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Codeine: Time to Say "No"

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Codeine has been prescribed to pediatric patients for many decades as both an analgesic and an antitussive agent. Codeine is a prodrug with little inherent pharmacologic activity and must be metabolized in the liver into morphine, which is responsible for codeine's analgesic effects. However, there is substantial genetic variability in the activity of the responsible hepatic enzyme, *CYP2D6*, and, as a consequence, individual patient response to codeine varies from no effect to high sensitivity. Drug surveillance has documented the occurrence of unanticipated respiratory depression and death after receiving codeine in children, many of whom have been shown to be ultrarapid metabolizers. Patients with documented or suspected obstructive sleep apnea appear to be at particular risk because of opioid sensitivity, compounding the danger among rapid metabolizers in this group. Recently, various organizations and regulatory bodies, including the World Health Organization, the US Food and Drug Administration, and the European Medicines Agency, have promulgated stern warnings regarding the occurrence of adverse effects of codeine in children. These and other groups have or are considering a declaration of a contraindication for the use of codeine for children as either an analgesic or an antitussive. Additional clinical research must extend the understanding of the risks and benefits of both opioid and nonopioid alternatives for orally administered, effective agents for acute and chronic pain.

INTRODUCTION

Effective pain management for pediatric patients remains problematic, with studies showing that significant improvements and alterations in practice may be needed to provide safe and adequate analgesia.[1–3] These issues are further complicated by the limited number of child-appropriate pain formulations and medications, parental perceptions about the need for such analgesics, and differences in metabolism and oral bioavailability between children and adults.[1,4] Similarly, there are few evidence-based therapies for children with cough.[5] The purpose of this clinical report is to present up-to-date information regarding risks related to pharmacogenetic variations in codeine metabolism and to

abstract

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outline the therapeutic and safety implications in the treatment of pain or cough in children.

BACKGROUND

Codeine (3-methylmorphine) is a naturally occurring methylated morphine that has seen widespread clinical use for >50 years as an analgesic and an antitussive agent. Historically, codeine was considered an optimal oral analgesic for the outpatient treatment of acute pain of various etiologies in children, partly because of the perception that it was a safe opioid analgesic with a wide therapeutic index and a limited risk of respiratory depression.[6] It was the primary agent used for outpatient analgesia after adenotonsillectomy in children and was recommended as a step 2 medication in the World Health Organization Pain Ladder for the treatment of moderate pain.[7] However, codeine itself has no analgesic effect; it is a prodrug that must be metabolized to morphine to be effective. Furthermore, increased understanding of pharmacogenetics and ongoing safety investigations have shown a large variation in the conversion of codeine to morphine. This genetics-based interpatient variation produces considerable variability in the therapeutic response to recommended codeine dosing, ranging from a lack of effect because of low morphine levels to fatalities related to excessive morphine levels.[8]

Despite these concerns and the potential hazards, codeine continues to be widely available from many pharmacies and inpatient hospital formularies for use in outpatient pediatric settings and is commonly prescribed to pediatric patients.[9,10] One study from 2011 reported that, among dispensed prescriptions for selected opioids, codeine was prescribed to >800 000 patients younger than 11 years, more than any other opioid in the study.[11]

During the years 2007–2011, otolaryngologists were the most frequent prescribers of codeine/acetaminophen liquid formulations (19.6%), followed by dentists (13.3%), pediatricians (12.7%), and general practice/family physicians (10.1%).[11] Two other studies reported the use of opioids in pediatric emergency departments in the period 2001–2010. In 1 study, the frequency of codeine administration in emergency departments both for pain associated with injury and for cough remained unchanged during this period.[9] The other longitudinal study covering the same time period showed that overall codeine use remained constant in adolescents but has decreased in younger age groups.[12]

In the last 5 years, various organizations and regulatory bodies have promulgated warnings regarding adverse responses associated with codeine, as follows:

1. March 2011: The World Health Organization deleted codeine from its list of essential medications for children because of concerns that its "efficacy and safety were questionable in an unpredictable portion of the paediatric population."[13]
2. August 2012: The US Food and Drug Administration (FDA) issued a safety alert regarding the use of codeine in children after tonsillectomy, adenoidectomy, or adenotonsillectomy.[14]
3. February 2013: An update from the FDA added a "black box warning" to the drug label of codeine and codeine-containing preparations. The warning advises health care professionals "to prescribe an alternative analgesic [to codeine] for postoperative pain control in children undergoing tonsillectomy and/or adenoidectomy." A contraindication was added to restrict codeine use in such patients. The "Warnings/Precautions," "Pediatric Use," and "Patient Counseling Information" sections of the label were also updated.[15]
4. June 2013: The European Medicines Agency issued a report recommending the restriction of codeine for the treatment of pain to children older than 12 years as well as a contraindication to its use in children younger than 18 years undergoing tonsillectomy and/or adenoidectomy. In addition, it recommended against codeine use in breastfeeding women.[16]
5. June 2013: Health Canada announced that it had reviewed the safety of prescription pain and cough medications containing codeine and recommended against their use in children younger than 12 years.[17]
6. March 2015: The European Medicines Agency completed a review of the use of codeine for cough and cold and recommended against its use in children younger than 12 years as well as children and adolescents between 12 and 18 years who have problems with breathing.[18]

GENETIC VARIABILITY IN CODEINE METABOLISM

Codeine is a prodrug that has limited affinity for the μ-opioid receptor and no analgesic effects. After an oral dose, the majority of codeine undergoes hepatic glucuronidation or N-demethylation to inactive metabolites. The analgesic properties result from hepatic metabolism and conversion of the parent compound (codeine) to morphine and the active metabolite morphine-6-glucuronide. The conversion from codeine to morphine is regulated by the cytochrome P450 2D6 (*CYP2D6*) enzyme system.[19,20]

The activity of *CYP2D6* varies significantly as a function of genetic polymorphisms. More than 70 different alleles have been identified, with individuals inheriting 1 allele from each parent. The level of enzyme activity from each allele has been broadly classified according to the following scheme: normal function = 1, reduced function = 0.5, and no function = 0. The enzyme activity for an individual is the sum of activity from each parent's allele. On the basis of these additive scores, individuals can be classified as extensive (score of 1–2), intermediate (0.5), or poor (0) metabolizers. It has also been increasingly recognized that some individuals may have significantly more activity related to gene duplication.

The prevalence of the different levels of activity varies among ethnic backgrounds, with poor metabolizers overrepresented in people of northern European Caucasian descent. Poor metabolizers initially received the greatest attention because of codeine's lack of efficacy in such patients.[21–23] As our understanding of the influence of genetic variations on pharmacokinetics has improved, attention has become more focused on individuals who are ultrarapid metabolizers secondary to gene duplications. This latter group has ≥2 copies of the *CYP2D6* gene, which can result in an enzyme activity score ≥3, indicating a very high level of enzyme activity. The result in these patients is the production of large amounts of morphine that can cause respiratory depression or apnea, even after normal therapeutic doses of oral codeine.[19,23,24] The frequency of the ultrarapid metabolizer genotype has been estimated at ∼29% of patients of African/Ethiopian heritage, ∼21% of those from Saudi Arabia and other Middle Eastern countries, and ∼3.4% to 6.5% of African-American and white persons.[19,20,23,24] Intermediate metabolism tends to be more common in Asians than in whites,[25] but poor metabolism is less common.[26]

REPORTS OF ADVERSE EFFECTS

The evidence linking the use of codeine with life-threatening or fatal respiratory depression is based on a series of case reports that have appeared in the literature regularly since 2004.[27–34] The publication of these reports initiated an evaluation by the FDA, which included a review of the literature as well as reports submitted to the FDA Adverse Event Reporting System from 1969 through May 2012.[35] The search revealed 13 cases of pediatric deaths (n = 10) or respiratory depression (n = 3) attributed to the therapeutic use of codeine, 7 of which had been published in the medical literature. The age range was slightly wider than the initial reports (21 months to 9 years of age). The majority occurred during the postoperative period after adenoidectomy or adenotonsillectomy with the recommended codeine dose and dosing interval. However, 1 clinical study proposed that repeated episodes of hypoxemia result in altered μ-opioid receptors and greater analgesic potency of opioids in this setting.[36]

Three additional pediatric deaths related to codeine were reported in 2013.[37] These included a 10-year-old child who had undergone orthopedic surgery, a 4-year-old treated after tonsillectomy, and a third child who received codeine as a cough suppressant, albeit in a higher dose than was prescribed.

Most recently, a review by the FDA of the Adverse Event Reporting System data from 1965 to 2015 in children who had used codeine or any codeine-containing products revealed a total of 64 cases of severe respiratory depression and 24 codeine-related deaths, 21 of which were in children younger than 12 years.[38]

USE OF CODEINE AND ITS ALTERNATIVES FOR ANALGESIA

Even before these reports of adverse events, many physicians had concerns regarding the efficacy of codeine, mostly related to its lack of effect in a significant proportion of the population (poor metabolizers). Although *CYP2D6* genotyping that could identify patients at higher risk is available (although currently expensive), patients with normal metabolism are also at theoretical risk of high morphine levels. Therefore, further investigation is required to determine the value of such testing, which will depend on the population in whom it is applied. As such, physicians are faced with considering alternative analgesic agents to use when oral administration is needed postoperatively or in the outpatient setting.

In the United States, many physicians have switched to prescribing oxycodone for analgesia. Oxycodone is a semisynthetic opioid that is an active analgesic, not a prodrug like codeine. Metabolism is via N-demethylation by the *CYP3A4* enzyme system to inactive metabolites. A minor percentage of oxycodone is metabolized by the *CYP2D6* enzyme system to the active metabolite noroxymorphone, so ultrarapid metabolizers may be at some risk of opiate toxicity. Oxycodone is available in a liquid formulation both alone and in combination with acetaminophen. However, data are currently insufficient to unequivocally endorse the widespread use of oxycodone in infants and children. One study has shown considerable variability in absorption and oral bioavailability in children.[39] Another recent preliminary pharmacokinetic study in children younger than 6 years

showed significant differences in onset of absorption and peak levels of oxycodone and plasma concentrations of noroxymorphone on the basis of *CYP2D6* genotypes.[40]

Hydrocodone is also a potential alternative for analgesia, but *CYP2D6* is responsible for the conversion of hydrocodone to an active metabolite, hydromorphone. Ultrarapid metabolizers may have up to an eightfold greater plasma concentration of hydromorphone, whereas poor metabolizers receive minimal analgesia.[41]

Given the problems with codeine and potential concerns with the other available agents, the use of an oral morphine elixir has been suggested by some as an alternative.[20,42] 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.

Additional options for pain relief include less familiar and less commonly used medications, such as tramadol. Tramadol has a longer half-life (6–7 hours) than other oral agents as well as an active metabolite with a half-life of 10 to 11 hours. Unlike other weak opioids, it has a unique dual mechanism of action, including agonism at the μ-opioid receptor, and inhibits reuptake of neurotransmitters (norepinephrine and serotonin) within the central nervous system. Primary metabolism occurs through hepatic N-demethylation by the cytochrome *CYP3A4* enzyme system to an inactive metabolite. A smaller percentage is metabolized by O-demethylation (*CYP2D6* enzyme) to the active metabolite desmethyltramadol. Although preliminary studies in the pediatric population have shown effective analgesia,[43–46] there are reasons to be concerned about potential problems with tramadol that are similar to those encountered with codeine. Although tramadol is not dependent on metabolism for its analgesic effect, it is partially dependent on the *CYP2D6* enzyme system for metabolism, which could lead to drug accumulation in poor metabolizers.[47] In addition, the O-demethylated (*CYP2D6*-dependent) metabolite has a much higher affinity for the μ-opioid receptor, and a case report of administration of tramadol to a child with ultrarapid metabolism and subsequent respiratory depression was recently published.[48] Furthermore, many other drugs, including selective serotonin reuptake inhibitors, tricyclic antidepressants, and some antiepileptic drugs, inhibit the metabolism of tramadol, leading to undesirable tramadol accumulation. As such, further investigation must be conducted before the widespread use of tramadol in children for pain relief.

A similar agent, tapentadol, is a centrally acting analgesic with a dual mode of action as an agonist at the μ-opioid receptor and as a norepinephrine reuptake inhibitor within the central nervous system. In contradistinction to tramadol, it has only weak effects on the reuptake of serotonin and is a significantly more potent opioid agonist. It has no active metabolites. It was approved by the FDA in 2011 for use in adults; to date, there are no data regarding its use in the pediatric population. There is 1 report from a poison control center review of 124 unintended exposures, one of which resulted in coma and respiratory depression in a 9-month-old child.[49]

Concerns regarding opioids in children with sleep-disordered breathing have led to a reevaluation of postoperative nonopioid analgesics, such as acetaminophen and nonsteroidal antiinflammatory drugs (NSAIDs), such as ibuprofen, for children with mild to moderate pain.[50–54] In addition, there are intravenous formulations of acetaminophen and an NSAID (ketorolac).[55,56] Although previously thought to potentially increase the incidence of postoperative bleeding, some evidence suggests that NSAIDs can be incorporated into the postoperative regimen without adversely affecting the postoperative course in most children without underlying bleeding diatheses.[53,54] The effective use of these nonopioid agents may significantly reduce or, in some cases, eliminate the need for opioids. Further studies of other nonopioid analgesics, including dextromethorphan and dexmedetomidine, are also needed.

It is clear that one of the keys to improving analgesia and reducing opioid-related adverse effects is both provider and parental education regarding the effective use of nonopioid analgesics.[1,57] The answer may not lie in using more medication or different medications but merely using more effectively other options that are currently available.

USE OF CODEINE AS AN ANTITUSSIVE AGENT IN CHILDREN

Codeine is also prescribed as an antitussive agent and is still available in over-the-counter cough and cold formulations without a prescription from outpatient pharmacies in 28 US states and the District of Columbia.[38] However, neither the value of suppressing cough nor the effectiveness of codeine in children with acute illnesses has been shown,[58–60] and the risks of codeine administration described previously also apply to children receiving this agent as an antitussive agent. In April 2015, the European Medicines Agency announced that codeine must not be used to treat cough and cold in children younger than 12 years[18] and further cautioned that codeine is not recommended in children and adolescents between 12 and 18 years of age with compromised respiratory function, including those with

asthma and other chronic breathing problems. On July 1, 2015, the FDA issued a drug safety communication stating that it is investigating the possible risks of using codeine-containing medicines to treat coughs and colds in children younger than 18 years because of the potential for serious adverse effects, including slowed or difficult breathing.[61] An FDA advisory panel met in December 2015[38] and, by an overwhelming majority vote, recommended that the use of codeine in the treatment of cough in all children up to 18 years of age should be contraindicated. Final agency action on this recommendation is pending at this time. Alternative therapies for cough have recently been reviewed.[62]

SUMMARY

Published reports and clinical evidence have shown the potential dangers of codeine as an analgesic or as an antitussive. Although these concerns have been emphasized by the FDA, the European Medicines Agency, Health Canada, and the American Academy of Pediatrics, regular codeine administration to children continues.[9,10,63] The life-threatening events and deaths in these reports share a number of common features in that the majority of the children (1) were relatively young, (2) were placed on a postoperative pain regimen of scheduled acetaminophen and codeine, and (3) had undergone adenotonsillectomy for sleep-disordered breathing. However, physicians cannot assume that such problems will occur only after adenotonsillectomy. Given the increasing prevalence of obesity in the United States, it is likely that some patients presenting for nonotolaryngologic procedures may have undiagnosed sleep-disordered breathing and may also be at risk if they require extended postoperative analgesia.

Additional measures are needed to prevent future problems with the use of codeine in the pediatric population. Improved education of parents and more formal restrictions regarding its use in children, regardless of age, are necessary. The evolving information about the genetic variability in drug metabolism will yield important insights to guide physicians in the safe and effective treatment of their patients. Additional clinical research must extend the understanding of the risks and benefits of both opioid and nonopioid alternatives for orally administered, effective agents for acute pain.

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ABBREVIATIONS

FDA: Food and Drug Administration
NSAID: nonsteroidal antiinflammatory drug

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