

# More Codeine Fatalities After Tonsillectomy in North American Children

**AUTHORS:** Lauren E. Kelly, MSc,<sup>a,b,c</sup> Michael Rieder, MD, PhD,<sup>a,b</sup> John van den Anker, MD,<sup>d</sup> Becky Malkin, BSc, Pharm,<sup>b</sup> Colin Ross, PhD,<sup>e</sup> Michael N. Neely, MD,<sup>f</sup> Bruce Carleton, PharmD,<sup>e,g</sup> Michael R. Hayden, MD, PhD,<sup>e</sup> Parvaz Madadi, PhD,<sup>h,i</sup> and Gideon Koren, MD<sup>c,h,i</sup>

<sup>a</sup>Schulich School of Medicine, and <sup>c</sup>Ivey Chair in Molecular Toxicology, University of Western Ontario, London, Canada;

<sup>b</sup>Department of Clinical Pharmacology, London Health Sciences Centre, London, Canada; <sup>d</sup>Children's National Medical Center, Center for Clinical and Community Research, Washington, District of Columbia; <sup>e</sup>Centre for Molecular Medicine and Therapeutics, University of British Columbia, Vancouver, Canada;

<sup>f</sup>Communication Sciences Institute, University of South California, Los Angeles, California; <sup>g</sup>Child and Family Research Institute, Vancouver, Canada; <sup>h</sup>Department of Clinical Pharmacology, University of Toronto, Toronto, Canada; and <sup>i</sup>Division of Clinical Pharmacology and Toxicology, Hospital for Sick Children, Toronto, Canada

## KEY WORDS

codeine, tonsillectomy, sleep apnea

## ABBREVIATIONS

AT—adenotonsillectomy

CNS—central nervous system

*CYP2D6*—cytochrome P 450 2D6

EM—extensive metabolizer

OSAS—obstructive sleep apnea syndrome

UM—ultra-rapid metabolizer

Ms Kelly is the first author and is responsible for the study concept and for collecting and analyzing data; Drs Rieder and van den Anker were responsible for the acquisition of data and patient consults; Ms Malkin collected the samples and coordinated their analysis with Dr Ross; Dr Neely prepared the pharmacokinetic modeling; the *CYP2D6* genotyping was completed at Centre for Molecular Medicine and Therapeutics (CMMT) by Dr Ross and were verified by Dr Hayden; Dr Carleton served as a consultant in both pharmacy and clinical population sciences; Drs Madadi and Koren were responsible for the study design, critical revisions, and drafting the manuscript; and all authors critically reviewed the manuscript and approved the final draft for submission.

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## abstract

In 2009 we reported the fatal case of a toddler who had received codeine after adenotonsillectomy for obstructive sleep apnea syndrome. The child was an ultra-rapid metabolizer of cytochrome P4502D6 (*CYP2D6*). We now report 3 additional fatal or life-threatening cases from North America. In the 2 fatal cases, functional gene duplications encoding for *CYP2D6* caused a significantly greater production of potent morphine from its parent drug, codeine. A severe case of respiratory depression in an extensive metabolizer is also noted. These cases demonstrate that analgesia with codeine or other opioids that use the *CYP2D6* pathway after adenotonsillectomy may not be safe in young children with obstructive sleep apnea syndrome. *Pediatrics* 2012;129:e1343–e1347

Pediatric obstructive sleep apnea syndrome (OSAS) is characterized by an increase in upper airway resistance and/or prolonged airway obstruction that leads to a disruption in ventilation and breathing patterns during sleep.<sup>1</sup> OSAS affecting 2% to 3% of all children from birth to adolescence induces hypoxic states that can alter gas exchange and cellular respiration.<sup>2</sup> According to the most recent census data, ~600 000 to 1 800 000 North American children under age 15 are affected by OSAS.<sup>3,4</sup> The most common cause of pediatric OSAS is adenotonsillar hypertrophy and the primary treatment is surgical intervention; generally adenotonsillectomy (AT).<sup>2</sup>

Untreated OSAS can cause several long-term sequelae including increased aggression, depressed mood, nocturnal enuresis, systemic hypertension, and delayed physical growth.<sup>2</sup> The pain associated with AT is classified as moderate to severe and due to a fear of increased tonsillar bleeding, many physicians are hesitant to prescribe nonsteroidal anti-inflammatory medications.<sup>5</sup> Commonly, the opioid codeine is given to young children post-AT.<sup>5</sup> Codeine is a prodrug, the analgesic properties of which are dependent on its conversion to morphine. The metabolism of codeine to active morphine depends on the highly polymorphic *CYP2D6* pathway. Identified polymorphisms in this gene have given rise to poor metabolizer, extensive (EM), and ultra-rapid (UM) metabolizer phenotypes resulting in varied amounts of morphine produced from a standard codeine dose. In the general population, ~10% of codeine is bioactivated to morphine; however, when administered to a poor metabolizer almost no morphine is produced.<sup>6,7</sup> A functional gene duplication resulting in a cytochrome P4502D6 (*CYP2D6*) UM shows a gene-dose effect; as the number of *CYP2D6* gene copies increases, so does

the amount of codeine converted to morphine. A patient with the *CYP2D6* UM can produce 50% up to 75% more morphine than a *CYP2D6* EM.<sup>7</sup> The purpose of this report is to discuss 3 previously unreported severe cases of opioid induced toxicity in children with OSAS post-AT.

## PATIENT PRESENTATION

Consent was received from the Coroner's office in Cases 1 and 3 and from the parents in Case 2.

### Case 1

At a regional hospital in northern Ontario, Canada, a 4-year-old (27.6 kg) First Nations' boy underwent AT for OSAS and recurrent tonsillitis. He was discharged from the hospital after an uneventful overnight stay on liquid codeine at an age-appropriate dose (8 mg per dose, up to 5 doses a day as needed).<sup>8</sup> His parents reported him to be sedated and lethargic the day after hospital discharge. The next afternoon, after a total of 4 codeine doses, he was brought to hospital without vital signs. His postmortem morphine serum concentration was 17.6 ng/mL (therapeutic morphine range  $4.5 \pm 2.1$  ng/mL).<sup>9</sup> His toxicology screen revealed a blood codeine level in the expected range after therapeutic use, and there were no other medications detected. Genotyping revealed a gene duplication and a *CYP2D6* UM phenotype (*CYP2D6* \*1/\*2AxM). His UM *CYP2D6* status resulted in an increased morphine leading to respiratory arrest. Postmortem analysis revealed the cause of death to be bilateral acute bronchopneumonia as a consequence of codeine and morphine toxicity after adenotonsillectomy.

### Case 2

A 3-year-old girl (14.4 kg) of Middle Eastern descent underwent tonsillectomy for OSAS and was discharged after

a 24-hour hospital stay at a Canadian Children's Hospital. In the hospital, she received 2 doses of codeine syrup (15 mg each). Upon discharge she was given a combination of codeine and acetaminophen (15 mg codeine/150 mg acetaminophen) every 4 to 6 hours as needed. More than 6 hours after her final codeine dose (total 60 mg codeine), she was found unresponsive with a fever of 100° as measured at home. On admission to the hospital, she presented with minimal respirations and an oxygen saturation of 65%. She experienced 1 bout of vomiting with mild-dark blood observed. Her blood morphine concentration measured 17 ng/mL. After successful resuscitation, mechanical ventilation and naloxone dosing (1.5 mg), she showed a prompt improvement in her symptoms. The next day, she was extubated and recovered fully. Her genotype was determined to be an EM (*CYP2D6* \*1/\*1). In this case, her morphine levels suggested ultra-rapid metabolism, which was not consistent with her genotype. However, the EM genotype often overlaps with the UM phenotype.<sup>6</sup>

### Case 3

A 5-year-old boy (29 kg) underwent bilateral myringotomy tube placement, and AT for recurrent tonsillitis and snoring in the Southern United States. After surgery, he was prescribed acetaminophen and codeine (12 mg codeine) every 4 hours. This total 72 mg/day is within the recommended range of 6 mg/kg per day.<sup>10</sup> The child was released home but was found without vital signs by his mother 24 hours after his surgery. The autopsy did not reveal a cause of death. This child's postmortem codeine concentration was 79 ng/mL, and morphine concentration was 30 ng/mL. A pharmacokinetic model using Pmetrics software (Los Angeles, CA) was constructed on the basis of published pediatric pharmacokinetic characteristics to simulate

expected time concentration profiles for codeine and morphine based on his age, weight, and dosing schedule (Appendix 1).<sup>11,12</sup> Finally, we compared his measured codeine and morphine concentrations to the expected ranges. The measured codeine concentration of 79 ng/mL ~8 hours after his last dose is at the 56th percentile of predicted pediatric codeine concentrations. In contrast, the measured morphine concentration of 30 ng/mL is at the 99th percentile of predicted concentrations at the normal pediatric rate of conversion. The codeine levels are consistent with his prescription of 0.41 mg/kg every 4 hours as needed, which is within the recommended dose according to the published prescribing recommendations.<sup>11</sup> It is highly likely that the child was a *CYP2D6* UM given his exceedingly high morphine concentration relative to codeine.

## DISCUSSION

In 2009, our group first reported fatal codeine toxicity in toddler with the *CYP2D6* UM phenotype after AT.<sup>13</sup> We now describe here 2 deaths and 1 severe case of apnea among young children administered standard doses of codeine. These children had morphine levels in the range associated with central nervous system (CNS) depression, apnea, and death. Although 70% to 80% of children undergoing AT for OSAS improve their apnea long term, many children's respiratory conditions worsen immediately after surgery.<sup>14</sup> It is conceivable that among children in whom the apnea was not resolved after surgery, morphine, as a powerful central nervous system depressant, may further worsen the respiratory condition. Children with a *CYP2D6* UM

phenotype have increased risk of serious CNS depression and apnea.<sup>13</sup> The *CYP2D6* UM status occurs in roughly 1% to 10% in individuals of European descent, but in up to 30% of North African descendants.<sup>9</sup> Genetic testing revealed UM status in Case 1 and the use of metabolic ratios suggests that Case 3 followed the same genetic pattern. Furthermore, between 6% and 10% of the Caucasian population are poor *CYP2D6* metabolizers.<sup>2</sup> In these individuals the ability to convert codeine to the active morphine is inhibited, resulting in therapeutic failure and ineffective pain relief. The elevated morphine levels seen in the *CYP2D6* EM genotype, as was detected in Case 2, often overlap with the UM phenotype.<sup>6</sup> The assay used in these case reports has several complexities described by Madadi et al.<sup>15</sup> Although the Caucasian *CYP2D6* alleles have been well-studied, single nucleotide polymorphisms in the First Nations population are not well characterized. It is therefore possible that the child in Case 1 possesses a rare nonfunctional allele undetected by the assay.

In 2 of the cases described here, despite overnight care in hospital, the child's sleep apnea critically worsened at home. These children were prescribed age-appropriate codeine doses and were taking their medications in accordance with the published dosing guidelines.<sup>8</sup> This suggests that a one night follow-up in hospital may not be able to effectively detect all children at increased risk of severe respiratory complications. Because *CYP2D6* polymorphisms are not routinely screened for before prescribing codeine, sending these children home without conclusive observations can mean that

a high-risk patient may go unnoticed. The children presented in these cases were receiving doses within the recommended weight-adjusted dose of 0.5 to 1 mg/kg every 4 to 6 hours (maximum 6 mg/kg per day).<sup>8</sup> Of potential importance, the children in Cases 1 and 3 were significantly overweight (97th percentile).<sup>16</sup> As morphine sparsely distributes to fatty tissue, dosing based on total body weight instead of lean mass could have partially contributed to morphine accumulation. Postmortem blood samples in Cases 1 and 3 were obtained ~14 hours and 8 hours after the last codeine dose. It is possible that some postmortem morphine redistribution out of organ and muscle compartments into the blood occurred, however in such a short time this is not thought to have been a major contributor. In Case 2, serum samples were taken immediately upon her presentation to the emergency department, 6 hours after her last dose. The active morphine-6-glucuronide metabolite is eliminated renally.<sup>17</sup> However, it is unlikely that the glomerular filtration rate was impaired in these children who were all healthy before surgery.

Pediatric OSAS is a common condition that presents high rates of analgesic complications for postoperative pain management. These 3 cases strongly suggest that codeine, and potentially other opioids metabolized by the *CYP2D6* pathway, cannot be considered safe analgesics for young children after AT for OSAS.

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Address correspondence to Gideon Koren, MD, Hospital for Sick Children, Division of Clinical Pharmacology and Toxicology, 555 University Ave, Toronto, Ontario, Canada M5G 1X8. E-mail: [gkoren@sickkids.ca](mailto:gkoren@sickkids.ca)

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**APPENDIX 1** Pharmacokinetic Modeling Parameters

Parameter	Value	Reference	Comments
ka	0.7	Williams	A value of 0.7 gives a tmax of about 1 h, consistent with the literature
V2	3.5 * 29	Williams	3.5 L/kg * body wt
KeC	ln(2)/3.5	Williams	KeC = natural log of 2 divided by half-life
f	0.02 <sup>a</sup> 0.005 <sup>b</sup>	Williams	<sup>a</sup> This number was empirically derived to correspond to ~10% conversion of a single dose of codeine to morphine, given the other parameters in the model, which is the widely quoted extent for normal adult individuals. <sup>b</sup> As described in the Williams article, children aged 5 typically have 25% of the conversion capability of adults.
V3	2.8 * 29	Kart	Kart et al summarized many studies of morphine in children.
KeM	ln(2)/2.0	Kart	See KeC.

The inputs provided into this 3-compartment model included Weight = 29 kg; dose = 12 mg at time 0, 4, 8, 11 hours; codeine concentration = 79 ng/mL at time 19 hours; and morphine concentration = 30 ng/mL at time 19 hours. A twofold variance around each value was used to account for variance in the population. f, rate of conversion of codeine to morphine in an intermediate metabolizer; ka, absorption rate constant from compartment 1 (the gut); KeC, codeine elimination rate (constant); KeM, morphine elimination rate (constant); V2, vol of distribution of codeine into compartment 2; V3, vol of distribution of morphine into compartment 3.

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