Codeine and opioid metabolism: implications and alternatives for pediatric pain management

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Purpose of review
Use of perioperative opioids for surgical pain management of children presents clinical challenges because of concerns of serious adverse effects including life-threatening respiratory depression. This is especially true for children with history of obstructive sleep apnea. This review will explore current knowledge of clinically relevant factors and genetic polymorphisms that affect opioid metabolism and postoperative outcomes in children.

Recent findings
Within the past several years, an increasing number of case reports have illustrated clinically important respiratory depression, anoxic brain injuries and even death among children receiving appropriate weight-based dosages of codeine and other opioids for analgesia at home setting particularly following tonsillectomy. Several national and international organizations have issued advisories on use of codeine in pediatrics, based on cytochrome P450 family 2 subfamily D type 6 (*CYP2D6*) pharmacogenetics. We have discussed the pros and cons of alternatives to codeine for pain management.

Summary
Although routine preoperative genotyping to identify children at risk and personalized opioid use for pediatric perioperative pain management is still a distant reality, current known implications of *CYP2D6* pharmacogenetics on codeine use shows that pharmacogenetics has the potential to guide anesthesia providers on perioperative opioid selection and dosing to maximize efficacy and safety.

Keywords
analgesia, anesthesia, codeine, obstructive sleep apnea syndrome, opioids, pharmacogenetics, pharmacogenomics, polymorphism

INTRODUCTION

Respiratory depression is the most serious adverse effect of opioids as it could potentially lead to hypoxic brain injury and fatality [1]. Opioids are responsible for 50% of postoperative respiratory failure events [2,3]. Unpredictable large interpatient variations in opioid responses and narrow therapeutic indices of opioids result in a high incidence of postoperative opioid-related respiratory depression (up to 41%) [4,5], especially in children who are sensitive to opioids and differ in physiology and pharmacology from adults [6]. A national survey (data from 252 institutions) of Patient/Proxy Controlled Analgesia practices in children aged less than 6 years reported *eight deaths* and 42 respiratory-depressant incidents requiring naloxone over 5 years [7]. A review of the LexisNexis database (1984–2010) for deaths and complications following tonsillectomy showed that 18% of death and 8.6% of injury claims (mainly anoxic brain injury) in children are opioid-related [8]. Although various patient risk factors for in-hospital opioid-induced respiratory children have been described, including age less than 1 year, obstructive sleep apnea (OSA), obesity, being underweight, prematurity and developmental delay [9], twin studies have also revealed significant heritability (30%) for respiratory depression from opioids [10]. In fact, in pediatrics, there has recently been multiple fatalities in children from the use of codeine, which has turned our attention to the role of genetics, especially cytochrome P450 family 2 subfamily D type 6 (*CYP2D6*) and OSA in this regard

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KEY POINTS

- A multimodal opioid-sparing analgesia strategy reduces the need for perioperative opioid use and improves analgesia and reduces serious risks associated with opioids in children, especially at unmonitored home setting.
- It is high time to avoid codeine and possibly other stronger opioids metabolized via *CYP2D6* pathway, especially in children with significant comorbidities, such as obstructive sleep apnea or significant respiratory disease.
- Genetic identification of known variant alleles that affect the pharmacokinetics or pharmacodynamics of opioid agents can enable anesthesia providers to better select the appropriate opioid and dosing regimen for an individual patient, instead of empirical selection and dosing escalation. Currently, personalized opioid selection and dosing for perioperative pain management is still a long way off. More studies are needed to improve genotype-based personalized perioperative care in children.

[11,12▪▪]. In this review, we will discuss briefly the role of pharmacogenetics with respect to opioid-induced respiratory depression, highlighting the implications of *CYP2D6* genetics on codeine safety, pros and cons of alternatives to codeine and the role of OSA as a major risk factor for opioid-induced respiratory depression.

CODEINE AND *CYP2D6*

Codeine metabolism

Codeine is a weak opioid that was endorsed by the WHO as the second step on the analgesic ladder for cancer pain and has been used routinely for postoperative and for breakthrough pain in chronic sufferers. It is a prodrug with a 200-fold weaker affinity for μ-opioid receptors than morphine; although 80% of the administered drug is inactivated by glucuronidation to codeine-6-glucuronide by uridine 5′-diphosphate glucuronosyltransferase-2B7 (*UGT2B7*) and *N*-demethylation to norcodeine by *CYP3A4*, 5–10% of codeine undergoes *O*-demethylation to morphine, its active form via *CYP2D6* [13] (Fig. 1). Without *O*-demethylation, codeine confers a small fraction of the analgesic potency of morphine, and much of its analgesic effect is likely contributed by a metabolite, codeine 6-glucuronide [14].

Codeine use in pediatrics

Codeine with and without acetaminophen has been a commonly prescribed medicine for pain

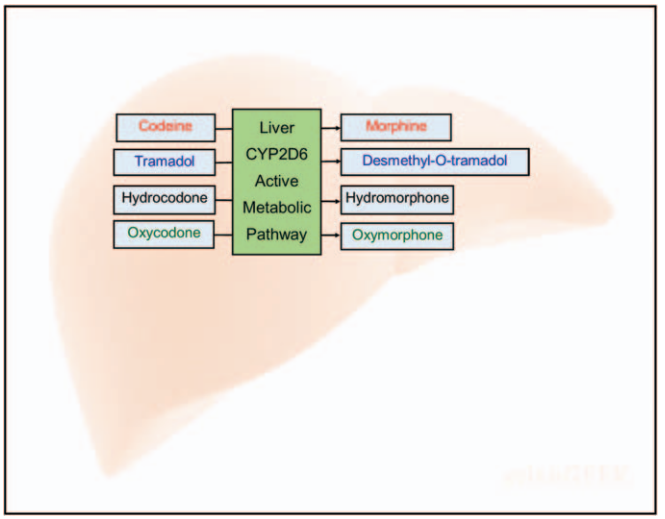

FIGURE 1. Cytochrome P450 family 2 subfamily D type 6 metabolic pathway of common oral opioids resulting in biologically active metabolites. Depending on cytochrome P450 family 2 subfamily D type 6 metabolic activity (poor, intermediate, extensive or ultrarapid metabolizing status) varying levels of respective active metabolites from codeine, tramadol, hydrocodone and oxycodone are formed resulting in clinically unpredictable interindividual variations in responses. Oral morphine, hydromorphone and tapentadol are not affected by the cytochrome P450 family 2 subfamily D type 6 metabolic pathway.

(>18 million US outpatient prescriptions in 2013) [15▪▪] as it is relatively inexpensive, widely available in both liquid and tablet form and was considered to be tolerated well. In fact, a study from 2011 reported that codeine was prescribed to more than 800 000 patients aged less than 11 years, more than any other opioid [16]. Codeine was mostly prescribed by otolaryngologists (19.6%), dentists (13.3%), pediatricians (12.7%) and general practitioner/family physicians (10.1%). Hydrocodone-containing analgesics were recently rescheduled from the Drug Enforcement Administration Schedule III to the more tightly regulated Schedule II. This left codeine coformulated with acetaminophen as the only opioid analgesic classified as a Schedule III controlled substance and cough formulations with codeine remain Schedule V under federal law [17]; unlike their Schedule II counterparts, Schedule III regulations allow for verbal and facsimile prescribing to pharmacies as well as refills with the original prescription. However, reports of fatalities in children from the use of codeine [18,19] have raised concerns about the safety of codeine use [20–22]. This was emphasized by the American Academy of Pediatrics recently in a report released recently titled 'Codeine: Time to Say 'No'' [12▪▪].

CYP2D6 polymorphisms and phenotypes

Variability in the clinical response to codeine prompted investigations into genetic variants or polymorphisms of *CYP2D6*. This enzyme is mapped to chromosome 22 at 22q13.1. More than 100 polymorphisms (functional and nonfunctional) of *CYP2D6* have been described to date (http://www.cypalleles.ki.se/cyp2d6.htm) [23]. *CYP2D6*1* is the wild-type allele and is associated with normal enzyme activity and the 'extensive metabolizer' phenotype. The *CYP2D6* alleles *2, *33 and *35 are also considered to have near-normal activity.

The mutant alleles, *3, *4, *5, *6 and *9, confer no *CYP2D6* activity [23–25] and account for more than 90% of poor metabolizer phenotypes. Variants *10, *17 and *41 have modestly reduced activity and are referred as intermediate metabolizers [25]. An individual who has multiple copies of functional genes [24], would have the ultrarapid metabolizer phenotype. Genetic testing is commonly available for common CYP2D6 variants. An activity score is assigned to each allele in the diplotype (0 for nonfunctional, 0.5 for reduced function and 1 for each copy of a functional allele). The patient's predicted metabolizer phenotype is defined by the sum of the two scores:

(1) Poor metabolizer has an activity score of 0.
(2) Intermediate metabolizers have an activity score of 0.5.
(3) Extensive metabolizer (normal) has an activity score of 1–2.
(4) Ultrarapid metabolizer has an activity score greater than 2.

There are interethnic differences in frequency of these phenotypes; although 10% of whites and 30% of Hong Kong Chinese are PM [25], 1% in Denmark and Finland, 10% in Greece and Portugal and 29% in Ethiopia [26] are ultrarapid metabolizer. Hence, although codeine may be less effective as an analgesic in about 2–10% of ethnic groups [27,28], it could be a dangerous analgesic in the latter populations, as excessive doses of morphine may be rapidly produced [25].

Reports of codeine fatalities

Several deaths or near deaths have been reported with 'standard' doses of oral codeine in children later found to be ultrarapid metabolizer of *CYP2D6* [18,29]. In 2009, a fatality after codeine administration was reported in a healthy 2-year-old boy given codeine 2 days after adenotonsillectomy. Autopsy results showed high blood concentrations of morphine (32 ng/ml) and low codeine concentrations (0.70 ng/ml); genotyping revealed functional duplication of the *CYP2D6* allele [18]. This was followed by further reports in 2012, of three deaths and two cases of respiratory insufficiency in postsurgical children, who had risk factors like OSA [19,30]. In 2013, obesity, codeine toxicity and polypharmacology were implicated in the deaths of three obese children aged 4–10 years given codeine doses based on ideal body weight [31].

Regulations against codeine use in pediatrics and breast-feeding mothers

These incidents ultimately led to new regulations by the WHO (March 2011) [32], US Food and Drug Administration (FDA) (August 2012) [33], European Medicines Agency [34], Health Canada (June 2013) [35] and the UK Medicines and Healthcare Products Regulatory Agency (July 2013 updated in April 2015) [36]. Restrictions were placed on use of codeine in children under the age of 12 years after adenotonsillectomy procedures [37▪▪]. In 2013, the joint FDA advisory committee recommended amendment of the codeine label to include a 'black box warning' contraindicating codeine treatment of pain and cough in all children aged less than 18 years and to remove codeine from the Over-the-Counter monograph [38].

A recent review of the adverse event reporting systems data of children who had codeine or codeine-containing products by the FDA over past 50 years showed 64 cases of severe respiratory depression and 24 deaths mostly in children aged younger than 12 years [39].

The 2014 Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for *CYP2D6* genotype and codeine therapy [40] suggest using alternative analgesics to codeine in patients who are *CYP2D6* poor for better efficacy and ultrarapid metabolizers for safety reasons. In fact, several pediatric hospitals have elected to remove codeine from their formularies.

ALTERNATIVES TO CODEINE

Nonopioid drugs

Acetaminophen and nonsteroidal anti-inflammatory drugs are good alternatives for treating mild pain as they do not have the adverse effects of respiratory depression. Increased use of nonopioids like oral and intravenous formulations of acetaminophen and nonsteroidal anti-inflammatory drugs, which do not have the respiratory depressant side effects, may be good alternatives to codeine in children. Ibuprofen was found to be least as effective as

acetaminophen with codeine for postoperative pain control in children after tonsillectomy and facial surgery, with no increased risks of bleeding [41–43].

Dexmedetomidine (DEX) sedation is a promising sedative agent and an adjunct to anesthetic regimen especially in patients with history of OSA [44,45▪▪]. Because of the increased risks with opioids in obese patients and those with OSA, DEX as an adjunct to anesthetic regimen may potentiate opioid analgesia with minimal additional respiratory depression. In comparison with fentanyl (1 μg/kg), intraoperative DEX (2 μg/kg bolus followed by 0.7 μg/kg/h) decreased the postoperative opioid requirements and the episodes of desaturation in children with OSA following tonsillectomy and adenoidectomy [46].

Tramadol

Is tramadol an alternative? Tramadol is a weak opioid agonist that is metabolized primarily through hepatic *N*-demethylation by *CYP3A4* to an inactive metabolite, and minimally through *CYP2D6*-mediated oxidation to *O*-desmethyltramadol (M1), which has a 200-fold greater affinity for μ-opioid receptors than the parent drug [47]. Tramadol exerts its analgesic activity through complementary mechanisms: activating the μ-opioid receptor by mainly M1 and weak inhibition of norepinephrine and serotonin reuptake. A prospective, double-blinded, randomized controlled trial in children undergoing tonsillectomy compared the efficacy and safety of tramadol versus codeine/acetaminophen. The authors found that tramadol achieved similar analgesia, with less potential for side effects [48]. However, studies have shown that children who are *CYP2D6* PM have lower plasma concentrations of the active metabolite and analgesia compared with extensive metabolizer, and in 2D6 ultrarapid metabolizer, plasma concentrations, analgesia and side effects are greater than in those who are extensive metabolizer [49–51]. There was also a recent case report of tramadol administration leading to respiratory depression in a child who was a *CYP2D6* ultrarapid metabolizer [52▪▪]. In fact, the 2010 FDA drug label reads that 'concomitant administration of *CYP2D6* and/or *CYP3A4* inhibitors, such as quinidine, fluoxetine, paroxetine and amitriptyline (*CYP2D6* inhibitors), and ketoconazole and erythromycin (*CYP3A4* inhibitors), may reduce metabolic clearance of tramadol increasing the risk for serious adverse events including seizures and serotonin syndrome'. Hence, its safety needs to be further investigated before widespread use.

Tapentadol

A similar agent, tapentadol, is a centrally acting analgesic with a dual mode of action as an agonist at the μ-opioid receptor and a weak norepinephrine reuptake inhibitor (compared with tramadol). It has no active metabolites and mainly undergoes glucuronidation [53]. A report from a poison control center reported two patients – a 9-month-old child who had coma and respiratory depression and a 16-month-old girl with dyspnea, drowsiness/lethargy, pallor and vomiting who was admitted to critical care and treated with oxygen. However, pediatric data on the safety of this medicine are limited.

Oxycodone

Would oxycodone, a semisynthetic opioid, be a safer alternative to codeine for managing post-tonsillectomy pain at home setting? We know that 80% of oxycodone undergoes *N*-demethylation by *CYP3A* producing noroxycodone, a metabolite with weak analgesic properties; and 10% undergoes *O*-demethylation to oxymorphone and noroxymorphone, by *CYP2D6* [54]. Oxymorphone is 14 times more potent than oxycodone [55]. The affinity of noroxymorphone at the opioid receptor is threefold and 10-fold higher than oxycodone and noroxycodone, respectively. Hence, in order of highest to lowest potency of oxycodone and metabolites, we have oxymorphone more than morphine more than noroxymorphone more than oxycodone more than noroxycodone [56]. In a postoperative setting, the *CYP2D6* PM were found to have decreased oxycodone metabolism and higher analgesic consumption [57]. The greatest oxymorphone/oxycodone concentration ratios occurred in those who are ultrarapid metabolizer and smallest in those who are PM [58]. Other adult studies in postsurgical patients and cancer patients detected clinical differences among the *CYP2D6* genotypes [59,60]. *CYP2D6* activity also correlated with oxycodone experimental pain assessment, with ultrarapid metabolizer experiencing increased pharmacodynamic effects [61]. Oxycodone overdose by wrong dosing has been reported before [62]. Interestingly, CYP2D6*4 allele (PM) implicated in the death of four fatalities from oxycodone, by a retrospective analysis of 15 cases from the Milwaukee County Medical Examiner's Office using pharmacogenomics for post-mortem forensic toxicology [63]. However, our ongoing pediatric oxycodone pharmacokinetic and pharmacogenetic study in perioperative setting revealed that compared with PMs, intermediate metabolizers and extensive metabolizers have higher oxymorphone concentration. Further large studies are needed to assess

whether oxycodone would be safer than codeine in children with CYP2D6 ultrarapid metabolizer metabolizing status and/or with significant sleep apnea. It has also been shown that like codeine, maternal oxycodone use also causes central nervous system depression in neonates, so oxycodone is unlikely to be a safer alternative in this clinical setting [64].

Hydrocodone

Hydrocodone is also a potential alternative for analgesia. It is about 12 times more potent at the opioid receptor than codeine [55] and about half the clearance is via *CYP2D6* and *CYP3A4*, into an active metabolite hydromorphone and norhydrocodone, respectively. *CYP2D6* ultrarapid metabolizer may thus have up to an eight-fold greater plasma concentration of hydromorphone, whereas PM receive minimal analgesia [65]. A common component of antitussive medications, the US FDA banned the sale of more than 200 hydrocodone products in response to occurrence of more than 400 cases of adverse events associated with its use between 1969 and 2005 [66].

Hence, although both hydrocodone and oxycodone undergo metabolism via *CYP2D6* to active metabolites, their analgesic effects are not as variable as codeine's because the parent drugs are nor prodrugs but themselves pharmacologically active. One case report demonstrates the complex interplay between drug–drug interactions and pharmacogenomics. A developmentally delayed 5-year-old Somalian child died after administration of high doses of hydrocodone for ear infection. On genotyping, she was found to be a *CYP2D6* PM and had low hydromorphone blood concentrations; but coadministration of clarithromycin (a potent *CYP3A4* inhibitor) and valproic acid for seizures since birth, prevented hydrocodone metabolism leading to high hydrocodone levels [67]. Hence, the dose–toxicity relationship of the alternative opioids needs to be further studied in the pediatric population.

Oral morphine

Lastly, the use of an oral morphine elixir has been suggested by some as an alternative [68]. The prescribers and pharmacists need to be vigilant when prescribing oral morphine as it is available in many concentrations [69]; however, although there is extensive experience with intravenous morphine in children, there is little clinical experience and very limited comparative clinical data on safety and efficacy available for the oral formulation.

In summary, drugs such as morphine (0.2–0.5 mg/kg/dose, every 4–6 h), oxycodone (0.05–0.15 mg/kg/dose, every 4–6 h) and hydrocodone (0.1–0.2 mg/kg/dose, every 6–8 h) on as needed basis for severe pain are likely alternatives for severe postoperative pain, but have their disadvantages [21].

MANAGING POSTTONSILLECTOMY PAIN SAFELY AND EFFECTIVELY WITHOUT CODEINE AT HOME

Pediatric OSA is associated with high incidences of adverse outcomes with the use of opioid analgesics for posttonsillectomy pain management. In addition to codeine, potentially other oral opioids metabolized by the *CYP2D6* pathway such as tramadol, hydrocodone and even oxycodone cannot be considered well tolerated analgesics without appropriate precautions to manage posttonsillectomy pain at unmonitored home setting, especially in young children with sleep apnea [64].

Though preoperative *CYP2D6* genotyping study in children undergoing tonsillectomy is an option, it is not widely available and third party payers do not readily reimburse for the genetic tests despite the CPIC guidelines [40] and other evidences; we observed significantly more adverse effects with codeine at home even when it was administered on as needed basis (Unpublished Data: Sadhasivam, MD 2012). Preoperative CYP2D6 testing before prescribing around the clock codeine, hydrocodone, tramadol and oxycodone at home setting would be preferable as all are at least partially metabolized by CYP2D6 pathway (Fig. 1), especially in young children with OSA and other respiratory comorbidities. Alternatively, using other analgesics (i.e. nonopioids and possibly oral morphine with appropriate doses) will lead to safer outcomes following tonsillectomy in young children.

CINCINNATI CHILDREN'S HOSPITAL MEDICAL CENTER PAIN MANAGEMENT PROTOCOL AFTER TONSILLECTOMY

An alternative and less-expensive approach to routine preoperative CYP2D6 genotyping would be to use safer and nonopioid analgesics in young children [70]. In our institution, we changed our tonsillectomy practice (in children <6 years) even before the 2013 FDA's warning based on many reported and unreported deaths related to opioid pharmacogenetics [71,72] and based on our prospective pharmacogenetic research in children undergoing tonsillectomy and receiving morphine in the hospital and codeine at home. To maximize

Table 1. Our current practice of opioid sparing pain management at home setting following pediatric tonsillectomy

Cincinnati Children's Hospital Medical Center's Standardized Post-Tonsillectomy Pain Management Protocol	
Children <6 years	**No codeine or other opioids** **Acetaminophen** around the clock **Dexamethasone** day of surgery, postoperative days 1 and 2 **Ibuprofen** from postoperative day 1
Children >6 years	**Acetaminophen** around the clock **Dexamethasone** day of surgery, postoperative days 1 and 2 **Ibuprofen** from postoperative day 1 **Oxycodone** every 4 hours prn from postoperative day 1

Prn, as needed basis.

pain relief and safety, we have successfully used opioid-sparing pain management at home setting following pediatric tonsillectomy. Our current practice is summarized in Table 1. We avoid all oral opioids at home setting on the day of tonsillectomy because of reports of high incidences of respiratory depression and deaths in the evening/night after tonsillectomy [69,73]. Despite our high annual volume of tonsillectomy, we have not seen any increase in incidence of inadequate pain control, postoperative bleeding or serious life-threatening complications with the above pain management regimen in the last 3 years.

FUTURE DIRECTIONS OF RESEARCH

Currently, robust evidence to change clinical practice based on underlying genetic risk factors, access to routine preoperative genotyping, affordability and payer coverage for genetic testing are limited. As compelling evidence for personalization of perioperative care based on genetic risk factors (e.g. *CYP2D6* and codeine-related deaths) increases, there will be better adaptability of routine preoperative genotyping and coverage of such services by third-party payers. For example, many third-party payers are covering perioperative *CYP2D6* genotyping for prescription of oral opioids in our pediatric institution. In future, pharmacogenetic studies also need to be complimented by epigenetic, proteomic, transcriptomic and metabolomic information to gain additional knowledge and insight to improving personalized care as these factors may influence clinical outcome measures. Another need of pharmacogenomics research, especially in pediatrics, is genetic counseling. Genetic counselors help patients and their families understand and adapt to the medical, psychological and familial implications of genetic contributions to clinical outcomes. As we transition from single-gene testing and genetic counseling to a full genomic medicine approach, clinical implications will get more complex [74].

CLINICAL TRANSLATION: BENCH TO BEDSIDE

As we routinely use the Global Positioning System to navigate maps and roads, in the future, it is anticipated that we will use a Genomic Prescribing System to proactively identify underlying genetic risks and guide personalized care [75]. Proactive identification of patients at risk of adverse perioperative outcomes is an important first step in guiding personalized interventions with preferably Electronic Health Record implemented clinical decision support integrating genetic risk factors and their implications for clinical interventions.

To implement pharmacogenomic-based clinical decision support, there is a need for more robust study designs, independent validations, larger populations and robust statistical approaches [76,77]. To realize the promise of personalized medicine to perioperative care, we need better evidences in terms of validating clinical association studies engaging physicians, patients, pharmaceutical industry, healthcare payers and policy-makers. Others have taken a more active stance by identifying the 2D6 isoforms in their patients. For example, pharmacogenetic data gathered under the 'Pharmacogenetics for kids' trial were incorporated into clinical decision support tools for the prescription of opioids in children with sickle-cell disease [78].

CONCLUSION

Current known implications of CYP2D6 pharmacogenetics on codeine use show that pharmacogenetics has the potential to guide anesthesiologists on perioperative opioid selection and dosing to maximize efficacy and safety. The current consensus seems to be that avoiding codeine whenever possible is the safest strategy. Currently, personalized opioid selection and dosing for perioperative pain management is still a long way. More studies are needed to improve genotype-based personalized perioperative care in children.

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Conflicts of interest

There are no conflicts of interest.

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