U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Drug Safety Communications

Safety review update of codeine use in children; new *Boxed Warning* and *Contraindication* on use after tonsillectomy and/or adenoidectomy

This update is in follow-up to the FDA Drug Safety Communication: Codeine use in certain children after tonsillectomy and/or adenoidectomy may lead to rare, but life-threatening adverse events or death issued on 8/15/2012.

Safety Announcement

[2-20-2013] The U.S. Food and Drug Administration (FDA) is updating the public about new actions being taken to address a known safety concern with codeine use in certain children after tonsillectomy and/or adenoidectomy (surgery to remove the tonsils and/or adenoids). Deaths have occurred post-operatively in children with obstructive sleep apnea who received codeine for pain relief following a tonsillectomy and/or adenoidectomy. Codeine is converted to morphine by the liver. These children had evidence of being ultra-rapid metabolizers of codeine, which is an inherited (genetic) ability that causes the liver to convert codeine into life-threatening or fatal amounts of morphine in the body.

A new *Boxed Warning*, FDA's strongest warning, will be added to the drug label of codeine-containing products about the risk of codeine in post-operative pain management in children following tonsillectomy and/or adenoidectomy. A *Contraindication*, which is a formal means for FDA to make a strong recommendation against use of a drug in certain patients, will be added to restrict codeine from being used in this setting. The *Warnings/Precautions*, *Pediatric Use*, and *Patient Counseling Information* sections of the drug label will also be updated.

In August 2012, FDA announced it was reviewing the safety of codeine due to cases of deaths and serious adverse events in children who took the drug after a tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine. FDA conducted a comprehensive safety review to identify additional cases of overdose or death in children taking codeine and to determine if these adverse events occurred in any other treatment settings. Many of the cases of serious adverse events or death occurred in children with obstructive sleep apnea who received codeine after a tonsillectomy and/or adenoidectomy (see Data Summary). Since these children already had underlying breathing problems, they may have been particularly sensitive to the breathing difficulties that can result when codeine is converted in the body to high levels of morphine. However, this contraindication applies to all children undergoing tonsillectomy and/or adenoidectomy because it is not easy to determine which children might be ultra-rapid metabolizers of codeine.

Health care professionals should prescribe an alternate analgesic for post-operative pain control in children who are undergoing tonsillectomy and/or adenoidectomy. Codeine should not be used for pain in children following these procedures.

For management of other types of pain in children, codeine should only be used if the benefits are anticipated to outweigh the risks.

Parents and caregivers who observe unusual sleepiness, confusion, or difficult or noisy breathing in their child should stop giving codeine and seek medical attention **immediately**, as these are signs of overdose.

Facts about codeine

- An opioid pain reliever used to treat mild to moderately severe pain
- Also used, usually in combination with other medications, to reduce coughing
- Available as a single-ingredient product or in combination with acetaminophen or aspirin and in some cough and cold medications
- In year 2011, approximately 1.7 million pediatric patients (0-17 years old) received a prescription for a codeine/acetaminophen combination product or single ingredient codeine product from U.S. outpatient retail pharmacies.[1]

Additional Information for Parents and Caregivers

- Deaths have occurred in children with obstructive sleep apnea who took codeine for pain relief after tonsillectomy and/or adenoidectomy. These children had evidence of being ultra-rapid metabolizers of codeine, which is a genetic variation that results in their liver changing codeine into morphine more rapidly and completely than other people. Ultra-rapid metabolizers are more likely to have higher-than-normal levels of morphine in their blood after taking codeine.
- Codeine should not be used to control pain in children following surgery to remove their tonsils and/or adenoids. If your child's health care professional prescribes codeine, ask for another pain medicine.
- If codeine is prescribed for other types of pain, it is often given on an "AS NEEDED" basis. Do not administer codeine to the child on a scheduled basis UNLESS the child requires the drug. Do not administer more than six (6) doses per day.
- Signs of serious side effects of codeine in children can include unusual sleepiness, confusion, and difficult or noisy breathing. **If your child shows these signs, stop giving your child codeine and seek medical attention immediately by taking your child to the emergency room or calling 911.**
- Talk to your child's health care professional if you have any questions or concerns about codeine.
- Report side effects from codeine to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Additional Information for Health Care Professionals

- Deaths have occurred in children with obstructive sleep apnea who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to a cytochrome P450 2D6 (CYP2D6) polymorphism. These children may be particularly sensitive to the respiratory depressant effects of codeine that has been rapidly metabolized to morphine.
- Routine CYP2D6 genotype testing is not being recommended for use in this setting because patients with normal metabolism may, in some cases, convert codeine to morphine at levels similar to ultra-rapid metabolizers.
- Prescribe an alternate analgesic for children who are undergoing tonsillectomy and/or adenoidectomy because codeine is now contraindicated in this setting.
- Codeine should only be used in children with other types of pain if the benefits are anticipated to outweigh the risks.
- If children are treated with codeine for other types of pain, monitor their respiratory status closely and advise parents/caregivers to monitor their children for signs of morphine overdose.
- When prescribing codeine-containing drugs, choose the lowest effective dose for the shortest period of time.
- Advise parents and caregivers to stop giving their child codeine and to seek medical attention immediately if their child is exhibiting signs of morphine overdose.
- Report adverse events involving codeine to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Data Summary

FDA conducted a comprehensive safety review of codeine use in children to identify cases of overdose or death in children taking codeine and to determine if these adverse events occur in any treatment setting. FDA first informed the public that it was reviewing the safety of codeine in children in its August 2012 Drug Safety Communication, due to cases of death and serious adverse events in children who took codeine after a tonsillectomy and/or adenoidectomy.

A search of FDA's Adverse Event Reporting System (AERS) database between 1969 to May 1, 2012 identified 13 cases of pediatric death (n=10) or overdose (n=3) associated with codeine. Seven of these cases were also described in the medical literature.[2-5] The patients ranged in age from 21 months to 9 years. Most of the cases (11/13) were reported in the setting of adenotonsillectomy (n=8) or respiratory tract infection (n=3). In most of these cases, the children appeared to receive appropriate doses of codeine. Cytochrome P450 2D6 (CYP2D6) metabolizer status was mentioned for the seven children described in the literature. Three children were characterized as ultra-rapid metabolizers, three as extensive metabolizers, and one as a likely ultra-rapid metabolizer.

FDA also sought to identify additional cases from other data sources. FDA reviewed a physician survey of mortality and major morbidity following tonsillectomy and/or

adenoidectomy conducted by the American Academy of Otolaryngology-Head and Neck Surgery. Limited information was available from these cases; however, one 3-year-old patient with obstructive sleep apnea who died after adenotonsillectomy was confirmed as being an ultra-rapid metabolizer, and one 12-year-old patient with obstructive sleep apnea who died after adenotonsillectomy was suspected of being an ultra-rapid metabolizer after high blood morphine levels were identified on autopsy.[6]

References

1. IMS Health, Total Patient Tracker (TPT). Year 2011. Data extracted January 2013.

2. Voronov P, Przybylo HJ, Jagannathan N. Apnea in a child after oral codeine: a genetic variant - an ultra-rapid metabolizer. Paediatr Anaesth 2007;17:684-7.

3. Hermanns-Clausen M, Weinmann W, Auwärter V, Ferreirós N, Trittler R, Müller C, et al. Drug dosing error with drops: severe clinical course of codeine intoxication in twins. Eur J Pediatr 2009;168:819-24.

4. Ciszkowski C, Madadi P, Phillips MS, Lauwers AE, Koren G. Codeine, ultrarapid-metabolism genotype, and postoperative death. N Engl J Med 2009;361:827-8.

5. Kelly LE, Rieder M, van den Anker J, Malkin B, Ross C, Neely MN, et al. More codeine fatalities after tonsillectomy in North American children. Pediatrics 2012;129:e1343-7.

6. Goldman JL, Baugh RF, Davies L, et al. Mortality and major morbidity after tonsillectomy: etiologic factors and strategies for prevention. Laryngoscope 2013. In press.