

# AMERICAN ACADEMY OF PEDIATRICS

Committee on Drugs

## Use of Codeine- and Dextromethorphan-Containing Cough Remedies in Children

**ABSTRACT.** Numerous prescription and nonprescription medications are currently available for suppression of cough, a common symptom in children. Because adverse effects and overdosage associated with the administration of cough and cold preparations in children have been reported, education of patients and parents about the lack of proven antitussive effects and the potential risks of these products is needed.

### INDICATIONS AND CONTRAINDICATIONS

Cough is a reflex response to mechanical, chemical, or inflammatory irritation of the tracheobronchial tree mediated by sensory neurons in the airways reflexly through neurons in the brainstem. Cough serves as a physiologic function to clear airways of obstructive or irritating material or to warn of noxious substances in inspired air.<sup>1</sup>

In some pathologic states (eg, asthma, bronchopulmonary dysplasia, cystic fibrosis, and a variety of inflammatory conditions), excessive and/or abnormal airway secretions may be produced. The cough reflex serves to maintain airway patency by clearing these secretions. Clearing of pathologic tracheobronchial secretions is essential to patient management and may be enhanced by chest physiotherapy. Cough suppression may adversely affect patients with these conditions by promoting pooling of secretions, airway obstruction, secondary infection, and hypoxemia.

Many common respiratory conditions in which cough is prominent (eg, respiratory viral infections) are self-limited (lasting a few days). Cough may be an expression of airway reactivity or asthma. The cough that is associated with these conditions may be satisfactorily managed with fluids and increased ambient humidity (especially of value with croup). When cough is persistent, it is usually secondary to infection, allergy (including asthma), environmental irritants (eg, cigarette smoke, dust particles) or, occasionally, a foreign body. Therapy should be directed at the underlying condition for lasting benefit.

### ANTITUSSIVE AGENTS

Most cough suppressant preparations are marketed as mixtures of dextromethorphan or codeine with antihistamines, decongestants, expectorants, and/or antipyretics. Some nonprescription prepara-

tions substitute diphenhydramine or eucalyptus oil in place of codeine or dextromethorphan. Prescription medications may substitute other narcotic agents (hydrocodone or hydromorphone) for codeine and may be more addictive than codeine.<sup>2,3</sup> In addition, many of these cough products are elixirs, which may contain up to 25% alcohol by volume.<sup>3</sup>

The over-the-counter availability of numerous cough and cold preparations promotes the perception that such medications are safe and efficacious. Although codeine and dextromethorphan are efficacious for cough suppression in adults,<sup>1</sup> similar efficacy has not been demonstrated in children. Taylor et al<sup>4</sup> conducted a randomized, controlled trial of codeine, dextromethorphan, and placebo in children with acute nocturnal cough without evidence of chronic underlying lung disease (asthma, cystic fibrosis, or bronchopulmonary dysplasia). Neither dextromethorphan nor codeine in the dosages used was significantly more effective than placebo in reduction of acute cough. Studies using larger dosages have not been performed. Other studies focusing exclusively on children with cough have not been placebo-controlled trials.<sup>5-7</sup> To our knowledge, studies of the use of other purportedly antitussive agents in children, such as diphenhydramine, have not been reported in the literature.

Demonstration of the efficacy of antitussive preparations in children is lacking, and these medications may be potentially harmful.<sup>8</sup> Decongestant (sympathomimetic) components of these mixtures administered to children have been associated with irritability, restlessness, lethargy, hallucination, hypertension, and dystonic reactions.<sup>8</sup> The clearance and metabolism of the components of cough mixtures may vary with age<sup>9</sup> and disease state.<sup>10,11</sup> Great variability in the enterohepatic circulation of these drugs is noted in adults, which affects drug response, especially with repeated dosing.<sup>3</sup> The relative immaturity of hepatic enzyme systems that metabolize drugs in young children may enhance the risk of adverse effects of such medications, especially in infants younger than 6 months.<sup>9</sup> Metabolism and/or toxicity also may be altered by concurrent use of medications such as acetaminophen.<sup>12</sup> Unfortunately, the dosing guidelines for these agents are based on extrapolation from adult data without consideration of their potentially unique metabolism and disposition in children.

### Codeine

In adults, codeine and dextromethorphan have been shown to suppress both artificially induced and

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disease-related cough, mainly through central nervous system mechanisms.<sup>13</sup> A linear relationship has been shown to exist between a codeine dosage in the range of 7.5 to 60 mg/d and a decrease in the frequency of chronic cough.<sup>14</sup> Complete suppression of cough was not achieved in these trials, even at the highest daily dose of codeine.

#### *Dosage*

Pharmacokinetic studies of codeine therapy in children are lacking. The published dosage recommendation for codeine in children is 1 mg/kg/d in four divided doses, not to exceed 60 mg/d.<sup>12</sup> To our knowledge, no well-controlled studies have documented the safety and efficacy of this dosage.

#### *Adverse Reactions and Overdosage*

The principal clinical manifestations of codeine toxicity are respiratory depression and obtundation.<sup>14,15</sup> In children, antitussive dosages of 3 to 5 mg/kg/d have produced somnolence, ataxia, miosis, vomiting, rash, facial swelling, and pruritis. Respiratory depression requiring mechanical ventilation occurred in 3% of children receiving dosages greater than 5 mg/kg/d; two of these patients died.<sup>16</sup> Dosages of codeine less than 2 mg/kg are unlikely to be associated with significant adverse reactions. Reports of adverse reactions to codeine are based on single dose ingestions; the repetitive administration of codeine for therapeutic purposes may be associated with adverse symptoms at doses lower than a single dose of 5 mg/kg. In adults, glucuronide conjugation in the liver apparently inactivates codeine, but 10% of an oral dose is demethylated to form morphine, which is believed by some to be the active form of the drug.<sup>17</sup> The hepatic glucuronidation pathway is incompletely developed in infants, which places them at particular risk for adverse dose-related effects. Furthermore, alteration of hepatic enzyme pathways by illness or concurrent drug therapy (such as acetaminophen) may further alter metabolism of this drug and increase the risk of drug toxicity.<sup>10,11</sup>

Other narcotic antitussives that are available in cough preparations, such as hydrocodone and hydromorphone, have no demonstrated advantage as antitussive agents compared with codeine, have similar adverse effects, and have a greater risk of dependency.<sup>12</sup> Hydrocodone and hydromorphone are classified as Schedule III drugs under the Controlled Substances Act.

#### **Dextromethorphan**

The addictive potential of codeine encouraged the marketing of dextromethorphan in a variety of cough and cold preparations. Although dextromethorphan is chemically derived from the opiates, it has no analgesic or addictive properties. The cough suppression potency of dextromethorphan in adults is nearly equal to that of codeine.<sup>2</sup> The drug, like codeine, acts on the central nervous system to elevate the threshold for coughing.<sup>2</sup>

#### *Dosages*

Pharmacokinetic studies and demonstrations of the efficacy of cough suppression in children are lacking. Dosages of dextromethorphan of equal antitussive potency to codeine produce comparable levels of central nervous system depression in adults.<sup>15</sup> The recommended dosage in children is similar to that for codeine (ie, 1 mg/kg/d divided into 3 to 4 doses).<sup>3</sup>

#### *Adverse Reactions and Overdosage*

Acute overdosage of cough mixtures containing dextromethorphan has resulted in behavioral disturbances, including respiratory depression.<sup>8</sup>

### **CONCLUSIONS AND RECOMMENDATIONS**

1. No well-controlled scientific studies were found that support the efficacy and safety of narcotics (including codeine) or dextromethorphan as antitussives in children. Indications for their use in children have not been established.
2. Suppression of cough in many pulmonary airway diseases may be hazardous and contraindicated. Cough due to acute viral airway infections is short-lived and may be treated with fluids and humidity.
3. Dosage guidelines for cough and cold mixtures are extrapolated from adult data and clinical experience, and thus are imprecise for children. Adverse effects and overdosage associated with administration of cough and cold preparations in children are reported. Further research on dosage, safety, and efficacy of these preparations needs to be done in children.
4. Education of patients and parents about the lack of proven antitussive effects and the potential risks of these products is needed.

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### REFERENCES

1. Eddy NB, Friebel H, Hahn KJ, Halbach H. Codeine and its alternates for pain and cough relief. *Bull WHO*. 1969;40:425-454
2. Reisine T, Pasternak G. Opioid analgesics and antagonists. In: Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 9th ed. New York, NY: McGraw-Hill Co; 1996:521-555
3. *Drug Information for the Health Care Professional (USP DI)*. 16th ed. Rockville, MD: United States Pharmacopeial Convention, Inc; 1996;1: 1008-1104
4. Taylor JA, Novack AH, Almquist JR, Rogers JE. Efficacy of cough suppressants in children. *J Pediatr*. 1993;122:799-802
5. Jaffe G, Grimshaw JJ. Randomized single-blind trial in general practice comparing the efficacy and palatability of two cough linctus preparations, "Pholcolix" and "Actifed" compound, in children with acute cough. *Curr Med Res Opin*. 1983;8:594-599
6. Weippl G. Therapeutic approaches to the common cold in children. *Clin Ther*. 1984;6:475-482
7. Smith MBH, Feldman W. Over-the-counter cold medications. A critical review of clinical trials between 1950 and 1991. *JAMA*. 1993;269: 2258-2263
8. Gadowski A, Horton L. The need for rational therapeutics in the use of cough and cold medicine in infants. *Pediatrics*. 1992;89:774-776
9. Kearns GL, Reed MD. Clinical pharmacokinetics in infants and children. A reappraisal. *Clin Pharmacokinet*. 1989;17(suppl 1):29-67
10. Spielberg SP, Schulman JD. A possible reaction to pseudoephedrine in a patient with phenylketonuria. *J Pediatr*. 1977;90:1026
11. Larrey D, Babany G, Tinel M, et al. Effect of liver disease on dextromethorphan oxidation capacity and phenotype: a study in 107 patients. *Br J Clin Pharmacol*. 1989;28:297-304
12. Drugs used to treat upper respiratory tract disorders. In: *Drug Evaluations Annual: 1995*. Chicago, IL: American Medical Association; 1995: 493-525
13. Matthys H, Bleicher B, Bleicher U. Dextromethorphan and codeine: objective assessment of antitussive activity in patients with chronic cough. *J Int Med Res*. 1983;11:92-100
14. Sevelius H, McCoy JF, Colmore JP. Dose response to codeine in patients with chronic cough. *Clin Pharmacol Ther*. 1971;12:449-455
15. Bellville JW, See JC. A comparison of the respiratory depressant effects of dextropropoxyphene and codeine in man. *Clin Pharmacol Ther*. 1968; 9:428-434
16. von Mühlendahl KE, Scherf-Rahne B, Krienke EG, Baukloh G. Codeine intoxication in childhood. *Lancet*. 1976;2:303-305
17. Huffman DH, Ferguson RL. Acute codeine overdose: correspondence between clinical course and codeine metabolism. *Johns Hopkins Med J*. 1975;136:183-186

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