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TREATMENT OPTIONS FOR ACUTE COUGH

James Terrell, Pharm.D. Candidate

Cough is the most common reason patients seek medical attention in the United States.[1] Since coughing may be provoked by a number of conditions such as allergies, the common cold, pneumonia, heart failure, or pulmonary embolism, proper diagnosis and treatment can be perplexing. Complicating the matter, many of the drugs available for cough, including the "gold standard" codeine, have failed to show efficacy in recent trials. This review will summarize the current data available for commonly used cough remedies and assess their appropriateness for treating acute cough.

Acute cough refers to any cough, regardless of etiology, that has persisted for less than 3 weeks. Chronic cough is defined as cough that lasts longer than 3 weeks. Current treatment guidelines for chronic cough differ from those of acute cough and will not be discussed in great detail.[1]

Before treating an acute cough, underlying chronic conditions, such as asthma and GERD, should be ruled out. Also, it is important to ensure that the patient does not have a upper respiratory tract infection, which may warrant antimicrobial therapy. This is especially true due to the recent increase in adult pertussis (whooping cough) throughout the U.S. Finally, the clinician should differentiate productive from non-productive cough. Cough suppressants should be avoided in the former.[2]

Epidemiology/Etiology

In 2005, a two-year prospective study evaluating 136 children (<18 years old, mean 2.7) with cough, defined as lasting 1-6 weeks, revealed that in 67% of the cases, an infectious agent was present. The results of this study (Table 1), indicate that 58% of cough-associated respiratory infections are caused by viruses.[3] However, the small sample size limits the reliability of these findings. In 2001, the World Health Organization (WHO) reported that rhinovirus is responsible for over 50% of colds in adults and that cough symptoms abate in 7-9 days.[4]

Data on frequency and prevalence of cough is difficult to interpret since many cases go untreated and/or are not reported. In 1985, it was estimated that over 2 billion dollars were spent on over the counter (OTC) cough and cold remedies.[4]

Physiology of cough

Coughing is a natural defense mechanism that can be mechanically (increased mucus or bronchoconstriction) or chemically induced (capsaicin, histamine, bradykinin, etc). Activation of either of these pathways sends signals to the nucleus tractus solitarius (NTS) which activates the cough reflex via efferent nerve fibers. The cortex can inhibit the NTS allowing some voluntary control. A local pulmonary

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Table 1. Common etiologies of acute cough[*3]

	Percentage (%)
Rhinovirus	32
B. pertussis	17
RSV	11
Rhinovirus + *B. pertussis*	10

* 136 screened specimens. One or more pathogens were found in 91 (67%) children

axon reflex can produce a cough when fibers innervating the lung release neurokinins, activating adjacent cough receptors.[5]

Treatment

In the United States there are over 1000 products marketed to treat cough.[6] The FDA has approved the following 6 agents for treatment of cough: dextromethorphan (DM), hydrocodone, codeine, dihydrocodeine, hydromorphone, and carbetapentane. Other drugs used to treat cough include histamine 1 (H1) receptor antagonists and benzonatate.

Dextromethorphan

DM is hypothesized to inhibit cough by binding to sigma-1 type receptors in the NTS and periphery. Some have suggested that it may also work on NMDA receptors.[5] Both mechanisms are theorized to suppress the cough reflex without a narcotic effect seen with opioid receptor stimulation. Dosing for DM is depicted in Table 2. Important pharmacokinetic parameters of DM are listed in Table 3.

Opioids

Opioids cause direct cough inhibition by binding to *mu* receptors in the medulla. At concentrations needed to suppress cough, opioids can lead to dependency, nausea, and respiratory depression. Of the available opioids, codeine has the lowest incidence of adverse effects and is considered the 'gold standard' for cough suppression.

Codeine is usually given orally in a suspension with an onset of action of less than an hour. The recommended doses are listed in Table 2. Relevant pharmacokinetic parameters for codeine are provided in Table 3.

Dose adjustments are recommended for patients with hepatic impairment or a creatinine clearance less than 50 ml/min. Side effects include drowsiness, constipation, and itching.

DM and codeine

Centrally acting antitussives, such as codeine and dextromethorphan, are proven to be an effective cough suppressant in animal models.[7] It is widely accepted that codeine and DM are effective cough suppressants. However, recent data in humans have shown codeine and DM to be ineffective at suppressing cough.[8-10] These newer studies tend to have larger populations and selectively recruited patients with upper airway disease, the major cause of acute cough.

It's been hypothesized that cough originating in the larynx (i.e. upper airway pathology) use neural pathways that are less sensitive to codeine and DM, whereas cough originating in the tracheobronchial tree responds well to these drugs.[7] Furthermore, cough associated with upper airway disease are actually "expiration reflexes". Expiration reflexes are specific to the larynx and are not true coughs in that they are not preceded by a large inhalation. These two hypotheses, which have been demonstrated in animal models, tend to explain why older human trials involving patients with lower airway disease concluded that codeine and DM were effective cough suppressants.

Human studies often utilize a nebulized chemical, like capsaicin or citric acid, to invoke a cough. Antitussive efficacy is then determined by administering the drug, rechallenging with the cough stimulant, and measuring the change in cough frequency and/or intensity. Repeated challenges to citric acid produces less reaction with each exposure, suggesting that the body adapts to it.[11] This adaptation may cause a false change from baseline in cough frequency and intensity, leading investigators to conclude that the intervention is efficacious.

Manap et al[10] administered 30 mg of DM, 60 mg of DM, and placebo to their study group. Citric acid was given every minute for 5 minutes to generate a cough. This was performed every hour for 12 hours. Results indicated 60 mg of DM significantly reduced cough response compared to placebo and 30 mg DM was no different than placebo. This experiment was powered to detect a 10% change in cough frequency. It is unclear whether a 10% change in cough frequency translates into clinically significant improvement. It has been reported that a 20% change is the minimal threshold for clinical improvement.

Lee et al[9] studied 43 adults aged 18-60 (mean 22.9) with recent URTI (<3 weeks) to detect a 20%

Table 2. Recommended dosing scheme for centrally-acting antitussives

	Dose	Maximum daily dose
Dextromethorphan		
1-3 months old	0.5-1.0 mg every 6-8 hours	NA
3-6 months old	1-2 mg every 6-8 hours	NA
7-12 months old	2-4 mg every 6-8 hours	NA
2-6 years old	2.5-7.5 mg every 4-8 hours (syrup)	30 mg
6-12 years old	5-10 mg every 4 hours or 15 mg every 6-8 hours	60 mg
> 12 years old	10-20 mg every 4 hours or 30 mg every 6-8 hours or 60 mg every 12 hours	120 mg
Codeine*		
< 2 years old	Not recommended	NA
2-6 years old	2-5 mg every 4-6 hours as needed	30 mg
6-12 years old	5-10 mg every 4-6 hours as needed	60 mg
> 12 years old	10-20 mg every 4-6 hours as needed	120 mg

* Maximum of 1.5mg/kg/day; NA = information not available

change from baseline. Patients were given either 30 mg DM or placebo. They found no significant difference between the effects of placebo or DM on either 1) cough frequency, expressed as number of coughs per 10 minutes 2) cough intensity, measured by decibel force, or 3) subjective assessment. A major advantage of this study is that disease-induced cough was chosen over chemically stimulated cough. Unfortunately, the study was underpowered to detect a 20% difference between groups due to attrition.

Lee's study was designed very similar to an earlier experiment that challenged the usefulness of codiene in patients with a recent URTI.[8] Patients were given 50 mg of codeine or placebo and their cough was assessed. No difference was found between the two groups using 1) frequency 2) intensity or 3) subjective assessment.

Trials that found no difference between antitussives and placebo did, however, detect a downward trend in cough symptoms suggesting a placebo effect. The placebo effect can be explained by the patient's cortical control over the cough reflex. A study by Hutchings et al[9] showed that patients asked to suppress their cough reflex, whether chemically induced or disease related (URTI), can almost completely eliminate it. In acute cough due to upper airway disease, the centrally acting antitussives codeine and dextromethorphan provide very little in terms of cough suppression and that any benefit is due to increased reflex inhibition imparted by cortical control.

Contrary to the findings in these trials, a recent meta-analysis of cough regimens suggested that DM is beneficial in acute cough, since two of the three studies indicated significant findings.[1] These conflicting results underscore the need for newer, sufficiently powered, randomized control trials that utilize cohorts accurately representing the patient population.

H1 antagonists

H1 antagonists like diphenhydramine and chlorpheniramine exert their effects peripherally by preventing mast-cell degranulation and decreasing vascular permeability and bronchoconstriction. By decreasing the vascular permeability, less mucus escapes into the airway; thus, decreasing the frequency of mechanically induced cough. This "drying effect" is also beneficial in patients with post-nasal drip syndrome, the leading cause of chronic cough. These drugs also exhibit anticholinergic and sedative side effects.

Currently, there are little available data sup-

Table 3. Pharmacokinetic parameters for centrally-acting antitussives

	Dextromethorphan	Codeine
Onset of action	15-30 minutes	30-60 minutes
Duration of action	< 6 hours	<6 hours
Metabolism	Hepatic to dextrorphan*	Hepatic to morphine*
Elimination	Urine – some unchanged	Urine – 3-16% unchanged
Renal adjustments	None	CrCl 10-50 ml/min: 75% of normal dose CrCl <10 ml/min: 50% of normal dose

* Active metabolites

porting the use of an antihistamine as monotherapy to treat acute cough. The current guidelines suggest using a first generation antihistamine combined with a decongestant for cough due to the common cold.[13] Studies have confirmed that only a combination with a decongestant, like pseudoephedrine, reduces cough frequency.[14] Non-sedating antihistamines have failed to show a similar benefit.[15]

Benzonatate

Benzonatate (Tessalon Perles®) is a chemical analog of tetracaine, a local anesthetic. Benzonatate exerts its action by suppressing nerve firing of stretch receptors in the lung endothelium to the NTS. Its onset of action is less than 30 minutes and duration of action may be as long as 8 hours.

The side-effect profile is more extensive than the other available options and includes: sedation, headache, nausea, vomiting, chest numbness, ocular irritation, and nasal congestion. Benzonatate is not FDA approved for cough and the only evidence of its efficacy comes from case reports on opioid-resistant patients with terminal cancer.[16]

Conclusion

At this point, there is little data to support treating acute cough. Patients suspected of having the common cold could be given an antihistamine/ decongestant combination. Patients with a non-productive acute cough of unconfirmed etiology may be offered dextromethorphan or codeine with the understanding that any benefit may be marginal. The side effect profile of codeine may make it less desirable. In addition, many states have enacted laws requiring prescriptions for codeine-containing products, making it more difficult for patients to obtain them. In most cases, dextromethorphan-containing products are a safe option to recommend for these patients. For non-productive cough not due to upper airway infections, codeine and dextromethorphan remain first line agents and should be offered.

References

1. Diagnosis and management of cough: ACCP evidence based clinical practice guidelines. Chest 2006. Available online: http://www.chestjournal.org/content/vol129/1_suppl/. Accessed March 7, 2006.
2. de Jongste JC, Shields MD. Cough 2: Chronic cough in children. Thorax 2003;58:998-1003.
3. Versteegh FG, et al. Community-acquired pathogens associated with prolonged coughing in children: a prospective cohort study. Clinical Microbiology and Infection 2005;11:801-7.
4. WHO. Cough and cold remedies for the treatment of acute respiratory infections in young children. Geneva, World Health Organization 2001.
5. Reynolds SM, Mackenzie AJ, Spina D and Page CP. The pharmacology of cough. TRENDS in Pharmacological Science 2004;25:569-576.
6. Clinical Pharmacology. Available online. http://cpip.gsm.com. Accessed March 18, 2006.
7. Bolser, Donald C. Current and future centrally acting antitussives. Resp Phys & Neurobiology 2006. Available online: www.sciencedirect.com. Accessed March 15, 2006.
8. Freestone C, Eccles R. Assessment of the antitussive efficacy of codeine in cough associated with common cold. J Pharm Pharmacol 1997; 49:1045-9.
9. Lee PCL, Jawad MSM, Eccles R. Antitussive

Efficacy of Dextromethorphan in Cough Associated with Acute Upper Respiratory Tract Infection. J Pharm Pharmacol 2000;52:1137-42.
10. Manap RA, Wright CE, Gregory A, et al. The antitussive effect of dextromethorphan in relation to CYP2D6 activity. Br J Clin Pharmacol 1999;48:382-7.
11. Rostami-Hodjegan A, Abdul-Manap R, Wright CE, et al. The placebo response to citric acid-induced cough: pharmacodynamics and gender differences. Pulmonary Pharmacology & Therapeutics 2001;14:315-9.
12. Hutchings HA, Eccles R, Smith AP, Jawad M. Voluntary cough suppression as an indication of symptom severity in upper respiratory tract infections. Eur Respir J 1993;6:1449-54.
13. Pratter MR, Brightling, CE, Boulet LP, Irwin RS. An empiric integrative approach to the management of cough: ACCP evidence based clinical practice guidelines. Chest 2006; 29:222S-231S.
14. Arroll B. Non-antibiotic treatments for upper-respiratory tract infections (common cold). Resp Med 2005;99:1477-84.
15. Dicpinigaitis PV, Gayle YE. Effect of the second-generation antihistamine, fexofenadine, on cough reflex sensitivity and pulmonary function. Br J Clin Pharmacol 2003;56:501-4
16. Doona M, Walsh D. Benzonatate for opioid-resistant cough in advanced cancer. Palliative Medicine 1997;12:55-8.

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