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Tramadol: Weighing the Risks in Children

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On August 21st, the Food and Drug Administration (FDA) issued a Drug Safety Communication to alert health care providers and the lay public to the risk for respiratory depression in children given tramadol.¹ Although not approved for use in children under 17 years of age,² tramadol has been used off-label in the United States for postoperative pain following tonsillectomy. It is approved for pediatric use in several other countries. Following a recent case report of tramadol-associated respiratory depression in a 5-year-old child,³ the FDA has initiated a review of the available data and recommends the use of alternative analgesics until their evaluation is complete.

Mechanism of Action

Tramadol, (+)-*cis*-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride, is a synthetic opioid analgesic. Both the parent compound and the active M1 metabolite, O-desmethyltramadol, bind to mu-opioid receptors. The M1 metabolite has been estimated to be 200 times more potent than the parent compound in binding to the mu-opioid receptor, and 6 times as potent of an analgesic. In addition to its opioid effects, tramadol produces weak monoamine reuptake inhibition, blocking reuptake of norepinephrine and serotonin into nerve terminals.²

Pharmacokinetics and Pharmacodynamics

Tramadol is rapidly absorbed after oral administration, with a bioavailability of 75%. It has an estimated volume of distribution of 2.7 L/kg in adults and exhibits limited protein binding (20%). Tramadol undergoes extensive hepatic metabolism via cytochrome P450 (CYP) enzymes: to O-desmethyltramadol (M1) by CYP2D6 and to N-desmethyltramadol by CYP3A4, followed by conjugation. Tramadol and its metabolites are excreted in the urine, with

an elimination half-life of 6.3 hours for the parent compound and 7.4 hours for the M1 metabolite.^{2,4}

Formation of the M1 metabolite, and the resulting degree of analgesia or toxicity experienced by the patient, is dependent on CYP2D6 activity. It is estimated that 7% of the population has reduced CYP2D6 activity and are poor metabolizers of tramadol, producing 20% higher plasma tramadol levels and 40% lower M1 metabolite levels than patients who are CYP2D6 extensive metabolizers. These patients may have a less robust analgesic response than intermediate or extensive metabolizers. In contrast, approximately 5% of the population may be ultrarapid metabolizers, producing higher levels of the active M1 metabolite that may lead to significant opioid toxicity.^{2,4}

The pharmacokinetic profile of tramadol in children has been described by several investigators.^{4,6} In 2002, Payne and colleagues evaluated tramadol kinetics in 24 healthy children (mean age 5.3 ± 1.1 years) who received oral tramadol drops (1.5 mg/kg) 30 minutes prior to anesthesia.⁵ Absorption was rapid, with a mean serum concentration of 352 ± 83.4 ng/mL at 30 minutes. Plasma concentrations remained above 100 ng/mL (the target for analgesia) for 6.8 ± 0.9 hours after dose administration. The mean volume of distribution was 4.1 ± 1.2 L/kg, larger than that observed in adults, with a tramadol elimination half-life of 3.6 ± 1.1 hours and a clearance of 5.6 ± 2.7 mL/kg/min. The M1 metabolite had an elimination half-life of 5.8 ± 1.7 hours. These values suggest a similar rate of elimination and duration of analgesia to that reported in adults.

In 2006, Garrido and colleagues at the University of Navarra compared plasma concentrations of tramadol and its M1 metabolite with analgesic

response in 104 children (mean age 4.55 years, range 2-8 years) undergoing abdominal or urologic surgery.⁶ Patients were given a 1 mg/kg dose of tramadol intravenously over 2.5 minutes at the end of surgery. If additional analgesia was needed, a second dose of 0.33 mg/kg could be given at 15, 30, and/or 45 minutes. Pain intensity was evaluated by a trained nurse using an objective pain scale. The mean plasma concentrations of tramadol and the M1 metabolite over a 6-hour period were 100 ng/mL and 15 ng/mL, respectively. These levels were associated with a 95% probability of adequate analgesia based on the authors' estimation.

Clinical Trials

To date, nearly all of the available clinical trials of tramadol in children have been conducted in the perioperative setting. In 1999, Payne and colleagues evaluated the safety and efficacy of tramadol in a randomized, double-blind, placebo-controlled study of 40 children undergoing dental extraction.⁷ Patients received 0.5 mg/kg oral midazolam and either a single 3 mg/kg dose of oral tramadol drops or placebo. Analgesic efficacy was evaluated by Oucher face pain scale scores. The combination group had significantly lower pain scores than the controls (11.42 ± 18.66 versus 29.80 ± 25.14 , $p < 0.05$). The percentage of patients with satisfactory induction conditions was similar between groups (95% in the tramadol group and 90% in the controls). There were no cases of respiratory depression or low oxygen saturation values and no difference in recovery times.

In 2002, Finkel and colleagues at Children's National Medical Center conducted a randomized, double-blind, multicenter study to evaluate postoperative tramadol tablet use in 81 children from 7 to 16 years of age.⁸ All patients initially received morphine patient-controlled analgesia. When ready to transition to oral therapy, they were randomized to receive single tramadol doses of 1 or 2 mg/kg. Patients were monitored for 8 hours. Patients receiving the 1 mg/kg tramadol dose required nearly twice the number of rescue morphine doses of the 2 mg/kg group ($p = 0.006$). Adverse effects were similar in both groups, with vomiting in 10%, nausea in 9%, pruritus in 7%, and rash in 4%. There were no cases of respiratory depression and no differences in oxygen saturation after treatment.

Three more randomized controlled trials of tramadol in children undergoing tonsillectomy were published earlier this year. Honarmand and colleagues compared peritonsillar infiltration of a combination of bupivacaine 1 mg/kg and tramadol 2 mg/kg to either drug alone or placebo.⁹ Use of the combination resulted in significantly less postoperative pain compared to the other groups. Yenigun and colleagues used peritonsillar infiltration of 2 mg/kg tramadol as a control group to compare with IV, rectal, and

peritonsillar infiltration of ketamine.¹¹ Overall, the three ketamine regimens were found to produce a level of analgesia similar to tramadol, with IV ketamine producing a better response than the other groups at hours 6 ($p = 0.045$) and 24 ($p = 0.011$).

Postoperative use of tramadol was compared to acetaminophen/codeine in 74 children between 4 and 15 years of age undergoing tonsillectomy by Friedrichsdorf and colleagues at the Children's Hospitals and Clinics of Minnesota.¹¹ Patients were treated on a scheduled basis for 5 days, followed by as-needed use for another 5 days. Efficacy was determined by pain scores recorded by the patients' parents. There were no significant differences between groups in pain scores. The frequency of oversedation was significantly higher in the codeine/acetaminophen group on the day of surgery. More children in the tramadol group experienced pruritus.

Experience with long-term tramadol use in children is limited. In 2003, Rose and colleagues studied tramadol use from 7 to 30 days in 113 children 7 to 16 years of age.¹² Forty-nine percent of the patients had pain associated with an orthopedic condition, eight had a hematologic disease, 7% had cancer, and 6% had a rheumatologic disease. The remaining patients had a range of other illnesses producing chronic pain. Treatment was initiated with a dose of 1 mg/kg orally every 4 to 6 hours and increased to a maximum of 2 mg/kg/dose or 100 mg. The mean effective dose was 3 ± 1.7 mg/kg/day, with a mean duration of 11.2 ± 7.5 days. Nearly half of the patients (48%) required additional analgesics during the study period. Adverse effects were reported in 75 (66%) of patients, but most were mild to moderate in severity. The most frequent adverse effects were nausea and vomiting (in 18-19% of patients), dizziness and headache (17-19%), somnolence (8%), and fatigue, pruritus, and abdominal pain (each in 6%). Twelve children discontinued therapy because of an adverse effect.

In 2004, Brown and Stinson at The Hospital for Sick Children reported successful long-term tramadol use in two brothers with frequent joint dislocations caused by their Ehlers-Danlos Syndrome – Hypermobility type.¹³ The older brother began treatment at 7 years of age with a dose of 50 mg twice daily. His dose was eventually titrated up to 50 mg four times daily. The younger brother began treatment at age 6 with a dose of 25 mg twice daily and remained on that dose. At the time of publication, the brothers had received tramadol for 30 and 12 months, respectively. Neither patient experienced adverse effects.

Risk for Respiratory Depression

While generally well tolerated, tramadol has been associated with respiratory depression in a small number of patients. In the March 2015 issue of *Pediatrics*, Orliaguet and colleagues at the Hôpital Universitaire Necker-Enfants Malades described a 5-year-old boy who developed respiratory depression after receiving tramadol.³ He had been diagnosed with obstructive sleep apnea syndrome and had undergone a tonsillectomy under general anesthesia. He was discharged to home after a 6 hour postoperative observation period. The evening of the surgery, approximately 8 hours after discharge, he was given a 20 mg dose of oral tramadol drops (1 mg/kg) for pain. The next morning he was found to be lethargic and brought to the hospital. On arrival he was comatose, with pinpoint pupils, minimal respiratory effort, episodes of apnea, and an oxygen saturation of 45%.

The patient was treated with noninvasive ventilation and three doses of naloxone (0.5 mg IV). He responded within minutes of receiving naloxone. By the following day, there was complete resolution of his symptoms. Urinary concentrations of tramadol and the M1 metabolite obtained during his admission were 38.0 mcg/mL and 24.0 mcg/mL, respectively, reflecting a much higher level of the M1 metabolite than would be expected for this dose and suggesting the mechanism of toxicity. Genotyping revealed three functional alleles, the CYP2D6*2x2/CYP2D6*2 genotype, confirming the patient as an ultrarapid metabolizer. The authors of the case report suggest that tramadol, like codeine, may pose a significant risk to children who are CYP2D6 ultrametabolizers.

Additional Contraindications and Precautions

Tramadol should not be given to patients with a history of hypersensitivity or anaphylactoid reactions to the drug or any other opioid. It should not be administered with other central nervous system or respiratory depressants unless the patient is in presence of health care providers to monitor for adverse effects. Management of tramadol toxicity should include supportive care; its adverse effects may be only partially antagonized by naloxone.²

Seizures have been reported after tramadol use in children and adults.² The risk for seizures may be increased in patients with an underlying seizure disorder or with the concomitant use of other serotonin reuptake inhibitors, opioids, or drugs that lower the seizure threshold. In 2008, Mazor and colleagues described seizures or seizure-like activity in two infants after ingestion of toxic doses of tramadol.¹⁴ The first patient, an 8-week-old boy developed stiffness and seizure-like activity, with tonic leg and back extension, arm flexion, and a right tonic head position. He had chewing movements of his mouth and a

disconjugate gaze. A urine screen was positive for tramadol, which was available in the patient's household. He experienced a full recovery within 3 days. The second patient was a 10-month-old girl who had a seizure at home and presented to the emergency department with continued seizures, respiratory depression, and lethargy. She was treated with lorazepam and phenobarbital, with resolution of the seizures over several hours. As with the first case, a urine drug screen was positive for tramadol. In both cases, tramadol toxicity resulted from an unsupervised ingestion of an adult's medication in the home.

Administration of tramadol in patients already receiving other serotonergic agents or ingestion of an overdose may result in serotonin syndrome. A case of moderate serotonin syndrome was reported in an 8-month-old child following an ingestion of a 200 mg tramadol tablet when she and her older brother were playing with her father's medication.¹⁵ The patient was brought to the hospital after becoming agitated and unable to sleep. Upon arrival, she was febrile and tachycardic. She developed epistaxis and hypertension, with episodes of agitation alternating with drowsiness, ataxia, and increased lower limb reflexes. A plasma tramadol level measured upon admission was 680 ng/mL, significantly well above the range associated with analgesia (100-300 ng/mL). Lab tests, an electroencephalogram, and imaging of the central nervous system were negative. Her symptoms began to improve within 2 days; she recovered without sequelae. Patients and families should be aware of the need to go to an emergency department immediately if their child develops difficulty breathing, a fever, rapid heart rate, or seizures after tramadol ingestion.

Adverse Effects

In clinical studies of tramadol in adults, the most commonly reported adverse reactions included dizziness (in 26% of patients), nausea or constipation (24%), headache (18%), somnolence (16%), vomiting (9%), pruritus (8%), asthenia or sweating (6%), and stomach upset, dry mouth, or diarrhea (5%).² Similar adverse effects have been reported in pediatric trials, with nausea and vomiting reported in approximately 10-19% of patients, dizziness and headache in 17-19%, somnolence in 8%, and pruritus in 7-13%.^{10,13}

Tolerance, dependence, and addiction have been demonstrated with repeated tramadol use. When approved in 1995, tramadol was believed to have low potential for abuse and was not classified as a controlled drug. In 2014, based on growing reports of its abuse, including 15,000 to 20,000 visits to emergency departments for adverse effects associated with nonmedical use of the drug each year, it was reclassified by the FDA as a schedule IV controlled substance.¹⁶

Abrupt discontinuation of tramadol after long-term use may result in withdrawal.² The symptoms of tramadol withdrawal typically include those associated with opioid withdrawal: irritability and restlessness, insomnia, tachycardia, tremor, sweating, vomiting, or diarrhea. Some patients also may experience symptoms associated with abrupt discontinuation of serotonin reuptake inhibitors, such as anxiety, panic attacks, hallucinations, confusion, and numbness or tingling of the extremities. Patients with long-term tramadol use should be considered at risk for withdrawal and slowly tapered off the drug.

Drug Interactions

Drugs that inhibit CYP2D6, including amitriptyline, fluoxetine, paroxetine, and quinidine may increase tramadol serum concentrations, but reduce M1 metabolite concentrations and decrease the level of analgesia provided. To date, the clinical impact of these interactions has not been studied. Tramadol should not be taken with other central nervous system or respiratory depressants. As with other serotonin reuptake inhibitors, tramadol should not be administered within 2 weeks after use of a monoamine oxidase (MAO) inhibitor. Use of these agents together may place the patient at a higher risk of serotonin syndrome.²

Dosing Recommendations

Tramadol is available as the brand name product (Ultram[®]) or generics in 50 and 100 mg tablets. The oral and injectable formulations available in other countries have not been approved in the United States. The recommended dose of tramadol in adults is 25 mg per day given as a single dose in the morning, followed by titration in 25 mg increments every 3 days to reach 25 mg four times daily. At that point, the dose may be further titrated to a maximum of 400 mg per day.² There are no standard pediatric dosing recommendations for tramadol. Most of the available pediatric studies have used doses of 1-2 mg/kg IV or orally in the perioperative setting.

Summary

At this time, there is a limited place for tramadol in the management of pain in children. A single dose following surgery has been found to be an effective and generally well tolerated adjunctive analgesic in several studies; however, there is very limited documentation of its use outside of the hospital setting. While the FDA evaluates the safety of tramadol in children, health care providers are encouraged to report any adverse effects related to it through MedWatch <http://www.fda.gov/Safety/MedWatch/default.htm>.

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