

Tapentadol Toxicity in Children

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abstract

BACKGROUND: Tapentadol (Nucynta) is indicated for the treatment of moderate to severe pain in adults. Tapentadol's mechanism of action consists of acting as an agonist on the μ -opioid receptor and by inhibiting the reuptake of norepinephrine. There are no published reports on the toxicity of tapentadol in pediatric patients. The goals of this study are to describe the incidence, medical outcomes, clinical effects, and treatment secondary to tapentadol exposure.

METHODS: This retrospective observational study used data from the National Poison Data System. Inclusion criteria were exposure to tapentadol from November 1, 2008 to December 31, 2013; age 0 to 17 years; single ingestion; and followed to a known outcome.

RESULTS: There were 104 patients who met the inclusion criteria. Eighty patients were aged ≤ 6 , 2-year-olds the most common age group (60.6%). There were 52 male and 52 female patients. Of the 104 patients, 93 had unintentional exposures. No deaths were reported. Sixty-two of the patients had no effect, 34 had minor effects, 6 had moderate and 2 had major effects. Thirty patients reported drowsiness and lethargy. Other effects reported included nausea, vomiting, miosis, tachycardia, respiratory depression, dizziness/vertigo, coma, dyspnea, pallor, vomiting, edema, hives/welts, slurred speech, pruritus, and hallucinations/delusions. Fifty-three patients were reported to have no medical intervention.

CONCLUSIONS: This is the first study examining the toxic effects of tapentadol in a pediatric population. Although a majority of the patients in this review developed no effect from their exposure, two had life-threatening events. The most common effects reported were opioidlike.

WHAT'S KNOWN ON THIS SUBJECT: Tapentadol is used in the treatment of chronic pain, specifically diabetic neuropathy. It has known action on the μ -opioid receptor leading to drowsiness and apneas. There is no published information on the effects of tapentadol in small children.

WHAT THIS STUDY ADDS: After an accidental overdose in a child, tapentadol may be expected to cause μ -opioid clinical effects similar to other opioids. While the opioid effects predominate sympathomimetic effects are also seen. The risk of respiratory depression and dyspnea should be acknowledged.

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The management of chronic pain is a balance between the benefits of pain relief against the risk of diversion, misuse, and abuse.¹ Between 1999 and 2010, sales of opioid pain relievers increased dramatically. During that same time, the number of opioid-related deaths and treatment admission also increased.^{2,3} The increased focus on pain treatment, coupled with the increased number of opioid related deaths, has led to the development of new analgesics.

Tapentadol is a novel analgesic approved for the management of moderate to severe acute pain. It was first approved as an immediate release product in 2008.⁴ Marketing and use began in April 2009. In 2011, the extended release product was approved. The extended release dosage form carries the additional indications of chronic pain and neuropathic pain secondary to diabetic peripheral neuropathy. Neither the immediate nor the extended release product has an indication for pediatric patients. Tapentadol has a novel mechanism of action. It is a μ -opioid agonist and a norepinephrine reuptake inhibitor.^{5,6,7,8}

Little is known regarding the effects of tapentadol in overdose. Data from clinical trials describe the adverse drug effects expected from a μ -opioid agonist.^{7,8} There has been a single death due to the intravenous injection of tapentadol reported in the literature.⁹ There are no data currently published describing the medical outcomes and clinical effects of tapentadol overdose in pediatric patients.

METHODS

This is a retrospective cohort study of tapentadol exposure calls in the National Poison Data System (NPDS). Each call to a US poison center is received by a trained nurse, physician, physician assistant, or pharmacist with the intent of first

assisting in the management of the patient and second documenting the interaction. All cases are documented electronically in a standardized data collection format that is maintained by the American Association of Poison Control Centers. The NPDS database of calls from all US poison centers is updated in real time with >2.2 million human exposures calls in 2012. It contains data on 50 million human exposures since 1985, when the data collection started. All data are published annually in December by the American Association of Poison Control Centers.¹⁰

Inclusion criteria were as follows: substance was tapentadol; age ≤ 17 years and younger; single substance ingestion only; reported from November 1, 2008 to December 31, 2013; and followed to a known medical outcome. Data elements included age, gender, date of exposure, medical outcome, route of exposure, clinical effects, substance, and therapy. All data were deidentified. This study was approved by the Concordia University Wisconsin institutional review board.

NPDS sets the definition for medical outcome.¹¹ Medical outcomes were coded as "No effect," "Minor," "Moderate," "Major," and "Death" according to NPDS medical outcome criteria.¹¹ As per NPDS, "No effect" is when the patient did not develop any signs or symptoms as a result of the exposure. "Minor effects" are signs or symptoms that are secondary to the exposure but are inconsequential and generally resolved rapidly. "Moderate effects" are signs or symptoms that are a result of the exposure and are more pronounced, more prolonged, or more systemic in nature than minor symptoms. Symptoms were not life-threatening, and the patient had no residual disability or disfigurement. Treatment is nearly always needed in those patients. "Major effects" are signs or symptoms that are life-threatening or result in significant residual disability or

disfigurement (eg, repeated seizures or status epilepticus, respiratory compromise requiring intubation, ventricular tachycardia with hypotension, cardiac or respiratory arrest, esophageal stricture, and disseminated intravascular coagulation). "Death" is when the patient died as a result of the exposure or as a direct complication of the exposure. NPDS defines tachycardia as a pulse rate >100 beats per minute, and it defines hypertension as diastolic blood pressure >90 mm Hg.¹¹ In addition, NPDS combines some similar effects within its definitions. Hives/welts is defined as urticaria, an acute or chronic reaction in which transient red or pale elevated patches develop on the skin; drowsiness/lethargy as fatigue or sleep or minor levels of central nervous system depression from which the patient can be awakened; dizziness/vertigo as a disabling sensation in which the affected individual feels that his or her surroundings are in a state of constant movement and hallucinations/delusions as a false perception of something that is not really there.¹¹

The American Association of Poison Control Centers (AAPCC; www.aapcc.org) maintains the national database of information logged by the country's poison control centers.^{10,11} Case records in this database are from self-reported calls: they reflect only information provided when the public or health care professionals report an actual or potential exposure to a substance (eg, an ingestion, inhalation, or topical exposure, etc) or request information/educational materials. Exposures do not necessarily represent a poisoning or overdose. The AAPCC is not able to completely verify the accuracy of every report made to member centers. Additional exposures may go unreported to poison centers, and data referenced from the AAPCC should not be construed to represent the complete incidence of national exposures to any substance.¹¹

Our primary goal was to determine the incidence of tapentadol exposure in pediatric patients. Our secondary goals were to determine the frequency of specific medical outcomes, clinical effects, and the use of specific treatments.

Data were provided by NPDS in a password-protected electronic spreadsheet (Microsoft Excel; Microsoft Corporation, Redmond WA, 2007). Excel was used to collect and organize the data and to determine mean age, median age, and age range of patients in this study.

RESULTS

One hundred four patients met the inclusion criteria. Of those patients, 80 (76.9%) were 6-years-old and under with 2-year-olds the most common (60.6%) age group. The mean age was 4.17 years, median age was 2 years, and the overall age range was 26 days to 17 years (Fig 1). There were 52 male and 52 female patients. The first exposure was reported in July 2009, 9 months after US Food and Drug Administration approval and 4 months after marketing commenced. The number of exposures per year increased from 2 in 2009 to 35 in 2012. Exposures reported to a poison center dropped to 13 in 2013.

All patients in the study had an acute ingestion. The vast majority of the patients, 93, were unintentional exposures. Included in that number

are 14 patients with an unintentional therapeutic error. An unintentional therapeutic error is defined as a deviation from proper therapeutic regimen that results in the wrong dose, incorrect route of administration, administration to the wrong person, or administration of the wrong substance.¹¹ Three teens (aged 13, 16, and 17 years) ingested tapentadol to abuse it, and 2 others (both aged 15 years) intentionally ingested the drug (intentional misuse) for a reason other than pursuit of psychotropic effect.¹¹ There were 3 suicide attempts, and all were teenagers. Three patients had an exposure reason of unknown. Sixty-two of the patients (59.6%) had no effect, 34 (32.7%) had minor effects, and 8 (7.7%) had moderate or major effects. No deaths were reported.

Drowsiness/lethargy was the most common clinical effect noted, 30 patients (28.8%). Other effects reported included nausea, vomiting, miosis, tachycardia, respiratory depression, and dizziness/vertigo. The total clinical effects reported are listed in Table 1. Clinical effects reported for the 8 patients with moderate or major medical outcomes included respiratory depression, coma, dyspnea, pallor, vomiting, edema, hives/welts, drowsiness/lethargy, slurred speech, pruritus, and hallucinations/delusions (Table 2).

Eighty-two of the 104 patients (78.8%) were treated in a health care facility. The majority of those patients,

64 of 82 (78%), were treated and released. Only 13 (12.5%) patients were admitted. Two patients were admitted to critical care units, 9 to non-critical care units, and 2 to a psychiatric care facility. Twenty-two children were managed on site, in a non-health care facility, including their home. All patients were followed until their medical outcome was determined with reasonable certainty.¹¹ The final level of care, be it home, intensive care, psychiatric, or other referral, for 5 patients could not be determined. Fifty-three patients (50.9%) were reported to have no intervention and were only observed. Therapies provided included single-dose activated charcoal (17 patients), dilution (10), naloxone (7), and food (7).

Two patients had major effects (life-threatening or resulted in significant residual disability). A 9-month-old child with coma and respiratory depression was treated with intravenous fluids and naloxone. He was treated and released. The second is a 16-month-old girl with dyspnea, drowsiness/lethargy, pallor, and vomiting who was admitted to critical care and treated with oxygen. Both of those exposures occurred at the child's residence, and the patients were referred to the hospital by the Poison Control Center.

DISCUSSION

We report collected and analyzed data regarding 104 pediatric patients reported to NPDS that were collected nationally over a 6-year period for tapentadol exposure. This is the first study of tapentadol toxicity in children. Our study shows that tapentadol exposures in children are uncommon. The vast majority of patients were under 6 with 2-year-olds as the largest single age group. That distribution mimics what has been reported by the American Association of Poison Centers in its National Poison Data System (NPDS) annual report.¹⁰ Unintentional

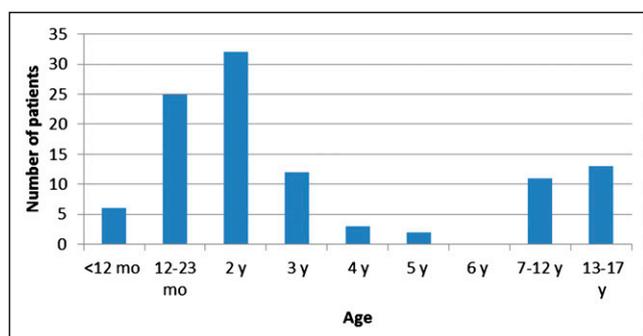


FIGURE 1
Age distribution.

TABLE 1 Clinical Effects Reported

Clinical Effect ⁹	No. of Patients
Drowsiness/lethargy	30
Nausea	4
Vomiting	4
Miosis	3
Tachycardia	2
Agitated, coma, cough/choke, depression, diaphoresis, dizziness/vertigo, dyspnea, edema, hallucinations/delusions, hives/welts, pallor, pruritus, respiratory depression, slurred speech	1 each

pediatric tapentadol exposures had predominately good medical outcomes. In this study, 92.3% of patients had no effect or only minor effects from their exposure.

Tapentadol possesses a novel mechanism of action. It is a μ -opioid receptor agonist with an affinity that is 24 times less than that of morphine.¹² Tapentadol is also a norepinephrine reuptake transporter inhibitor resulting in increased extracellular norepinephrine levels.¹³ The amount of transporter inhibition demonstrated is similar to venlafaxine.¹² Tapentadol is also a weak serotonin reuptake inhibitor resulting in only moderate increases in extracellular serotonin.¹² Despite its low affinity for μ -opioid receptors, studies have shown tapentadol is comparable to morphine or oxycodone in the management of pain. Central blockade of norepinephrine reuptake is projected to have an agonist effect on α -2 adrenergic receptors.¹² Tapentadol immediate release demonstrated efficacy in the treatment of acute moderate and severe pain in adults. The extended-release product has

exhibited clinical benefits in the treatment of neuropathic pain associated with diabetic peripheral neuropathy in addition to pain when daily long-term treatment is required. Adverse effects that have been reported during clinical trials and postmarketing data collection are similar to those reported from other opioid analgesics.^{5,6,7,8} There is a single report of a 34-year-old adult who died after injecting tapentadol.⁹ Postmortem femoral and heart blood levels both far exceeded published maximum concentrations after therapeutic dosing. Before his death the patient was found in distress gasping for breath. There are no published reports of tapentadol overdose in a child. Tapentadol product information has warnings regarding respiratory depression that is expected with opioids and hypotension that may be secondary to its central α -2 effects. In addition, it has a drug-drug interaction warning for the development of serotonin syndrome if taken in combination with other serotonergic medications.^{7,8} In our study of pediatric patients, the most common

clinical effect noted was that of drowsiness, an effect common to both central α -2 and μ -opioid receptor agonist. Miosis, respiratory depression, and dyspnea are consistent with opioid toxicity. Seven patients were treated with the μ -opioid receptor antagonist naloxone. Agitation and tachycardia have been associated with peripheral adrenergic effects.

Because tapentadol is a US Drug Enforcement Administration schedule II medication with abuse and addiction potential, that 5 teenagers whose reason for exposure was listed as intentional abuse or misuse is not unexpected.^{7,8} Dart et al reviewed tapentadol reports from the Researched Abuse, Diversion and Addiction-Related Surveillance System and found the rates of abuse to be similar to tramadol but less than hydrocodone and oxycodone.^{14,15} The single tapentadol death reported in the literature was secondary to intravenous abuse.⁹ Of the 5 teenagers in this study whose reason for exposure was listed as intentional abuse or misuse, 3 were treated for minor or moderate effects in the emergency department and subsequently released. One patient was observed at school and did not develop symptoms. The fifth patient was observed at home and developed only drowsiness.

Two of our patients developed life-threatening signs and symptoms and were coded in NPDS with a medical outcome of major effect. Both had signs of opioid toxicity: respiratory depression, dyspnea, drowsiness, and

TABLE 2 Patients With Moderate or Major Medical Outcome

Age	Reported Dose	Clinical effects	Clinical Outcome	Treatment Performed	Disposition
9 mo	1 tablet	Coma, respiratory depression	Major effect	IV fluids, naloxone	T/R
16 mo	2 tablets	Drowsiness/lethargy, dyspnea, pallor, vomiting	Major effect	Oxygen	Admit to critical care
4 y	1 tablet	Edema, hives/welts	Moderate effect	Antihistamines, steroids, IV fluids	T/R
3 y	1 tablet	Drowsiness/lethargy	Moderate effect	None	T/R
16 y	1 tablet	Drowsiness/lethargy, slurred speech, pruritus	Moderate effect	None	T/R
11 mo	50 mg	Respiratory depression	Moderate effect	None	T/R
1 y	1 tablet	Drowsiness/lethargy	Moderate effect	None	T/R
4 y	100 mg	Hallucinations/delusions	Moderate effect	None	Unknown

IV, intravenous; T/R, treated and released.

coma. Both patients were small children, a 9-month-old boy and 16-month-old girl, with unintentional ingestions. Neither patient developed signs of overt norepinephrine overload.

The NPDS is a powerful tool to monitor childhood poisonings, the strengths of which as a public health database were described by Wolkin et al. Each exposure is captured in report form by trained health care providers using compatible data systems that use standardized definitions.¹⁶ However, the NPDS also has many limitations. All exposures are reported to the poison center by others. The data rely on accurate and complete information from parents and caregivers. There is no uniform quality assurance program in place nationally to validate the accuracy of the data. Reporting is also passive and likely incomplete. The amount ingested is unreliable, and there are no blood concentrations to verify that a poisoning even occurred. Despite its limitations, NPDS contains a high number of exposures that are coded to by a standardized list of medical outcomes (eg, no effect, minor effect, moderate effect, major effect, death, not followed, unable to follow, or unrelated effect).

CONCLUSIONS

We report 104 children exposed to the novel opioid analgesic tapentadol. Patients presented with signs and symptoms similar to other opioid analgesics. Although most of the

patients in this study had no effect or only minor effects after tapentadol exposure, a 9-month-old and a 16-month-old had severe life-threatening effects. Although care should therefore be taken in any symptomatic child exposed to tapentadol, most have only minor effects or no consequences. Additional prospective study is required to define a toxic dose in children as well as any difference between immediate and extended-release products.

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