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.

**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 3PM). The same evening (at 11 PM), he complained of increasing pain and received 1 oral 20-mg dose of tramadol (~1 mg/kg). 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
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 7.40 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. 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. 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 recommendations 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. 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. This polymorphic enzyme activity may in turn influence postoperative analgesia efficacy and safety of tramadol as reported for other analgesic drugs such as codeine.

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 recommendations for codeine based on CYP2D6 genotype. Similarly, to avoid severe complications with tramadol, alternative therapies in CYP2D6 poor and ultrarapid metabolizers may be considered. Incidences of respiratory depression after tramadol have been reported in postoperative adults with impaired renal function in association with or without CYP2D6 gene duplication. 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.

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*Pediatrics* 2015;135;e753; originally published online February 2, 2015; DOI: 10.1542/peds.2014-2673

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