New clinical report calls attention to safety issues with codeine use in children
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Codeine is a naturally occurring methylated morphine compound that has seen widespread clinical use for more than 50 years as an analgesic, antitussive and anti-diarrheal agent. Morphine was isolated in 1804 by German pharmacist Friedrich Sertürner. This was followed by the isolation of codeine in 1832 by French chemist and pharmacist Pierre Robiquet.

For many years, codeine was considered the optimal oral analgesic for the outpatient treatment of acute pain of various etiologies in children and was recommended as a step two medication in the World Health Organization Pain Ladder for the treatment of moderate pain (Ewah BN, et al. Anaesth. 2006;61:116-122; Tremlett M, et al. Paediatr Anaesth. 2010;20:183-194). Its widespread use and popularity appeared to be partially based on the misconception that it provided effective analgesia with a wide therapeutic index and a limited risk of respiratory depression.

However, increased understanding of pharmacogenetics and ongoing safety investigations have demonstrated significant inter-patient variation in the conversion of the prodrug, codeine, to its active metabolite, morphine (Madadi P, et al. Pharmacogenomics. 2008;9:1267-1284). This genetic-based variation produces considerable variability in response, ranging from a lack of effect to excessive morphine levels, which have resulted in fatal outcomes.

An updated AAP clinical report reviews recent information pertaining to the safety of codeine use in pediatric patients. Codeine: Time to Say "No," from the Section on Anesthesiology and Pain Medicine and the Committee on Drugs, is available at http://dx.doi.org/10.1542/peds.2016-2396 and will be published in the October issue of Pediatrics.

The report summarizes recent clinical concerns regarding the pharmacogenetics of codeine metabolism, highlights reports from the literature on the potential for mortality with codeine use in children, and summarizes guidance from various organizations and regulatory bodies regarding adverse responses associated with codeine and recommendations for changes in clinical practice.


It is imperative that pediatricians and all health care providers who care for children educate themselves on these issues. Although codeine has been removed from many hospital formularies, more formal restrictions regarding the use of codeine in children are needed, according to the clinical report. As there is no special
indication or need for codeine in clinical practice, significant consideration needs to be given to terminating its use.

Given the problems with the outpatient management of acute pain in children, emphasis must be placed on the investigation and development of novel oral opioids that are not subject to such genetic variation in their metabolism. An additional intervention that may improve analgesia and reduce opioid-related adverse effects is both provider and parental education regarding the effective use of non-opioid analgesics, including acetaminophen and non-steroidal anti-inflammatory drugs.

Dr. Tobias, immediate past chair of the AAP Section on Anesthesiology and Pain Medicine Executive Committee, is a lead author of the clinical report.