye AM, Kaye AD (2015) Tramadol, Pharmacology, Side Effects, and Serotonin Syndrome: A Review. *Pain Physician* 18: 395-400.
2. Grond S, Sablotzki A (2004) Clinical pharmacology of tramadol. *Clin Pharmacokinet* 43: 879-923.

3. Orliaguet G, Hamza J, Couloigner V, Denoyelle F, Lorient MA, et al. (2015) A case of respiratory depression in a child with ultrarapid CYP2D6 metabolism after tramadol. *Pediatrics* 135: e753-755.
4. Thundiyil JG, Kearney TE, Olson KR (2007) Evolving epidemiology of drug-induced seizures reported to a Poison Control Center System. *J Med Toxicol* 3: 15-19.
5. Mazor SS, Feldman KW, Sugar NF, Sotero M (2008) Pediatric tramadol ingestion resulting in seizurelike activity: a case series. *Pediatr Emerg Care* 24: 380-381.
6. Maréchal C, Honorat R, Claudet I (2011) Serotonin syndrome induced by tramadol intoxication in an 8-month-old infant. *Pediatr Neurol* 44: 72-74.
7. Kahn LH, Alderfer RJ, Graham DJ (1997) Seizures reported with tramadol. *JAMA* 278: 1661.
8. Márquez-Romero JM, Zermeño-Pohls F, Soto-Cabrera E (2010) [Convulsive status epilepticus associated with a tramadol overdose]. *Neurologia* 25: 583-585.
9. Perdreau E, Iriart X, Mouton JB, Jalal Z, Thambo JB (2015) Cardiogenic shock due to acute tramadol intoxication. *Cardiovasc Toxicol* 15: 100-103.
10. Grosek S, Mozina M, Grabnar I, Primožic J (2009) Diagnostic and therapeutic value of naloxone after intoxication with tramadol in a young girl. *Pediatr Int* 51: 842-843.
11. Hassanian-Moghaddam H, Farnaghi F, Rahimi M (2015) Tramadol overdose and apnea in hospitalized children, a review of 20 cases. *Res Pharm Sci* 10: 544-552.
12. Allegaert K, van Schaik RH, Vermeersch S, Verbesselt R, Cossey V, et al. (2008) Postmenstrual age and CYP2D6 polymorphisms determine tramadol o-demethylation in critically ill neonates and infants. *Pediatr Res* 63: 674-679.
13. Saudan , Habre W (2007) [Pharmacokinetics of tramadol in children]. *Ann Fr Anesth Reanim* 26: 560-563.
14. Shadnia S, Soltaninejad K, Heydari K, Sasanian G, Abdollahi M (2008) Tramadol intoxication: a review of 114 cases. *Hum Exp Toxicol* 27: 201-205.
15. Ryan NM, Isbister GK (2015) Tramadol overdose causes seizures and respiratory depression but serotonin toxicity appears unlikely. *Clin Toxicol (Phila)* 53: 545-550.
16. Srinivas NR (2015) Differential Consequences of Tramadol in Overdosing: Dilemma of a Polymorphic Cytochrome P450 2D6-Mediated Substrate. *J Pain Palliat Care Pharmacother* 29: 272-275.
17. Volpi-Abadie J, Kaye AM, Kaye AD (2013) Serotonin syndrome. *Ochsner J* 13: 533-540.
18. Shadnia S, Brent J, Mousavi-Fatemi K, Hafezi P, Soltaninejad K (2012) Recurrent seizures in tramadol intoxication: implications for therapy based on 100 patients. *Basic Clin. Pharmacol. Toxicol.* 111: 133-136.
19. Clarot F, Goullé JP, Vaz E, Proust B (2003) Fatal overdoses of tramadol: is benzodiazepine a risk factor of lethality?. *Forensic Sci Int* 134: 57-61.
20. Dewhirst E, Naguib A, Tobias JD (2012) Chest wall rigidity in two infants after low-dose fentanyl administration. *Pediatr Emerg Care* 28: 465-468.
21. Lynch RE, Hack RA (2010) Methadone-induced rigid-chest syndrome after substantial overdose. *Pediatrics* 126: e232-234.
22. Saidi H, Ghadiri M, Abbasi S, Ahmadi SF (2010) Efficacy and safety of naloxone in the management of postseizure complaints of tramadol intoxicated patients: a self-controlled study. *Emerg Med J* 27: 928-930.
23. Spiller HA, Gorman SE, Villalobos D, Benson BE, Ruskosky DR, et al. (1997) Prospective multicenter evaluation of tramadol exposure. *J Toxicol Clin Toxicol* 35: 361-364.
24. Stamer UM, Stüber F, Muders T, Musshoff F (2008) Respiratory depression with tramadol in a patient with renal impairment and CYP2D6 gene duplication. *Anesth Analg* 107: 926-929.
25. Elkalioubie A, Allorge D, Robriquet L, Wiart JF, Garat A, et al. (2011) Near-fatal tramadol cardiotoxicity in a CYP2D6 ultrarapid metabolizer. *Eur J Clin Pharmacol* 67: 855-858.
26. Ingelman-Sundberg M (2005) Genetic polymorphisms of cytochrome P450 2D6 (CYP2D6): clinical consequences, evolutionary aspects and functional diversity. *Pharmacogenomics J* 5: 6-13.