New FDA Black Box Warning for Codeine: How Will This Affect Dentists?

On February 20, 2013, the U.S. Food and Drug Administration (FDA) issued a public warning to address a safety concern with the use of codeine in children after tonsillectomy and/or adenoidectomy. It will implement a "Black Box Warning," the FDA's strongest safety statement, on the labeling of all codeine-containing drugs regarding increased risk in postoperative pain management in children following tonsillectomy and/or adenoidectomy. In fact, it appears that codeine will receive an official FDA contraindication for children in this specific posttonsillectomy setting. The FDA is also recommending that parents and caregivers of children receiving codeine for pain from other causes should closely monitor the child for signs of opioid overdose and to seek medical attention immediately by taking the child to the emergency room or calling 911 if the child has unusual sleepiness, difficulty waking up, disorientation or confusion, labored or noisy breathing, shallow breathing with a sighing pattern, or if the child is taking deep breaths followed by long pauses. The FDA is aware that several deaths have occurred postoperatively in children with obstructive sleep apnea (OSA) who were prescribed codeine for pain relief after tonsillectomy.

Why is this happening now, after decades of apparently safe use of codeine-containing products for children following all types of surgical procedures, including tonsillectomy? Your editor believes that modern high-speed communication has led to the FDA receiving more reports of these untoward events that may have not been reported in the past. Additionally, the actual number of these cases may be increasing because of the increased prevalence of OSA among children and the increased percentage of tonsillectomy cases currently being performed to treat OSA. Whatever the true cause, the FDA initially expressed its concern in August 2012, and its subsequent investigation resulted in the current Black Box Warning.

Codeine is a prodrug, meaning that it has to be converted into its active form, morphine, for its analgesic effect to be fully realized. Cytochrome P450 isoenzyme-2D6 (CYP2D6) is responsible for its hepatic conversion, and of course this extra biotransformation step increases the chances for alterations in the extent and speed of the enzyme's conversion of codeine to morphine. There are considerably more drugs that inhibit CYP2D6 than accelerate it. Drugs that inhibit the CYP2D6 enzymatic process can decrease or even essentially block it, making

codeine less effective or essentially ineffective. Fluoxetine (Prozac), paroxetine (Paxil), bupropion (Wellbutrin), and duloxetine (Cymbalta) are examples of drugs that can substantially inhibit CYP2D6 and thereby have the potential to reduce the efficacy of codeine. Alternatively, multiple doses of drugs such as dexamethasone and rifampin can increase the CYP2D6 conversion process, and this could increase the conversion of codeine into morphine such that higher than expected blood levels of morphine could develop fairly quickly, causing signs and symptoms of acute narcotic overdose.

In addition to drug interactions, other factors can modify the activity of CYP2D6 enzymes. CYP2D6 demonstrates the largest phenotypical variability among the various CYPs, primarily because of genetic polymorphism. Slow, intermediate, normal, and ultrarapid metabolizers have been discovered, depending on the genetic makeup of a patient's enzymes. In ultrarapid metabolizers, multiple copies of the CYP2D6 gene are expressed, leading to greater than normal CYP2D6 function. The FDA has collected 13 reports of deaths of children between 1969 and 2012 who were prescribed codeine-containing products for postoperative pain. Most of these tragic events took place following tonsillectomy, and many of the children had OSA. Based perhaps on elevated levels of morphine in the blood compared to the dose of codeine prescribed, but not necessarily taking into account the amount actually given by the parent or caregiver, the FDA believed that there was evidence that some of these children were CYP2D6 ultrarapid metabolizers. However, since many of these children had OSA, they may simply have been more sensitive to the respiratory depressant effects of the elevated levels of morphine or more sensitive to a larger-than-prescribed dose actually given by the parent or caregiver. Parents and caregivers have all levels of intellect and capability to read and understand directions on how to give medications to their children, so overdose is always a possibility when any medication is prescribed for a child.

Despite less than impressive evidence to impugn ultrarapid metabolism of codeine as a cause of morphine overdose in these children, rather than excessive doses given by parents and caregivers or the increased sensitivity of children with OSA to the respiratory depressant effects of codeine, the FDA's warning is probably accurate but too narrow and somewhat off target. The risk of respiratory complications may not be specific to codeine but rather to any opioid that could have been given to these children. It may eventually be

discovered that otolaryngologists who no longer prescribe codeine-containing products will prescribe other opioids that may be even less safe than codeine in this tonsillectomy patient group, which includes a high prevalence of children with OSA. An important point here is that the physiological abnormalities that develop as a result of OSA are not immediately altered after tonsillectomy, and thus these children are still assumed to have OSA in the immediate postoperative period. In addition, tonsillectomy is not always successful in treating severe OSA.

More than 500,000 children 15 years old and younger have their tonsils removed each year in the United States, according to the American Academy of Otolaryngology–Head and Neck Surgery (AAOHNHNS). In 2011, the AAOHNHNS published clinical practice guidelines for tonsillectomy in children that stated that, although acetaminophen with codeine is widely used, there is significant evidence that it does not provide superior control of pain compared with acetaminophen alone following tonsillectomy. Nevertheless, more than 1.7 million codeine-containing prescriptions were written in 2011 for children 17 years old and younger, many of which were for postsurgical pain following a variety of surgical procedures, including tonsillectomy. With those large numbers in mind, although any death is a horribly regrettable event, it would seem that 13 codeine-related deaths over 43 years is concerning but perhaps not worthy of a Black Box Warning for codeine. The obvious question, therefore, concerning the FDA's interpretation of the data is whether the major culprit is ultrarapid metabolism of codeine to unsafe levels of morphine; the use of any opioid, not just codeine, in postoperative tonsillectomy children; or the use of an opioid in a child with OSA that is so severe that tonsillectomy is indicated. The answer is not clear, but in this era, in which a definite pathological diagnosis is necessary to justify a tonsillectomy and when the current primary reason to remove tonsils in children is OSA, the operation itself may not be a major factor; rather, it may be the compromised airway of patients with OSA who need the surgery and who are later given an opioid, most commonly codeine. Perhaps the FDA Black Box Warning should instead be for all narcotics prescribed for children who have severe OSA, such as those who need or have just received tonsillectomy.

How does this FDA change affect dentistry? Children who undergo surgery in or around their airway, whether tonsillectomy or an oral surgery procedure, have a higher potential risk of postoperative airway compromise and respiratory obstruction, in contrast to many other common surgical procedures that do not involve

the airway. In children who normally have relatively small airways, dental postoperative complications such as swelling, infection, and hematoma involving the airway may be exacerbated by the presence of opioid-induced respiratory depression, even more so in the presence of OSA. We therefore need to carefully evaluate all children for their risk of OSA, not only for their increased risk during sedation or general anesthesia, but also to ensure safe postoperative pain control. Loud snoring that can be heard through a closed door, abnormal breathing patterns, poor quality of sleep, unusual daytime sleepiness, learning/behavioral problems, and obesity are all risk factors for OSA. Every preoperative evaluation therefore should include documentation of our estimation of the patient's risk for OSA.

There is sound evidence that nonsteroidal anti-inflammatory analgesics and acetaminophen provide excellent postoperative analgesia and should be considered for all children who are at risk for OSA, even if they have not been diagnosed with it. We need to consider the risk:benefit ratio of prescribing opioids versus nonopioid alternatives for all children and especially for those at risk for OSA, since opioids increase the risk of precipitating life-threatening events when the child is at home. We also need to take extra time to ensure to the best of our ability that the parent or caregiver fully understands that he or she cannot administer more than the prescribed dose of an analgesic and inform them of the potential adverse consequences of giving more than the prescribed dose or giving the next dose too soon after the previous dose. We need to understand that as more parents and caregivers learn that codeine is no longer prescribed for children having tonsillectomy, they may also be concerned about it being prescribed by a dentist for children experiencing pain after dental surgery. If there is a bad outcome, attorneys also will undoubtedly attempt to apply this codeine contraindication for tonsillectomies to surgery done in the oral cavity immediately adjacent to the tonsils. Therefore, the die appears to be cast that the codeine contraindication for tonsillectomy may eventually include all dental procedures for children. We need to therefore consider changing our prescribing habits for children from opioids to equally effective nonopioid analgesics for postoperative dental pain and recognize that patients with OSA must be treated intraoperatively and postoperatively with additional due care.

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