

A Case of Respiratory Depression in a Child With Ultrarapid CYP2D6 Metabolism After Tramadol

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We discuss a case of severe respiratory depression in a child, with ultrarapid CYP2D6 genotype and obstructive sleep apnea syndrome, after taking tramadol for pain relief related to a day-case tonsillectomy.

abstract

Pain management is challenging after ambulatory tonsillectomy in children and has become more so since the publication of restrictions on the use of codeine for pain relief in children.¹ These restrictions followed reports of severe and fatal respiratory depression in children after the use of codeine for pain relief.^{2–6}

Tramadol, a racemic opioid widely used for mild to moderately severe acute pain management, has been proposed as an alternative to codeine because it is thought to be associated with decreased postoperative sedation and respiratory depression.⁷ Tramadol is extensively metabolized in the liver by the cytochrome P450 monooxygenases followed by conjugation reactions producing inactive glucuronides and sulfates (for details, <https://www.pharmgkb.org/pathway/PA165946349>). Its main analgesic metabolite (M1) results from the O-demethylation catalyzed by the cytochrome P450 CYP2D6. The N-demethylation to N-desmethyltramadol (M2) is catalyzed by CYP2B6 and CYP3A4.⁸ The O-desmethyltramadol (M1) has a 200-fold higher affinity for μ -opioid receptors than the parent drug and other metabolites. Finally, tramadol and its metabolites are mainly eliminated by the kidneys.

We report a case of severe respiratory depression in a child with ultrarapid

CYP2D6 genotype after taking tramadol for pain relief after day-case tonsillectomy.

CASE REPORT

A 5.5-year-old boy (21.0 kg, BMI 16.0) underwent ambulatory adenotonsillectomy under general anesthesia for obstructive sleep apnea syndrome (OSAS). There was no clinical evidence to suspect a severe OSAS that could contraindicate outpatient surgery. He had undergone dental extractions under general anesthesia without complications in 2012. On clinical examination, the ear, nose, and throat surgeon noted tonsillar and adenoidal hypertrophy, without any other visible airway obstruction. Under general anesthesia, the tonsils were completely removed using cold instruments and bipolar coagulation. The patient was discharged from the hospital after an uneventful postoperative stay of 6 hours (at 3 PM). The same evening (at 11 PM), he complained of increasing pain and received 1 oral 20-mg dose of tramadol (8 drops of oral tramadol ~ 1 mg/kg⁻¹). The next morning (day 1 after hospital discharge), the parents found him lethargic and brought him back to our center. On arrival at the emergency department, he was comatose (pediatric Glasgow coma scale score of 8) with pin-point pupils, minimal respiratory effort, frequent

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episodes of apnea, and an oxygen saturation of 48% in room air. Arterial blood gases were abnormal (pH: 7.06; Pco₂: 12.5 kPa; PO₂: 8.0 kPa; and standard base excess: -3.9). His other vital functions were normal with no evidence of renal impairment (blood urea 6.0 mmol/L⁻¹; plasma creatinine 74.0 μmol/L⁻¹). He was transferred to the PICU. He improved dramatically with noninvasive ventilation and intravenous naloxone (0.5 mg × 3), normalizing consciousness, pupils, and respiration within minutes. Two hours later, he was weaned from noninvasive ventilation. The next day, he fully recovered and was discharged from the PICU. Urinary tramadol concentration was 38.0 μg/mL⁻¹. Urinary concentrations of O-desmethyltramadol (M1) and N-desmethyltramadol (M2) were 24.0 and 4.6 μg/mL⁻¹, respectively. The metabolic ratio ([tramadol] / [M1] = 1.58) was significantly decreased.⁹ Genotyping of CYP2D6 revealed the presence of 3 functional alleles corresponding to CYP2D6*2 × 2 / CYP2D6*2 genotype, consistent with an ultrarapid metabolism.

DISCUSSION

To our knowledge, this is the first case of opioid intoxication associated with severe respiratory depression in a child taking tramadol after day-case tonsillectomy.⁶ In this case, the ultrarapid CYP2D6 metabolism resulted in an increased M1 concentrations leading to severe respiratory depression. The biochemical results, in conjunction with the clinical presentation and the rapid improvement in the clinical condition of the patient after naloxone administration, support this diagnosis. The recent European restrictions on the use of codeine for pain relief in children who undergo tonsillectomy to treat obstructive sleep apnea has prompted a search for an alternative to codeine for pain

management after hospital discharge. Tramadol was proposed instead of codeine because it is thought to be associated with decreased postoperative respiratory depression. Tramadol is a weak μ agonist, which also inhibits noradrenaline and serotonin reuptake. In addition, tramadol exerts analgesic effects via his opioid agonist metabolite M1, after a O-demethylation mediated by CYP2D6.¹⁰ The μ-opioid-derived hypoalgesic effect of tramadol is dependant of CYP2D6 activity. This enzyme is subject to genetic polymorphisms, resulting in poor, intermediate, extensive, or ultrarapid metabolizers (UMs) of CYP2D6 substrates. The UM phenotype affects 5.5% of the population in western Europe.¹¹ This polymorphic enzyme activity may in turn influence postoperative analgesia efficiency and safety of tramadol as reported for other analgesic drugs such as codeine.^{12,13} It is likely that tramadol may also have reduced clinical efficacy in CYP2D6 poor metabolizers. In contrast, UMs and some extensive metabolizers of CYP2D6 may produce more active opioid metabolites (ie, M1 in the case of tramadol), resulting in life-threatening adverse effects. The Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2D6 genotype and codeine therapy provide therapeutic recommendations for codeine based on CYP2D6 genotype.¹⁴ Similarly, to avoid severe complications with tramadol, alternative therapies in CYP2D6 poor and ultrarapid metabolizers may to be considered. Incidences of respiratory depression after tramadol have been reported in postoperative adults with impaired renal function in association with¹⁵ or without CYP2D6 gene duplication.¹⁶ In contrast, the renal function was normal in our patient, and he did have CYP2D6 gene duplication. However, children with a history of OSAS are particularly sensitive to the respiratory-depressant effects of opioids.¹⁷ Our patient was reported

to be an ultrarapid CYP2D6 metabolizer and suffered from OSAS, which explains the severity of the respiratory depression observed.

CONCLUSIONS

Tramadol may be associated with a risk of respiratory depression after ambulatory tonsillectomy in children with ultrarapid CYP2D6 metabolism. This report, together with the restrictions on use of codeine for pain relief in children, leads to the question of what alternatives exist to provide pain relief after ambulatory tonsillectomy in children. These alternatives might be pharmacological, such as the use of steroidal¹⁸ or nonsteroidal antiinflammatory drugs¹⁹ in addition to acetaminophen, but also surgical, because the use of the intracapsular tonsillectomy technique has been shown to substantially reduce postoperative pain.²⁰ Finally, this case supports the clinical utility of determining CYP2D6 genotype or phenotype in preventing serious drug adverse effects and developing more individualized analgesic therapy based on therapeutic recommendations according to CYP2D6 genotype.

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