Codeine was first approved by the US Food and Drug Administration (FDA) in 1950 for the relief of mild to moderate pain and has since been used in the adult and pediatric population as an analgesic and antitussive agent. Historically, codeine was considered an optimal choice to treat pain in the pediatric population based on the perception that it was a safe medication with a wide therapeutic index and low risk of respiratory depression.\(^1\)

Codeine was often used as a post-operative medication to treat pain associated with tonsillectomy and adenoidectomy.

Recently, however, case reports of pediatric overdose and death associated with codeine use have prompted Federal and worldwide warnings associated with the use of this medication in the pediatric population. These cases have been reported in the adult and pediatric population. These case reports have documented the occurrence of respiratory depression and death of pediatric patients who received codeine for post tonsillectomy/adenoidectomy pain control, and also, in breastfed neonates who experienced poisoning through mothers who were prescribed codeine.\(^2\)\(^-\)\(^8\)

Based on these reports, patients who are classified as CYP2D6 ultrarapid metabolizers have an increased risk of serious CNS depression and respiratory depression when given codeine. It should also be noted that recurrent episodes of hypoxemia can lead to changes in the μ-opioid receptor and increased sensitivity to morphine. Patients who continue experience apnea post tonsillectomy/adenoidectomy and who are also classified as ultrarapid metabolizers of codeine, may have a significantly increased risk of respiratory depression.\(^2\)\(^-\)\(^3\)

Additional information released during a December 2015 Joint FDA Advisory Committee meeting cited that between 1965 and 2015, there were 64 cases of severe respiratory depression and 24 cases of death (21 of which were in children < 12 years of age) reported in children who had used codeine or codeine containing products.\(^9\)

Codeine (3-methylmorphine) itself is a prodrug and has no analgesic effect or affinity for the μ-opioid receptor. After oral administration, codeine undergoes hepatic glucuronidation or N-Demethylation to metabolites. Analgesia occurs after codeine undergoes metabolism by hepatic enzyme CYP2D6 and is converted to the demethylated form of morphine. Once metabolized to morphine, the drug can exert a pharmacologic and analgesic effect through the μ-opioid receptors.\(^10\)

Because there is substantial genetic variability when considering CYP2D6, different metabolizers can experience varied responses to codeine administration.

Generally, individuals can be classified as ultrarapid, extensive, intermediate, or poor metabolizers based on genetic polymorphisms, and activity of CYP2D6 is seen as a function of this classification. Poor 2D6 metabolizers have a low level of enzyme activity and do not efficiently metabolize codeine to the active form of morphine. When a standard dose of codeine is administered to these patients, they will experience little to no pharmacologic and analgesic effect from the medication.
Extensive or ultrarapid 2D6 metabolizers have a high level of enzyme activity and metabolize codeine to the active form of morphine very quickly and efficiently. When a standard dose of codeine is administered to these patients, they can experience excessive pharmacologic and analgesic effects from the medication and are at a greater risk of adverse events associated with morphine such as CNS depression, respiratory depression and even death.11

Federal and Worldwide Agencies have taken action to warn the public about the risk of using codeine in the pediatric population, and listed below is a timeline of these warnings:

March 2011 – The World Health Organization (WHO) 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.”7

August 2012 – The US FDA issued a safety alert regarding the use of codeine in children after tonsillectomy, adenotonsillectomy, or adenotonsillectomy.13

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” section of the label were also updated.14

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.15

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.16

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.17

July 2015 - The U.S. 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 under 18 years because of the potential for serious side effects, including slowed or difficult breathing.18

December 2015 – A joint FDA advisory committee met to discuss the amendment of the codeine label to contraindicate codeine treatment of pain and cough in all children < 18 years of age and to remove codeine from the over-the-counter (OTC) monograph. Based on that meeting and a majority vote, it was recommended that the use of codeine in the treatment of cough in all children < 18 years of age be contraindicated.9 Final action on the committee’s recommendation is currently pending.

References:

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