Efficacy of cough suppressants in children

James A. Taylor, MD, Alvin H. Novack, MD, Jan R. Almquist, MD, and James E. Rogers, MD
From the Department of Pediatrics, University of Washington, Seattle

To test the hypothesis that codeine and dextromethorphan are effective in alleviating the symptoms of acute cough, we conducted a randomized, controlled trial. Eligible patients were children 18 months to 12 years of age, seen in private pediatric practices, with significant night cough of less than 14 days’ duration. Study patients were randomly selected to receive codeine, dextromethorphan, or placebo at bedtime for 3 consecutive nights. Outcomes were assessed by the use of a parent questionnaire rating the severity of symptoms at the initiation of therapy, and after each night of the study. Every patient had a cough score (range 0 to 4) and composite symptom score (range 0 to 9) computed for each day of the study. One hundred forty-one doses of study medication were evaluated in 49 patients, including 13 children receiving placebo, 19 dextromethorphan, and 17 codeine. Mean cough and composite symptom scores decreased in each of the three treatment groups on each day of the study; there were no significant differences. Regression analysis, with reduction in cough score as the outcome of interest, showed that neither dextromethorphan nor codeine was significantly more effective than placebo (p = 0.41 and 0.70, respectively). Reduction in cough score was positively correlated with the severity of cough at the start of treatment (p = 0.007). Our data suggest that, in the doses used, neither codeine nor dextromethorphan is superior to placebo in treating night cough in children. (J PEDIATR 1993;122:799-802)

A 1980 survey of pediatricians in the United States revealed that “expectorants and cough preparations” were prescribed during 6.8% of all office visits. Medications to control cough were the fourth most often recommended class of drug, behind only antibiotics, antihistamines, and immunizations.1 In 1978 the American Academy of Pediatrics Committee on Drugs stated that children who were losing significant amounts of sleep because of coughing were candidates for cough suppressant therapy.2 Despite this ubiquitous usage and Academy validation, both theoretic and actual problems with cough suppressants exist. Coughing is a physiologic response to respiratory illness; some pediatricians believe that by suppressing cough a child may be placed at risk for pneumonia.3 Additionally, codeine and dextromethorphan, the two most commonly used antitussive agents, have potential for misuse.4-9

Despite widespread use of cough suppressants, there are few data on efficacy. In one of the few comparative trials, a study of codeine, DM, and placebo in 16 adults with chronic cough revealed that both active medications were superior to placebo.10 The applicability of these data to pediatric patients is unclear. Studies focusing exclusively on children with cough have not been placebo-controlled trials.11,12

We postulated that DM and codeine are significantly better than placebo in alleviating the symptoms of night cough in children. To test our hypothesis, a placebo-controlled, double-blind study was conducted.
METHODS

During the winter months of 1988 through 1991, children with night cough were recruited from private pediatric practices, mostly from one practice in Federal Way, Wash. Eligible patients were 18 months to 12 years of age and had significant night cough of less than 14 days' duration. Children were excluded if they had a history of underlying lung disease (asthma, cystic fibrosis, bronchopulmonary dysplasia), if the cause of their current cough was reactive airway disease, or if other medications such as antibiotics or bronchodilators were necessary during the study period. Parents of potentially eligible patients who expressed an interest in the study were asked to complete an intake questionnaire. The parent was asked to rate the frequency of their child's cough on the night before the visit to the pediatrician. Only those patients whose cough was rated as "often—one prolonged coughing episode or about 10 to 20 coughs during the night or both" or "very often—more than one prolonged coughing episode or more than 20 coughs during the night or both" were eligible for the study. The parent was also questioned about loss of sleep because of coughing (possible responses ranging from "slept all night peacefully," to "slept almost none") and about whether the child had posttussive emesis.

Children enrolled in the study were randomly selected to receive guaifenesin, 100 mg/5 ml, and DM, 15 mg/5 ml (DM); guaifenesin, 100 mg/5 ml, and codeine, 10 mg/5 ml (codeine); or placebo (cherry syrup). All study medications were identical in appearance; a minute amount of quinine was added to the placebo to impart a medicinal taste. Both parents and pediatricians were unaware of treatment assignments throughout the study period. Parents were instructed to give the medication at bedtime for 3 consecutive nights. Patients 18 months through 5 years of age received 2.5 ml of medication each night; participants 6 to 12 years of age received 5 ml nightly. On the following morning, parents rated the amount of coughing and the loss of sleep because of coughing, and noted any posttussive emesis in their child during the previous night, on a form identical to the intake questionnaire. After the last day of the study, parents noted any side effects in their child.

To evaluate the data, we transformed responses on the study questionnaires to an ordinal scale. Thus each patient had a cough score (0 = none to 4 = very often) computed for each day of the study, including the day before the visit to the pediatrician (day 0). Additionally a composite symptom score was calculated for each day by adding the cough score, loss of sleep score, and posttussive emesis score (range for composite symptom score: 0 to 9). The results were analyzed by two different methods. Reduction in cough and composite symptom scores among patients in different treatment groups were compared by using Mann-Whitney tests. Overall reduction in cough score was evaluated with generalized estimation equation techniques, a form of regression analysis that takes into account the correlated nature of multiple observations on the same individual. This technique also allows for analysis of other factors that might affect improvement in cough symptoms, including severity of symptoms at the initiation of therapy, age of the patient, and natural resolution of symptoms during the 3 days of study. For all analyses, differences were considered significant when the p value was <0.05.

The study was approved by the University of Washington Human Subjects Committee.

RESULTS

During the course of the study, 57 patients were enrolled. Two patients were disqualified because they inadvertently received an insufficient dose of study medication, and questionnaires were never completed by the families of six children. Thus data were available on 49 study patients. The mean age of these children was 4.7 ± 2.3 years; 27 were female and 47 were white. Upper respiratory tract infection was listed as the cause of the cough in 31 of 40 patients in whom a diagnosis was recorded; other diagnoses included "viral bronchitis" in 3 children, "flu" syndrome in 2, croup in 1, and cough (unspecified) in 3.

As a result of the randomization process, 13 children received placebo, 19 DM, and 17 codeine. Characteristics of patients in each treatment group at the beginning of therapy are presented in Table I; there were no significant differences for any variable. Overall, 141 doses of study medication were evaluated, including 39 doses of placebo, 57 DM, and 45 codeine.

Cough and composite symptom scores improved in each group on each day of the study, with no significant difference between placebo and either DM or codeine on any day (Table II). When regression analysis was performed, neither codeine nor DM was significantly better than placebo in reducing cough (p = 0.70 and 0.41, respectively). Reduction in cough was related to severity of cough at the initiation of therapy (p = 0.007); the most marked decrease in cough score occurred in children with the most severe cough at the start of the study. Regardless of treatment group, the cough score decreased significantly on day 3 of the study (coefficient = 0.87; p <0.0002).

Side effects were reported by parents of 18 patients, including 7 of 13 children in the placebo group, 6 of 19 receiving DM, and 5 of 17 codeine recipients. Drowsiness was reported by the parents of 3 children receiving placebo and 3 DM recipients. Diarrhea occurred in 3 patients in the placebo group and 1 each in the codeine and DM groups. "Hyperactive" behavior was reported in 2 children receiving DM and 3 codeine recipients. One patient, a 4-year-
old-boy in the codeine group, had radiographic evidence of pneumonia 2 days after completing the study. At the initial physician visit, the diagnosis was upper respiratory tract infection.

Given the number of doses of study medications evaluated, and after adjustment for the correlated nature of the data, the difference in mean decrease in cough score between placebo and either DM or codeine detectable with regression analysis (alpha level = 0.05; power = 0.8) was approximately 0.9 point.

**DISCUSSION**

Our data suggest that neither codeine nor DM is superior to placebo in alleviating the symptoms of acute night cough in children. The two medications and placebo were virtually identical in efficacy regardless of the outcome measure employed.

By using regression analysis techniques, we were able to evaluate the relative effects of several factors that contribute to reduction in cough. In our analyses, only the severity of symptoms at the start of therapy and the inherent decrease in symptoms on day 3 of the study were significantly correlated with a reduction in cough or composite symptom score. It may seem intuitively obvious that reduction in coughing is a function of both time and the severity of symptoms, but these findings indicate the reason that clinicians and patients believe cough suppressants to be effective. The results of our study demonstrate that by 3 days after a visit to a pediatrician because of cough symptoms, the cough will be significantly reduced regardless of specific therapy. This reduction is most noticeable in children whose coughing symptoms are the most severe at the start of treatment. Thus, if a child receives DM or codeine, his or her cough would be expected to be reduced during the course of treatment. Unfortunately the findings of this study indicate that specific cough suppressants contribute little to the reduction in coughing or related symptoms.

Although the number of children in each treatment group was modest, multiple measurements for each patient and adjustment for the correlated nature of these observations gave this study a power of 0.8 to detect a decrease in the cough score of 0.9 point as a result of either DM or codeine therapy. This point of 0.9 is roughly equivalent to the reduction noted in cough score on day 3 of the study. Thus we had an 80% chance of detecting a cough reduction caused by either cough suppressant that was at least as great as the reduction resulting from the natural resolution of cough symptoms with time. It is possible that smaller but statistically significant differences in the reduction of cough scores among codeine, DM, and placebo exist but were not detected because of the size of this study. Such slight reduction in symptoms as a result of cough suppressant therapy would be of questionable clinical significance.

A potential problem with evaluating treatment of symp-
toms is the appropriateness of the outcome measures. Cough is somewhat simpler to study than other symptoms (e.g., rhinorrhea, nausea) because it is easier to quantify. We designed our questionnaire to be reproducible by describing the amount of coughing quantitatively. We also measured alleviation of symptoms, rather than grading improvement for a longer period, so that our data would better correspond to the function of cough suppressants (i.e., to provide short-term relief, rather than shortening the disease process itself). It is possible that the doses of codeine and DM were inadequate. The doses of medication used in this study were based on recommendations published in a text on drug therapy. However, larger doses of the active drugs might have resulted in more significant reductions in cough symptoms.

Cough may be the predominant symptom of illnesses such as pneumonia, asthma, and sinusitis, for which specific therapy is available. We excluded children with a history of asthma, those in whom the cough had persisted for more than 14 days, and patients receiving other medications such as antibiotics or bronchodilators. However, it is conceivable that patients with acute night cough as the only sign of reactive airway disease might have been inadvertently included in the study. Similarly the one patient who had pneumonia after completing the study may have had an undiagnosed lower respiratory tract infection at the time of enrollment.

The results of this study suggest a need to reevaluate the indications for cough suppressants in children. It is estimated that in 1990 $26 million was expended on cough suppressants for use in pediatric patients (data from the National Prescription Audit and National Disease and Therapeutic Index, 1990, IMS International, Plymouth Meeting, Pa.). A substantial cost savings could be realized by decreased use of these drugs. Further, unless and until data become available that demonstrate the effectiveness of these medications, it may be inadvisable to expose a child to the rare but recognized adverse outcomes associated with cough suppressant use.

REFERENCES