

New Evidence about an Old Drug — Risk with Codeine after Adenotonsillectomy

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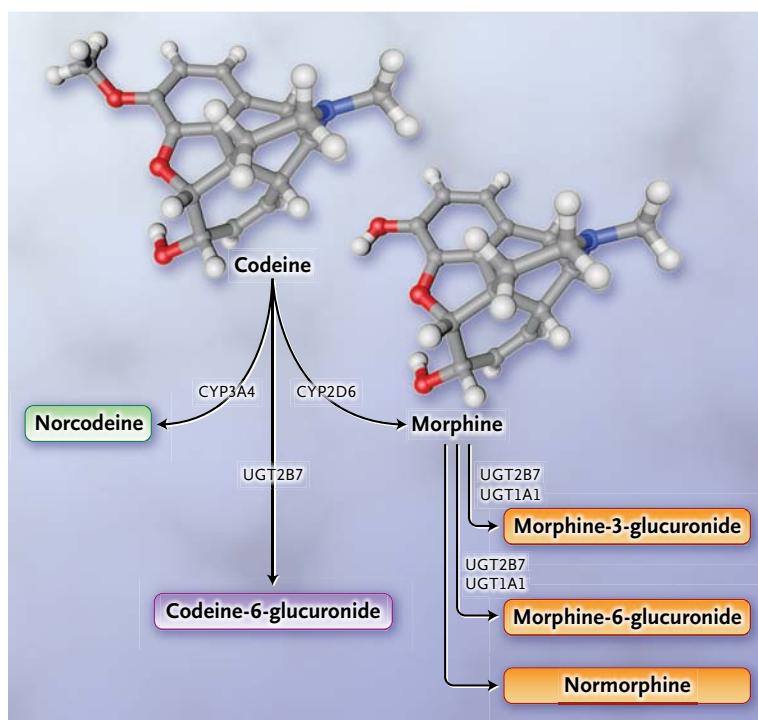
During the past 10 years, efforts in pharmacogenomics have generated insights into the efficacy and safety of drugs, enhancing our understanding of the safety profile of even some of the oldest drugs, such as codeine sulfate, an opioid analgesic first approved in 1950 for relief of mild or moderate pain. Simultaneously, an increased awareness of the value of both personalized medicine and the reporting of rare adverse outcomes has resulted in the publication of information on adverse events that previously might not have been reported. These developments, in

turn, led the Food and Drug Administration (FDA) to reanalyze the safety of — and ultimately restrict — codeine use in patients after adenotonsillectomy.

The activity of codeine depends on its conversion to morphine by the cytochrome P-450 isoenzyme 2D6 (CYP2D6); morphine is subsequently metabolized to the active morphine-6-glucuronide by means of UDP-glucuronosyltransferase 2B7 (see diagram).¹ The gene encoding CYP2D6 has many genetic variations that affect the amount of codeine that is converted to an active form and that result in the drug's var-

iable effect. Patients with a normal range of CYP2D6 activity represent 75 to 92% of the population and are called extensive metabolizers. At the low end of the activity spectrum are poor metabolizers (approximately 5 to 10% of the population), who have no functional alleles and therefore receive little to no morphine or analgesia from codeine. At the high end of the CYP2D6 activity spectrum, ultrarapid metabolizers have two or more functional alleles, and their bodies can convert codeine into large amounts of morphine. The prevalence of ultrarapid metabolism varies by ethnic group: it is lower than 1% among Chinese and Japanese patients but potentially higher than 15% among Middle Eastern and North African patients. Clinically significant toxic effects related to opioid excess have been reported in ultrarapid metabolizers, which suggests that the risk of toxic effects from codeine depends, in part, on genotype.¹

In April 2012, a case series was published reporting two deaths and one case of respiratory depression in children 3 to 5 years of age who had received typical doses of codeine after tonsillectomy, adenoidectomy, or both performed because of obstructive sleep apnea.² The two deaths occurred in children who had evidence of being ultrarapid metabolizers, and the postmortem morphine levels in these children were substantially high-



Codeine Metabolism Pathway.
Data are from Crews et al.¹

er than the therapeutic range. The third child was an extensive metabolizer. Signs of morphine toxicity developed within 1 to 2 days after codeine treatment began.

In response to that publication, the FDA initiated an evaluation of the safety of codeine in children. This assessment included a comprehensive review of the literature and case reports that were submitted to the FDA's Adverse Event Reporting System (AERS, now known as FAERS) between 1969 and May 1, 2012. This search identified 13 cases, including 10 deaths and 3 cases of life-threatening respiratory depression associated with therapeutic codeine use. Seven of these 13 cases (including the 3 from the case series mentioned above) had been reported in the medical literature. Patients ranged in age from 21 months to 9 years. Most of the patients had undergone adenotonsillectomy (eight patients) or had a respiratory tract infection (three patients), and they appeared to receive appropriate doses of codeine. Of the seven children described in the published cases, three were characterized as ultrarapid metabolizers, three as extensive metabolizers, and one as a probable ultrarapid metabolizer. A search of the medical literature and AERS for cases of pediatric death or life-threatening respiratory depression with therapeutic use of hydrocodone, oxycodone, or morphine was also conducted and did not identify robust cases of unexplainable or unconfounded death or life-threatening respiratory depression after the use of these drugs.

In late 2011, the Patient Safety and Quality Improvement Committee of the American Academy of Otolaryngology–Head and Neck

Surgery (AAO-HNS) was also becoming concerned about adverse events, particularly respiratory depression, after adenotonsillectomy. Such events have been described informally for decades but rarely reported. In 2012, the committee conducted a nationwide, anonymous survey of otolaryngologists to learn more about these events. When the FDA announced its investigation (www.fda.gov/Drugs/DrugSafety/ucm313631.htm), the committee reached out to share prepublication results with the agency. Limited information was available; however, two children (a 3-year-old and a 12-year-old) with obstructive sleep apnea who died after adenotonsillectomy were confirmed (by genotype) to be ultrarapid metabolizers or suspected (because of high post-mortem blood morphine levels) of being ultrarapid metabolizers.³

The only well-documented cases of death or respiratory arrest after codeine treatment in ultrarapid-metabolizing children have involved patients who have just undergone adenotonsillectomy. That does not mean that the risk is not present in other situations, but currently available evidence suggests that the risk is most substantial in children after they have undergone tonsillectomy, adenoidectomy, or both. Many such children have sleep-disordered breathing, and children with sleep-disordered breathing are known to be more sensitive to opioids.⁴

Therefore, the FDA recently required that the manufacturers of all codeine-containing products add a boxed warning to the labeling of their product that describes the risk posed by codeine after a child has undergone tonsillectomy or adenoid-

ectomy. A contraindication will be added to restrict codeine use in such patients. The “Warnings/Precautions,” “Pediatric Use,” and “Patient Counseling Information” sections of the labeling will also be updated.

Performing routine genotyping before prescribing codeine was not recommended for several reasons. Some of the patients who died or in whom respiratory depression developed were genetically extensive metabolizers, so patients with “normal” genotyping results may still be at risk. Also, since the number that would need to be screened to prevent such a rare toxic effect would be very high, and since preoperative laboratory assessments are not routine before adenotonsillectomy, the practicality of genotyping is questionable.

Although it did not participate in the FDA's decision process, the AAO-HNS supported the labeling changes because of the increasing evidence that these extremely rare but catastrophic events can be related to codeine use, because codeine is ineffective in some patients (poor metabolizers), and because of emerging clarity that a variety of other drugs (e.g., some nonsteroidal antiinflammatory drugs) are safe to use and do not increase the risk of bleeding.⁵ The AAO-HNS informally surveyed opinion leaders in academic medicine, private practice, and pediatric otolaryngology and reached a consensus that the availability of other analgesic agents and the risk of catastrophic events outweighed the value of codeine.

Even old and commonly used drugs may cause rare but catastrophic events that will not be recognized without a vigorous effort by the profession to share

information in the literature. In the case of codeine, a combination of case reporting and our evolving understanding of genetic influences on drug response has clarified the need to avoid this drug after adenotonsillectomy.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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1. Crews KR, Gaedigk A, Dunnenberger HM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for codeine therapy in the context of cytochrome P450 2D6 (CYP2D6) genotype. *Clin Pharmacol Ther* 2012;91:321-6.
2. Kelly LE, Rieder M, van den Anker J, et al. More codeine fatalities after tonsillectomy in

North American children. *Pediatrics* 2012; 129(5):e1343-e1347.

3. Goldman JL, Baugh RF, Davies L, et al. Mortality and major morbidity after tonsillectomy: etiologic factors and strategies for prevention. *Laryngoscope* (in press).

4. Brown KA, Laferrrière A, Lakheeram I, Moss IR. Recurrent hypoxemia in children is associated with increased analgesic sensitivity to opiates. *Anesthesiology* 2006;105: 665-9.

5. Baugh RF, Archer SM, Mitchell RB, et al. Clinical practice guideline: tonsillectomy in children. *Otolaryngol Head Neck Surg* 2011; 144:Suppl:S1-S30.

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