Inhibition of cough-reflex sensitivity by benzonatate and guaifenesin in acute viral cough

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Received 8 September 2008; accepted 9 December 2008
Available online 1 January 2009

Summary
Acute cough due to viral upper respiratory tract infection (URI) is the most common form of cough and accounts for tremendous expenditure on prescription and non-prescription cough products worldwide. However, few agents have been shown in properly conducted clinical trials to be effective for cough due to URI. The present study evaluated the effect of benzonatate 200 mg (B), guaifenesin 600 mg (G), their combination (B + G), and placebo (P) on capsaicin-induced cough in 30 adult nonsmokers with acute URI. On 3 separate days within a 7-day period, 1 h after ingesting randomly assigned study drug in a double-blind fashion, subjects underwent capsaicin cough challenge testing, which involved inhalation of incremental doubling concentrations of capsaicin until the concentration of capsaicin inducing 5 or more coughs (C5) was attained. Each subject received 3 of 4 possible study drugs. G (p = 0.01) but not B (p = NS) inhibited cough-reflex sensitivity (log C5) relative to P. The combination of B + G suppressed capsaicin-induced cough to a greater degree than B alone (p < 0.001) or G alone (p = 0.008). The mechanism by which the combination of B + G causes a potentiation of antitussive effect remains to be elucidated. Our results suggest that B + G may be an effective therapy for acute cough due to the common cold (URI).

Introduction
Cough is the most common complaint for which patients in the United States seek medical attention. Acute cough due to viral upper respiratory tract infection (URI) is the most common form of cough and results in tremendous financial expenditure on prescription and non-prescription...
(over-the-counter) cough and cold products worldwide. However, few of the currently available antitussive agents have been shown, in properly conducted clinical trials, to be effective in suppressing cough due to URI.\textsuperscript{2,3} The narcotic opioids, such as codeine, have been demonstrated to be ineffective for acute cough associated with URI.\textsuperscript{4,5} If achieved, the antitussive effect of opioids often occurs at the expense of troubling or intolerable side effects, such as sedation or gastrointestinal disturbance.\textsuperscript{6}

Guaifenesin, the glyceryl ether of guaiacol (a constituent of guaiac resin from the wood of \textit{Guajacum officinale} Linné), is a component of numerous cough and cold products available worldwide. Guaifenesin is termed an expectorant since it is believed to alleviate cough discomfort by increasing sputum volume and decreasing its viscosity (hydration hypothesis), thereby promoting effective cough.\textsuperscript{7} Guaifenesin remains the only expectorant approved by the United States Food and Drug Administration (FDA).\textsuperscript{8} Despite its availability and common usage for decades, few studies have evaluated the antitussive effect of guaifenesin. A recently published trial demonstrated the ability of guaifenesin to inhibit cough-reflex sensitivity in subjects with acute URI, thus suggesting an antitussive as well as expectorant action for the drug.\textsuperscript{9}

Benzonatate, a long chain polyglycol derivative chemically related to procaine, is a peripherally-acting, oral anesthetic agent whose mechanism of cough suppression is believed to involve inhibition of pulmonary stretch receptors.\textsuperscript{10} Studies performed soon after its approval in the United States a half century ago showed benzonatate able to inhibit experimentally-induced cough as well as to suppress subjectively-measured pathological cough.\textsuperscript{11} No further clinical trials of benzonatate have been published in decades.

Given the urgent need for better cough suppressant therapy, the goal of the present study was to evaluate, in a prospective, randomized, double-blind, placebo-controlled manner, the antitussive effect of the combination of benzonatate and guaifenesin in subjects with acute URI. Cough-reflex sensitivity was measured by capsaicin cough-reflex sensitivity in subjects with acute URI, thus suggesting an antitussive as well as expectorant action for the drug.\textsuperscript{9}

**Methods**

**Subjects**

Subjects were otherwise healthy adult nonsmokers (lifet ime nonsmokers or ex-smokers having abstained from smoking \(\geq 5\) years) who developed symptoms consistent with acute viral URI within 72 h of study enrollment. Suggestive symptoms included acute onset of cough, fever, myalgias, rhinitis, nasal congestion, and sneezing. Symptoms suggestive of a possible bacterial infection, such as sinus pain and purulent nasal discharge, excluded a subject from enrollment. Other exclusion criteria included: history of asthma or other pulmonary disease; use of medications potentially affecting cough-reflex sensitivity (i.e., opiates and angiotensin converting-enzyme (ACE) inhibitors); and ingestion of the following types of medications within the following time periods prior to study entry: short-acting antihistamines (48 h); short-acting pseudoephedrine (12 h); long-acting pseudoephedrine (24 h); non-steroid nasal sprays (12 h); cough suppressants and expectorants (24 h). Female subjects were required to be using adequate contraception.

**Study design**

This was a randomized, double-blind, placebo-controlled study of crossover design whose aim was to evaluate the effect of a combination of benzonatate and guaifenesin, relative to each individual drug and placebo, on cough-reflex sensitivity to inhaled capsaicin in 30 otherwise healthy volunteers with acute viral URI. Upon enrollment, subjects were randomized to receive 3 of 4 possible study drug combinations, one on each of 3 successive visits occurring on 3 separate days within a 7-day period. The 4 possible study drug combinations included: benzonatate 200 mg (Inwood Laboratories, Commack, NY); guaifenesin 600 mg (BI Chemicals, Petersburg, VA); benzonatate 200 mg + guaifenesin 600 mg; and placebo, all prepared as identically-appearing capsules. Subjects underwent capsaicin cough challenge testing, to measure cough-reflex sensitivity, 1 h after ingestion of study drug, administered in a double-blind manner, on each of the 3 visits. The 1-h pre-test interval was chosen to coincide with high plasma levels of each study drug. The dosages of study drugs were chosen to concur with current FDA-approved standards. The FDA regulates the use of capsaicin in clinical trials and required that no more than 3 successive doses (challenges) be administered to a single subject in this study. Therefore, the 4 study treatments were investigated with a \((4,3,N)\) balanced incomplete block design, in which each subject received 3 of the 4 treatments according to a pre-determined randomization scheme, over the course of 3 study visits. This study was approved by the Institutional Review Board of Montefiore Medical Center, Bronx, New York. All subjects provided written, informed consent.

**Capsaicin cough challenge testing**

Capsaicin was prepared and administered as previously described.\textsuperscript{12} Briefly, a stock solution (0.01 M) of capsaicin (Formosa Laboratories, Taiwan, ROC) was prepared and subsequently diluted with physiological saline to yield serial doubling concentrations ranging from 0.49 \(\mu\)M to 1000 \(\mu\)M. Fresh dilutions were prepared on each day of testing.

Subjects inhaled single, vital-capacity breaths of capsaicin aerosol administered via nebulizer (model 646; DeVilbiss Health Care Inc., Somerset, PA) controlled by a dosimeter (KoKo DigiDoser; nSpire Health Inc., Louisville,
CO). The nebulizer used in this study was modified in two ways. First, an inspiratory flow regulator valve (RIFR; nSpire Health Inc.) was added, which limited inspiratory flow to 0.5 L/s regardless of excessive inspiratory force, thereby guaranteeing a constant and reproducible inspiratory effort with each breath. Second, the straw and baffle assembly of the nebulizer was welded in place, thereby eliminating the variations in nebulizer output that occur when these components are detached for washing and then reattached, with resulting variable distances between the jet orifice and straw. Given the nebulizer output of 1.007 mL/min, duration of aerosol delivery was programmed at 1.2 s to provide 0.02 mL aerosol per inhalation. Single breaths of capsaicin were given in ascending order, with inhalations of saline randomly interspersed to increase challenge blindness, until the concentration inducing 5 or more coughs (C5) was attained. Inhalations were delivered at 1-min intervals. Subjects were unaware that the end point of the study was the number of coughs induced.

**Statistical analysis**

A (4,3,N) balanced incomplete block design was used, in which each subject received 3 of the 4 possible treatments according to a predetermined randomization scheme, over the course of 3 study visits. Subjects were assigned to one of 16 possible sequences of 3 of the 4 treatments, with the following constraints: each of the 4 treatments was to be received by the same number of subjects at any visit and each of the 16 sequences was to appear 2 or 3 times in the subject cohort.

Based on the observed variability in capsaicin cough challenge data previously reported by the authors, 9 sample size estimates based on 80% power and 5% level of significance in a crossover design yielded \( n = 16 \) to detect a 40% mean difference in log C5 before and after treatment. The proposed sample size of 30 subjects in a (4,3,N) balanced incomplete block design as described above provided approximately 20–24 observations per treatment. This level of statistical power was deemed acceptable for this initial exploratory study.

Log C5 and log C2 were analyzed using the analysis of variance model commonly applied to crossover designs, with fixed terms for sequence, subject within sequence, period, and treatment. Treatments were compared pairwise using Fisher’s Least Significant differences.

**Results**

Thirty subjects (19 female, 11 male; mean age 42.2 ± 14.0 [SD]) were enrolled and completed all 3 required study visits. No significant adverse events were reported. Twenty-three subjects (77%) were lifetime nonsmokers; 7 subjects (23%) were distant ex-smokers (>5 years). The number of subjects receiving each of the four possible study drugs was: guaifenesin alone \(( n = 22)\); benzonatate alone \(( n = 23)\); guaifenesin + benzonatate \(( n = 23)\); placebo \(( n = 22)\).

Characterizing the effect of study drug on cough-reflex sensitivity (C5), mean log C5 was 0.43 with benzonatate alone, 0.49 with placebo, 0.55 with guaifenesin, and 0.70 with guaifenesin + benzonatate. The overall difference among the treatments was statistically significant \((p < 0.001)\). In the pairwise comparisons, the log concentration of the guaifenesin/benzonatate combination was statistically significantly higher than either guaifenesin alone \((p = 0.008)\) or benzonatate alone \((p < 0.001)\). The log concentration was statistically significantly higher than placebo with both the guaifenesin/benzonatate combination \((p < 0.001)\) and guaifenesin alone \((p = 0.010)\) [see Table 1].

Effects of study drugs on cough-reflex sensitivity in terms of C2 very closely mirrored, but were not identical to, C5. In terms of mean log C2, the overall difference among the treatments was statistically significant \((p = 0.007)\), as were the pairwise comparisons between guaifenesin and placebo \((p = 0.050)\); guaifenesin/benzonatate combination and placebo \((p = 0.008)\); and, guaifenesin/benzonatate combination and benzonatate alone \((p = 0.004)\). Mean log C2 data demonstrated an effect of guaifenesin alone compared to benzonatate alone \((p = 0.026)\) that was not evinced by log C5 data. However, mean log C2 values did not demonstrate a statistically significant difference between guaifenesin alone and guaifenesin/benzonatate combination therapy.

| Table 1 Effect of study drugs on cough-reflex sensitivity to inhaled capsaicin. |
|-----------------------------------|---------------------|---------------------|---------------------|---------------------|
|                                   | Guaifenesin \((n = 22)\) | Benzonatate \((n = 23)\) | Guaifenesin + benzonatate \((n = 23)\) | Placebo \((n = 22)\) |
| **log C5**<sup>a</sup>            | 0.545               | 0.430               | 0.704               | 0.491               |
| Mean                              | 0.389               | 0.502               | 0.467               | 0.399               |
| S.D.                              | 0.060               | 0.060               | 0.060               | 0.060               |
| Median                            |                     |                     |                     |                     |
| Range                             | −0.30–1.20          | −0.30–1.50          | −0.30–1.50          | −0.30–1.20          |
| p value vs. placebo               | 0.010               | 0.104               | <0.001              |                     |
| p value vs. Guaifenesin + benzonatate | 0.008               | <0.001              |                     |                     |
| p value vs. Placebo               |                     |                     |                     | 0.298               |

<sup>a</sup> The differences in log-transformed concentrations between treatments were analyzed using an analysis of variance with factors for sequence, subject within sequence, period, and treatment.

<sup>b</sup> C5 = concentration of capsaicin inducing 5 or more coughs.
Carryover effects were tested using the analysis of variance with terms for sequence, subject within sequence, carryover, and treatment. In the analysis of C4, the p value for the effect of carryover was 0.3739 and, in the analysis of C5, the p value was 0.4280. Thus, carryover effects were not statistically significant. A similar analysis was performed to test the effect of visit number (i.e., time) and was also found not to be significant.

Discussion

We have demonstrated the ability of guaifenesin, and the combination of guaifenesin and benzonatate, to inhibit cough-reflex sensitivity in subjects with acute URI, whose cough receptors are presumed to be transiently hypersensitive.15,16 While the inhibitory effect, if any, of benzonatate alone on the capsaicin-induced cough reflex did not achieve statistical significance in this study, guaifenesin alone produced significantly greater cough-reflex inhibition than placebo. In addition, the results of the study showed a statistically significant increase in cough-reflex suppression when guaifenesin and benzonatate were used in combination compared to either agent alone and to placebo. These data suggest that benzonatate acts to potentiate the antitussive efficacy of guaifenesin through a mechanism as yet unknown. The antitussive effect of guaifenesin using the capsaicin challenge model in subjects with acute URI has been observed in an earlier trial,9 but its potentiation by benzonatate has not been previously reported.

Acute viral cough is often difficult to treat. Indeed, two prospective placebo-controlled studies have shown the narcotic opioid codeine to be clinically ineffective in patients with acute cough due to URI.4,5 Recently published cough management guidelines by the American College of Chest Physicians (ACCP) did not recommend central cough suppressants for cough due to URI, and furthermore, did not recommend over-the-counter combination cold medications (with the exception of an older generation antihistamine-decongestant) for acute cough due to the common cold, until randomized, controlled trials demonstrate their efficacy.3

Cough-reflex sensitivity during acute viral URI appears difficult to suppress in the laboratory. The authors, using a PubMed search of the English language literature limited to human trials, were unable to find a single study demonstrating the ability of codeine or dextromethorphan, probably the two most commonly used antitussive agents, to inhibit capsaicin-induced cough in subjects with URI. The present study confirms the results of an earlier trial that showed a single, 400-mg dose of guaifenesin able to inhibit capsaicin-induced cough in subjects with the common cold.17 Thus, guaifenesin appears to have a dual mechanism of action: as an antitussive, as well as an expectorant, for which it is approved by the FDA. A recent study has also demonstrated the ability of the anticholinergic bronchodilator tiotropium to inhibit cough-reflex sensitivity to inhaled capsaicin in subjects with URI.17

Given the need for better cough suppressant therapies and the results of the present exploratory study, the combination of guaifenesin and benzonatate merits further evaluation in clinical trials to assess its effect in acute as well as other types of troublesome cough.

Conflict of interest statement

PVD received an unrestricted, investigator-initiated research grant to perform this work. PVD is currently serving as a consultant to Reckitt Benckiser on a project unrelated to the content of this manuscript. YEG has no conflicts related to this manuscript. GS is an employee of Reckitt Benckiser. RDG is a biostatistician whose company, TKL Research, Inc., is engaged on an as-needed basis by the study sponsor.

Role of funding source

This study was supported by an unrestricted, investigator-initiated grant from Reckitt Benckiser. The study sponsor had no role in study design; collection, analysis and interpretation of data; in the writing of the manuscript; or in the decision to submit the manuscript for publication.

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