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## Drugs

### 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

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#### Safety Announcement

**[8-15-2012]** The U.S. Food and Drug Administration (FDA) is reviewing reports of children who developed serious adverse effects or died after taking codeine for pain relief after tonsillectomy and/or adenoidectomy for obstructive sleep apnea syndrome. Recently, three pediatric deaths and one non-fatal but life-threatening case of respiratory depression were documented in the medical literature<sup>1,2</sup> (see Data Summary below). These children (ages two to five) had evidence of an inherited (genetic) ability to convert codeine into life-threatening or fatal amounts of morphine in the body. All children had received doses of codeine that were within the typical dose range.

When codeine is ingested, it is converted to morphine in the liver by an enzyme called cytochrome P450 2D6 (CYP2D6). Some people have DNA variations that make this enzyme more active, causing codeine to be converted to morphine faster and more completely than in other people. These "ultra-rapid metabolizers" are more likely to have higher than normal amounts of morphine in their blood after taking codeine. High levels of morphine can result in breathing difficulty, which may be fatal. Taking codeine after tonsillectomy and/or adenoidectomy may increase the risk for breathing problems and death in children who are "ultra-rapid metabolizers." The estimated number of "ultra-rapid metabolizers" is generally 1 to 7 per 100 people, but may be as high as 28 per 100 people in some ethnic groups (see Table 1 below).

- 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

FDA is currently conducting a safety review of codeine to determine if there are additional cases of inadvertent overdose or death in children taking codeine, and if these adverse events occur during treatment of other kinds of pain, such as post-operative pain following other types of surgery or procedures.

**Health care professionals** should be aware of the risks of using codeine in children, particularly in those who have undergone tonsillectomy and/or adenoidectomy for obstructive sleep apnea syndrome. If prescribing codeine-containing drugs, the lowest effective dose for the shortest period of time should be used on an as-needed basis (i.e., not scheduled around the clock).

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

FDA will update the public with more information once it has completed its review.

#### Additional Information for Parents and Caregivers

- Certain children may be at risk for life-threatening side effects, such as breathing difficulty, or death when taking codeine for pain relief after tonsillectomy or adenoidectomy. This can occur even with use of codeine at recommended doses.
- Codeine is usually prescribed on an "AS NEEDED" basis. Do not administer codeine to the child on a regular 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

- Life-threatening adverse events and death have occurred in certain children who received codeine after tonsillectomy and/or adenoidectomy for obstructive sleep apnea syndrome. These children had evidence of being "ultra-rapid metabolizers" of substrates of cytochrome P450 2D6 (CYP2D6), including codeine.
- If prescribing codeine-containing drugs, use the lowest effective dose for the shortest period of time on an as-needed basis (i.e., not scheduled around the clock).
- Counsel parents and caregivers on how to recognize the signs of morphine toxicity, and advise them to stop

- giving the child codeine and to seek medical attention immediately if their child is exhibiting these signs.
- FDA-cleared tests are available for determining a patient's CYP2D6 genotype.
  - The estimated number of ultra-rapid metabolizers varies among different racial/ethnic groups (see Table 1 below).
  - Consider prescribing alternative analgesics for children undergoing tonsillectomy and/or adenoidectomy for obstructive sleep apnea syndrome.
  - 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

Recently, three deaths and one case of severe respiratory depression were reported in children who received codeine after undergoing tonsillectomy and/or adenoidectomy for obstructive sleep apnea syndrome. The children ranged in age from two to five years old. The three deaths occurred in children who had evidence of being "ultra-rapid metabolizers" of substrates of the cytochrome P450 isoenzyme 2D6 (including codeine), and the life-threatening case occurred in a child who was an extensive metabolizer. All children received doses of codeine that were within the typical dose range. In these cases, signs of morphine toxicity developed within one to two days after starting codeine. The post-mortem morphine concentrations in the three children who died<sup>1,2</sup> were substantially higher than the typical therapeutic range.<sup>3</sup>

FDA is conducting a review to determine if there are additional cases of inadvertent overdose or death in children taking codeine, and if these adverse events occurred during treatment of other kinds of pain such as post-operative pain following other types of surgery or procedures. FDA will update the public when more information is available.

**Table 1. Prevalence of Ultra-rapid Metabolizers in Different Populations**

Population	UM Genotypes/Phenotypes (↑ Activity)	Prevalence % (UM/Total n)
African/Ethiopian <sup>4</sup>	UM (active duplicate genes)	29% (35/122)
African American <sup>5, 6</sup>	UM (three active duplicate genes)	3.4% (3/87) 6.5% (60/919)
Asian <sup>7, 8, 9</sup>	UM (active duplicate genes)	1.2% (5/400) 2%
Caucasian <sup>5, 6</sup>	UM (three active duplicate genes)	3.6% (33/919) 6.5% (18/275)
Greek <sup>10</sup>	CYP2D6*2xN/UM	6.0% (17/283)
Hungarian <sup>11</sup>	UM (active duplicate genes)	1.9%
Northern European <sup>10, 12</sup>	UM (active duplicate genes)	1-2%

UM = ultra-rapid metabolizer; CYP2D6 = cytochrome P450 2D6

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#### Related Information

- Codeine Information<sup>1</sup>
- Is Post-Surgery Codeine a Risk for Kids?<sup>2</sup>
- FDA warns of risk of death from codeine use in some children following surgeries<sup>3</sup>
- FDA Drug Safety Podcast: Codeine use in certain children after tonsillectomy and/or adenoidectomy may lead to rare, but life-threatening adverse events or death<sup>4</sup>

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