Effect of Guaifenesin on Cough Reflex Sensitivity*

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Background: Guaifenesin, a commonly used agent for the treatment of cough, is termed an expectorant since it is believed to alleviate cough discomfort by increasing sputum volume and decreasing its viscosity, thereby promoting effective cough. Despite its common usage, relatively few studies, yielding contrasting results, have been performed to investigate the action and efficacy of guaifenesin.

Study objectives: To evaluate the effect of guaifenesin on cough reflex sensitivity.

Design: Randomized, double-blind, placebo-controlled trial.

Setting: Academic medical center.

Participants: Fourteen subjects with acute viral upper respiratory tract infection (URI) and 14 healthy volunteers.

Interventions: On 2 separate days, subjects underwent capsaicin cough challenge 1 to 2 h after receiving a single, 400-mg dose (capsules) of guaifenesin or matched placebo.

Measurements and results: The concentration of capsaicin inducing five or more coughs (C_5) was determined. Among subjects with URI, mean ($\pm$ SEM) log C_5 after guaifenesin and placebo were 0.92 ± 0.17 and 0.66 ± 0.14, respectively ($p = 0.028$). No effect on cough sensitivity was observed in healthy volunteers.

Conclusions: Our results demonstrate that guaifenesin inhibits cough reflex sensitivity in subjects with URI, whose cough receptors are transiently hypersensitive, but not in healthy volunteers. Possible mechanisms include a central antitussive effect, or a peripheral effect by increased sputum volume serving as a barrier shielding cough receptors within the respiratory epithelium from the tussive stimulus.   *(CHEST 2003; 124:2178–2181)*

Key words: capsaicin; common cold; cough; cough reflex; expectorant; guaifenesin; respiratory tract infection

Abbreviations: C_5 = concentration of capsaicin inducing five or more coughs; RAR = rapidly adapting pulmonary stretch receptor; URI = acute viral upper respiratory tract infection

Cough results from the stimulation of airway sensory receptors whose afferent impulses activate a brainstem cough center. The mechanism of cough production involves the rapidly adapting pulmonary stretch receptors (RARs) as well as pulmonary and bronchial C-fiber receptors. RARs appear to induce cough through a primary sensory pathway, whereas C-fibers, whose central pathways inhibit cough, may stimulate cough peripherally by releasing sensory neuropeptides that activate RARs.[1] The nature of the communication between these peripheral receptors and the CNS remains poorly understood.

Guaifenesin, the glyceryl ether of guaiacol (a constituent of guaiac resin from the wood of *Guajacum officinale* Linné), is a component of numerous cough and cold preparations available worldwide.[2] Guaifenesin is termed an expectorant since it is believed to alleviate cough discomfort by increasing sputum volume and decreasing its viscosity, thereby promoting effective cough. Indeed, guaifenesin is the only expectorant considered effective by the US Food and Drug Administration.[3] Interestingly, another established role for guaifenesin is as an anesthetic agent in veterinary medicine.[4] Despite the common usage of guaifenesin in the treatment of cough, previous studies have yielded contradictory results in terms of its efficacy as an expectorant[5,6] and antitussive,[5,7,8] as well as its ability to alter sputum characteristics[5,6,9,10] and mucociliary clearance.[11–13]

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Little attention has been paid to the effect of guaifenesin on the sensitivity of the cough reflex. Therefore, we performed the present study to evaluate the effect of a single dose of guaifenesin on cough reflex sensitivity to inhaled capsaicin in healthy subjects as well as in subjects with acute viral upper respiratory tract infection (URI). The tussive agent capsaicin has been shown, in humans, to induce cough in a reproducible and dose-dependent manner,[14] thereby rendering it an excellent tool for the evaluation of the effect of a pharmacologic intervention on the sensitivity of the cough reflex.

MATERIALS AND METHODS

Subjects

Fourteen healthy volunteers (5 men and 9 women; mean age $\pm$ SEM, 36.1 $\pm$ 1.2 years), as well as 14 otherwise healthy subjects with symptoms consistent with URI (4 men and 10 women; mean age, 30.8 $\pm$ 1.2 years) were recruited for the study, which was approved by the Institutional Review Board of Albert Einstein Hospital/Montefiore Medical Center. All participants were nonsmokers without a history of pulmonary disease, and without history or symptoms suggestive of gastroesophageal reflux. Healthy volunteers denied recent (within 4 weeks) symptoms of respiratory tract infection, seasonal allergies, or postnasal drip syndrome. No use of any medications known to affect the sensitivity of the cough reflex was reported by the healthy volunteers. Subjects with URI abstained from all medications for at least 24 h prior to study enrollment; nine subjects had received no medication at all for their illness. Symptoms reported by subjects with URI included (number of subjects with symptom): cough (n = 12), rhinorrhea (n = 11), nasal congestion (n = 11), sneezing (n = 10), sore throat (n = 8), hoarseness (n = 8), headache (n = 5), sinus pain/pressure (n = 4), myalgias (n = 3), fever (n = 2), and chills (n = 2). Among subjects with cough, seven subjects described an exclusively dry cough, and five subjects reported a predominantly dry cough with occasional production of scant amounts of nonpurulent, clear, or yellow secretions. Symptoms had been present for a mean of 3.3 $\pm$ 0.5 days (range, 1 to 7 days) prior to study enrollment. The authors used their clinical judgment in recruiting subjects who were very likely to be suffering from a viral, rather than bacterial, URI. Signs that suggested the presence of a bacterial infection, such as purulent sputum or purulent nasal discharge, excluded an individual from study participation.

Study Protocol

On enrollment, subjects received capsules containing 400 mg of guaifenesin (Wallace Laboratories; Cranbury, NJ) or matched placebo in a randomized, double-blind, cross-over fashion on 2 separate days. In subjects with URI, mean interval between studies was 1.6 $\pm$ 0.3 days (range, 1 to 4 days). In healthy volunteers, mean interval between studies was 2.4 $\pm$ 0.6 days (range, 1 to 7 days). At approximately the same time each day, spirometry and capsaicin cough challenge testing were performed 1 to 2 h after ingestion of study drug, to correlate with high blood levels of guaifenesin.[2]

Capsaicin Cough Challenge

Solutions of capsaicin were prepared and administered as previously described.[15] Briefly, subjects inhaled single breaths (from functional residual capacity to total lung capacity) of capsaicin aerosol from a compressed air-driven nebulizer (model 646; DeVilbiss Health Care; Somerset, PA) controlled by a dosimeter (KoKo DigiDoser; Pulmonary Data Service Instrumentation; Louisville, CO). The nebulizer used in these studies was modified by the addition of an inspiratory flow regulator valve (RIFR; Pulmonary Data Service Instrumentation) that limited the inspiratory flow rate to 0.5 L/s regardless of inspiratory force, thereby guaranteeing a consistent and reproducible amount of solution delivered with each breath. Single breaths of capsaicin aerosol were administered in ascending order, with inhalations of saline solution aerosol randomly interspersed to increase challenge blindness, until the concentration of capsaicin inducing five or more coughs (C_5) was reached. Breaths were delivered at 1-min intervals, and the number of coughs occurring in the initial 15 s after each inhalation of capsaicin was recorded. Subjects were unaware that the end point of the study was the number of coughs induced.

Data Analysis

Mean ($\pm$ SEM) values for log C_5 as well as spirometric data (FVC, FEV_1, and forced expiratory flow, midexpiratory phase) after guaifenesin and placebo were calculated and compared by a paired Student t test for dependent samples; $p < 0.05$ was considered significant.

RESULTS

The induction of five or more coughs was achieved in all participants. In subjects with URI, there were no significant differences in pulmonary function values (FVC, FEV_1, and forced expiratory flow, midexpiratory phase) after guaifenesin and placebo. In terms of cough sensitivity, mean log C_5 after guaifenesin was significantly higher than after placebo: 0.92 $\pm$ 0.17 and 0.66 $\pm$ 0.14, respectively (p = 0.028). Seven of 14 subjects demonstrated a two doubling-concentration increase in C_5 after guaifenesin compared to placebo (Fig 1).

In healthy volunteers, no differences were noted in pulmonary function values or cough reflex sensitivity between the two studies. Mean log C_5 after guaifenesin and placebo were 0.86 $\pm$ 0.14 and 0.92 $\pm$ 0.13, respectively (p = not significant). Furthermore, no healthy subject demonstrated a greater than one doubling-concentration difference in C_5 between studies (Fig 2). Although mean log C_5 in subjects with URI was lower than in healthy volunteers, this difference did not achieve statistical significance.

DISCUSSION

The present study has demonstrated that a single, 400-mg dose of guaifenesin inhibits cough reflex sensitivity to inhaled capsaicin in subjects with acute viral URI. In contrast, cough sensitivity was not
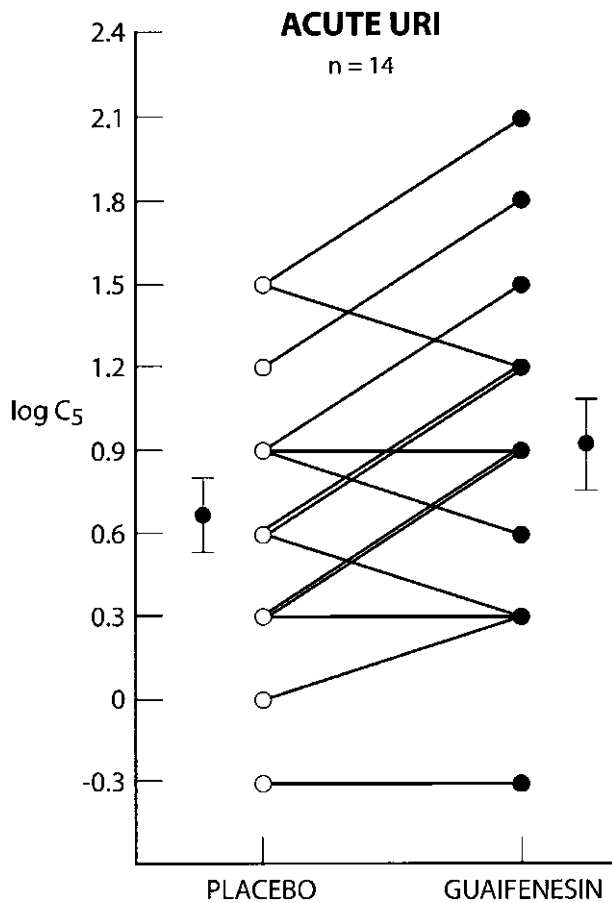
FIGURE 1. Effect of a single 400-mg dose of guaifenesin on cough reflex sensitivity to inhaled capsaicin compared to placebo in subjects with URI. Mean ($\pm$ SEM) log C_5 after guaifenesin and placebo: 0.92 ± 0.17 and 0.66 ± 0.14, respectively (p = 0.028). Error bars indicate $\pm$ SEM.
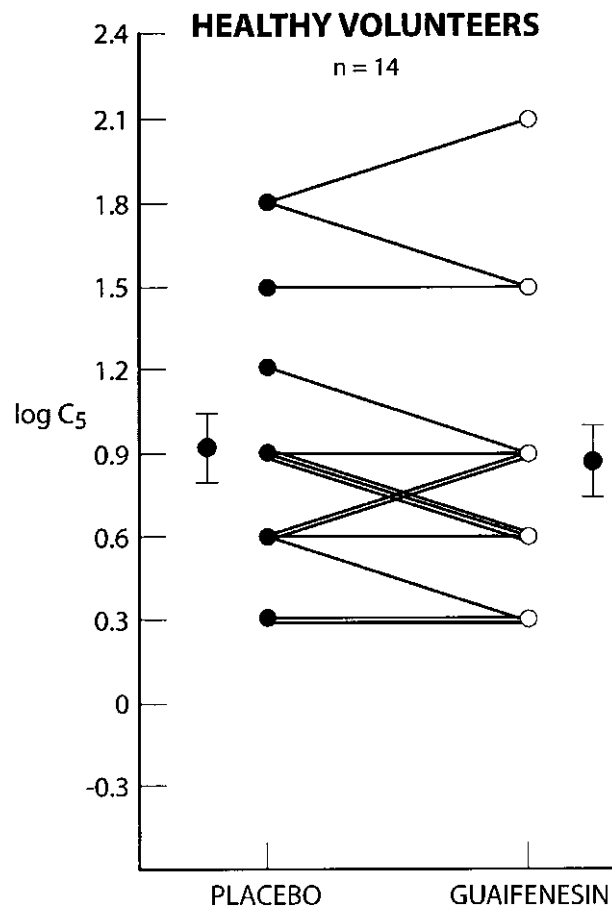

FIGURE 2. Effect of a single 400-mg dose of guaifenesin on cough reflex sensitivity to inhaled capsaicin compared to placebo in healthy volunteers. There was no significant difference in mean log C_5 between studies. Error bars indicate $\pm$ SEM.

altered by guaifenesin in healthy volunteers. Thus, the observed antitussive effect of guaifenesin appears limited to subjects in whom cough receptor sensitivity is enhanced, in this case by the presence of a viral URI. To the best of our knowledge, the only prior study[16] that has evaluated the effect of guaifenesin on experimentally induced cough demonstrated, over a quarter century ago, that citric acid-induced cough was not inhibited in healthy volunteers.

Previous studies[17] have documented the transient increase in cough reflex sensitivity during URI. Therefore, our subjects with URI were in a hypertussive state relative to their baseline. Because of the huge variation in cough sensitivity among the population, studies such as this one, assessing the effect of a pharmacologic intervention on cough reflex sensitivity, must use each subject as his or her own control. Furthermore, the tremendous variation in baseline cough reflex sensitivity among individuals renders comparison of small groups irrelevant. In other words, subjects in our acute URI group are

hypertussive relative to their own healthy baseline, not relative to the healthy volunteer group. The absence of a statistically-significant difference in baseline cough sensitivity between our two study groups does not imply, therefore, a lack of a state of cough receptor hypersensitivity among the URI subjects. The question of whether guaifenesin has an inhibitory effect in other hypertussive states, such as with gastroesophageal reflux, cough-variant asthma, or with the use of angiotensin-converting enzyme inhibitors, awaits elucidation in future trials.

The mechanism by which guaifenesin inhibits cough reflex sensitivity remains speculative. Given its use as an anesthetic agent in horses,[4] a central antitussive effect of guaifenesin may be suggested. However, if indeed cough inhibition by guaifenesin was predominantly central, one might expect antitussive activity to be demonstrated in some healthy volunteers as well, as has been shown with centrally acting antitussive agents such as codeine,[18] dextromethorphan,[19] and baclofen.[20]

A peripheral mechanism of antitussive activity may be postulated by invoking the presumed effect of guaifenesin on airway mucus. The "hydration hypothesis" proposes that guaifenesin, by increasing the effective hydration of the respiratory tract, maintains the sol layer needed for ciliary clearance and reduces the viscosity of respiratory mucus, thereby further facilitating its removal by natural clearance processes.[2] Perhaps the findings of the present study may be explained by increased mucus volume, or otherwise altered airway mucus, serving as a more effective barrier shielding cough receptors within the respiratory epithelium from the tussive stimulus.

REFERENCES

1 Widdicombe JG. Neurophysiology of the cough reflex. Eur Respir J 1995; 8:1193–1202

2 Ayres PJW. Experimental and clinical methodologies in efficacy of expectorants using the example of guaifenesin. In: Loew D, Rietbrock N, eds. Phytopharmaka III. Darmstadt, Germany: Steinkopff Verlag, 1997; 151–160

3 Expectorant drug products for over-the-counter human use: final monograph. Washington DC: US Department of Health and Human Services, 1989; Federal Register 54:8494–8509

4 Spadavecchia C, Stucki F, Moens Y, et al. Anaesthesia in horses using halothane and intravenous ketamine-guaiphenesin: a clinical study. Vet Anaesth Analg 2002; 29:20–28

5 Robinson RE, Cummings WB, Deffenbaugh ER. Effectiveness of guaifenesin as an expectorant: a cooperative double-blind study. Curr Ther Res 1977; 22:284–296

6 Hirsch SR, Viernes PF, Kory RC. The expectorant effect of glyceryl guaiacolate in patients with chronic bronchitis: a controlled *in vitro* and *in vivo* study. Chest 1973; 63:9–14

7 Kuhn JJ, Hendley O, Adams KF, et al. Antitussive effect of guaifenesin in young adults with natural colds. Chest 1982; 82:713–718

8 Cohen BM. Antitussive effect of guaifenesin [letter]. Chest 1983; 84:118–119

9 Burgi H. Changes in the fibre system and viscosity of the sputum of bronchitis during treatment with bromhexine and guaiphenesin (guaiacol glyceryl ether). Scand J Respir Dis 1974; 90(suppl):81–85

10 Heilborn H, Pegelow K-O, Odeblad E. Effect of bromhexine and guaiphenesine on clinical state, ventilator capacity and sputum viscosity in chronic asthma. Scand J Respir Dis 1976; 57:88–96

11 Thomson ML, Pavia D, McNicol MW. A preliminary study of the effect of guaiphenesin on mucociliary clearance from the human lung. Thorax 1973; 28:742–747

12 Houtmeyers E, Gosselink R, Gayan-Ramirez G, et al. Effects of drugs on mucus clearance. Eur Respir J 1999; 14:452–467

13 Rubin BK. An *in vitro* comparison of the mucoactive properties of guaifenesin, iodinated glycerol, surfactant, and albuterol. Chest 1999; 116:195–200

14 Midgren B, Hansson L, Karlsson J-A, et al. Capsaicin-induced cough in humans. Am Rev Respir Dis 1992; 146:347–351

15 Dicpinigaitis PV, Grimm DR, Lesser M. Cough reflex sensitivity in subjects with cervical spinal cord injury. Am J Respir Crit Care Med 1999; 159:1660–1662

16 Packman EW, London SJ. The utility of artificially induced cough as a clinical model for evaluating antitussive drug combinations: part I; Liquid and solid formulations of systemic drugs. Curr Ther Res 1977; 21:855–866

17 O'Connell F, Thomas YE, Studham JM, et al. Capsaicin cough sensitivity increases during upper respiratory infection. Respir Med 1996; 90:279–286

18 Empey DW, Laitinen LA, Young GA, et al. Comparison of the antitussive effects of codeine phosphate 20 mg, dextromethorphan 30 mg and noscapine 30 mg using citric acid induced cough in normal subjects. Eur J Clin Pharmacol 1979; 16:393–397

19 Pavesi L, Subburaj S, Porter-Shaw K. Application and validation of a computerized cough acquisition system for objective monitoring of acute cough: a meta-analysis. Chest 2001; 120:1121–1128

20 Dicpinigaitis PV, Dobkin JB. Antitussive effect of the GABA-agonist baclofen. Chest 1997; 111:996–999