Guaifenesin Has No Effect on Sputum Volume or Sputum Properties in Adolescents and Adults With Acute Respiratory Tract Infections

Agathe Hoffer-Schaefer, Henry J Rozycki MD, Melissa A Yopp, and Bruce K Rubin MEngr MD MBA FAARC

BACKGROUND: Guaifenesin (glyceryl guaiacolate ether [GGE]) has been studied as a cough suppressant and as an expectorant; however, published studies to date have failed to find a consistent benefit. METHODS: An 8-day multi-center clinical trial was conducted to study the effect of two 600-mg extended-release GGE tablets twice daily for 1 week on cold symptoms, sputum volume, and properties in adolescents and adults with productive cough from an acute respiratory tract infection (RTI). The study enrolled 378 subjects (GGE, $n = 188$; and placebo, $n = 190$) who were otherwise healthy and had an RTI for up to 5 days before enrollment. Subjects suffered from at least 2 of 3 symptoms of cough, thickened mucus, and chest congestion. A total of 151 GGE and 144 control subjects completed the full protocol. Single-sputum samples were collected from each subject on days 1, 3, 4, and 8 of the study. The rheology and interfacial tension of sputum were measured, and 24-h collected samples from days 1 and 4 were analyzed for total volume and hydration. RESULTS: Symptoms in both the GGE and placebo groups improved to a similar degree over time. There were no significant differences between the GGE and placebo groups for sputum volume ($P = .41$), percent solids ($P = .69$), interfacial tension ($P = .88$), elasticity ($P = .71$), viscosity ($P = .45$), or mechanical impedance ($P = .75$). CONCLUSIONS: The recommended dose of GGE had no measurable effect on sputum volume or properties and is unlikely to be an expectorant or mucolytic when used to treat acute RTI. (ClinicalTrials.gov registration NCT01046136.) *Key words: expectorant; mucus; guaifenesin; upper respiratory infection; cough therapy.* [Respir Care 2014;59(5):631–636. © 2014 Daedalus Enterprises]

Introduction

Guaifenesin (3-(2-methoxyphenoxy)-1,2-propanediol), or glyceryl guaiacolate ether (GGE), was originally derived from the guaiac tree. It has been used to treat respiratory disease since the 19th century. GGE is approved by the FDA as an over-the-counter expectorant, with sales of the Mucinex extended-release brand (Reckitt Benckiser Pharmaceuticals, Bristol, United Kingdom) accounting for approximately $135 million in the United States annually. GGE has been studied both as a cough suppressant and as an expectorant; however, published studies have failed to find a consistent benefit.[1-5] The only available assessment of the effect of GGE in young adults with natural (ie, community-acquired) colds found no objective changes in sputum properties.[6]

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All authors are affiliated with the Department of Pediatrics, Virginia Commonwealth University, Richmond, Virginia.

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Correspondence: Bruce K Rubin MEngr MD MBA FAARC, Department of Pediatrics, Virginia Commonwealth University School of Medicine, Richmond, VA 23298. E-mail: brubin@vcu.edu.

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The purpose of this study was to determine whether two 600-mg extended-release GGE tablets (Mucinex) or matching placebo given twice daily for 7 days to subjects with an acute respiratory tract infection (RTI), that is a common cold, would improve the volume or properties of sputum and to evaluate the effect of GGE on subjective assessments of symptoms and symptom-associated quality of life. We are reporting only the objective measures of sputum volume and properties in this article.

QUICK LOOK

Current Knowledge

Guaifenesin (GGE) is approved by the FDA as an over-the-counter expectorant, with sales accounting for approximately $135 million in the United States annually. GGE has been studied both as a cough suppressant and as an expectorant with inconsistent findings.

What this paper contributes to our knowledge

At the recommended dose, GGE has no measurable effect on sputum volume or sputum properties and is unlikely to be an expectorant or mucolytic when used to treat acute respiratory infection.

Methods

Subjects

This was an 8-day multi-center double-blind randomized placebo-controlled trial comparing the administration of two 600-mg GGE tablets every 12 h for 7 d with placebo. Subjects were 12 y of age or older and met the following inclusion criteria, as judged by their primary physician/investigator: (1) an RTI for 5 d or less; (2) a productive cough beginning within 72 h of the first dose of study medication; (3) at least 2 of 3 target symptoms of cough, thickened mucus, and chest congestion; (4) if female, a negative pregnancy test; and (5) likely to comply with the study requirements. Exclusion criteria included respiratory symptoms due to chronic pulmonary disease (eg, cystic fibrosis, COPD, asthma, allergic rhinitis), had been febrile (> 101°F) in the previous 7 d, or clinically important physical or psychiatric disorders that could interfere with adherence or study outcomes. Subjects were also excluded if they were taking prescription or over-the-counter cough or cold medications. Concomitant nasal symptoms were not regarded as an exclusion criterion. Randomization of consenting eligible subjects was done by sequential number assignment, blocked by study site to achieve an approximately equal distribution for each group. Masking was achieved by packaging GGE and matching placebo product in identical blister packs and delivering them to each study site with no identifying markings other than the protocol and randomization numbers. Codes were withheld from patients and personnel until the study was completed and data locked.

Approval by the institutional review board at each study site was obtained before study initiation, and written informed consent was obtained from each subject before enrollment. Analysis of symptom scoring and quality-of-life data are not within the scope of this article. A portion of those results have been published.[7]

Sputum Collection

Spontaneously produced sputum was collected from each subject during morning clinic on days 1, 3, 4, and 8. On days 1, 3, and 4, sputa were collected immediately before the test drug was administered and at 3 and 6 h after. On day 8, only a baseline sample was collected. Sputum was visually separated from saliva and detritus, and samples were stored at −80°C until analysis. Twenty-four-hour collections of sputa were done by subjects at home on days 1, 2, 4, and 5; stored in a sputum cup in home refrigerators; and returned to the clinic on days 2 and 8, whereby they were frozen at −80°C. Sputa were thawed on ice for analysis. Analysis of sputum biophysical properties was performed immediately upon thawing.

Sputum samples were analyzed only if they met visual examination criteria for sample integrity. Samples that were clearly watery and degraded or contaminated by saliva were not analyzed. Ideal samples were also free of food or other detritus. Samples that were not identifiable because of missing or illegible labels were discarded without analysis. The median number of sputum samples provided by

Table 1. Sample Distribution

	GGE (n = 188)	Placebo (n = 190)	Total (n = 378)
Day 1			
Predrug	118	117	235
3 h	51	62	113
6 h	107	109	216
Day 3			
Predrug	99	95	194
3 h	55	62	117
6 h	85	82	167
Day 4			
Predrug	106	110	216
3 h	44	43	87
6 h	84	86	170
Day 8	40	47	87

Number of sputum samples available for analysis for each scheduled collection by group assignment
GGE = guaifenesin

each subject was 6 (interquartile range 4–7). The sample distribution per collection is outlined in Table 1.

Rheology

To assess whether GGE improves the properties of sputum that influence the effectiveness of sputum clearance, each of the serially collected sputa was evaluated for dynamic rheology using a rheometer (AR1500ex, TA Instruments, New Castle, Delaware). Parallel plate geometry was used across the dynamic frequency range of stress-strain of a 20-μL sputum sample over driving frequencies 0.01–1000 rad/s using nondestructive creep transformation and triplicate analyses. Rheology measurements were made if the measured strain from 1 to 100 rad/s was linear and reproducible.[8] By a priori determination, specimens with nonreproducible results indicated by a $>$ 20% variability in the linear testing range were considered degraded or contaminated with air, and results were not recorded.

Interfacial Tension

Interfacial tension was evaluated using the du Noüy ring distraction method. A 90% platinum/10% iridium ring was pulled from the mucus at a distraction velocity of 10 mm/s until separation was achieved. Interfacial tension was measured at the air-mucus interface by a strain gauge connected to the ring (Tensiomat Model 21, Fisher Scientific, Pittsburgh, Pennsylvania). A purpose-made calibrated ring with a circumference of 1.7145 $\pm$ 0.0381 cm was used as described previously.[9] Interfacial tension measures the force separating a gel and gas phase; this is called surface tension when measured at the interface between a liquid and air. The work of adhesion of a sessile drop can be calculated by Young's equation as work of adhesion $= \gamma(1 + \cos \theta)$, where γ is the interfacial tension of mucus in air and θ is the contact angle of mucus on the epithelium. Sputum with high work of adhesion is more difficult to clear by cough.

Mucus Hydration and Volume

To determine whether GGE works as an expectorant and increases the volume of mucus or fluid produced, the total weight and hydration (% solid material) of the two 24-h samples were calculated by measuring the wet weight of the sputum, freeze-drying the sputum, and determining the ratio of the solid weight to wet weight to obtain the percent solids.[10]

Statistical Analysis

Prestudy sample size determination was based on previous studies of sputum properties, so 120 subjects per group were needed to detect a 50% change in sputum dynamic viscosity with 80% power. The goal of the study was to enroll at least 375 subjects and collect data on 300 to provide a sufficient sample to have an 80% power to detect a statistically significant ($P < .05$) difference between groups for both rheology and sputum volume outcome measures. Although we were unable to collect uncontaminated sputum from all participants at every time point, post hoc power calculation, using the means and variability of the results obtained, confirmed that the study sample size was sufficient to detect any clinically important changes in the volume or biophysical properties of the sputum.[11]

Data were logged in spreadsheets and analyzed by JMP 9.0 or StatView 5.0 (both from SAS Institute, Cary, North Carolina). Analyses were based on per protocol subjects defined as those who met all inclusion and exclusion criteria; were 100% dosing-compliant from days 1 to 4; had 80% of their diaries complete on days 1 and 4, with some diary information on days 2 and 3; and had their visits on the designated study day. Subject demographics and sputum were compared among groups using the *t* test for continuous variables, Mann-Whitney U test for categorical variables, and chi-square test for proportions. Sputum rheology and interfacial tension were analyzed by two-way analysis of variance (ANOVA). Post hoc correction for multiple comparisons was calculated using the Sidak method. Where applicable, results are reported as means $\pm$ standard error of the mean. Significance was defined as $P < .05$.

Table 2. Subject Demographics

	GGE (n = 188)	Placebo (n = 190)	P
Age (mean $\pm$ SD y)	41.2 $\pm$ 13.9	40.8 $\pm$ 15.0	.41
Sex (%)			
Male	49	56	.22
Female	51	44	
Ethnicity (%)			
Hispanic/Latino	7	5	.41
Not Hispanic/Latino	93	95	
Race (%)			
Caucasian	61	61	.34
African-American	37	33	
Asian	2	4	
American Indian/Alaska Native	1	2	
Native Hawaiian/Pacific Islander	1	0	

Subject demographics for the placebo and guaifenesin groups. There were no statistically significant differences between groups by chi-square analysis or *t* test for age.
GGE = guaifenesin

Results

Patient Demographics

The study enrolled 378 subjects (GGE, n = 188; and placebo, n = 190) at 12 centers; the subjects were other-

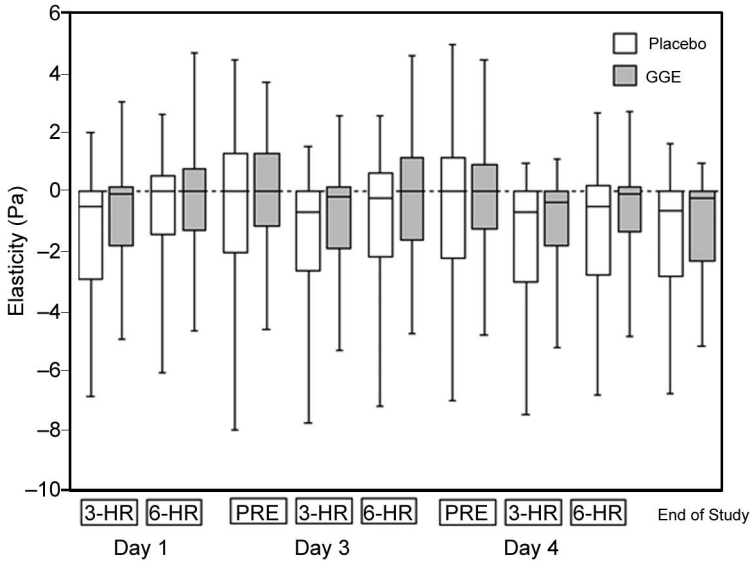

Fig. 1. Changes in elasticity from baseline in the placebo and GGE (glyceryl guaiacolate) groups over the course of the study. There were no significant differences in the change from baseline between the two groups by ANOVA. Whiskers represent 95% CI.

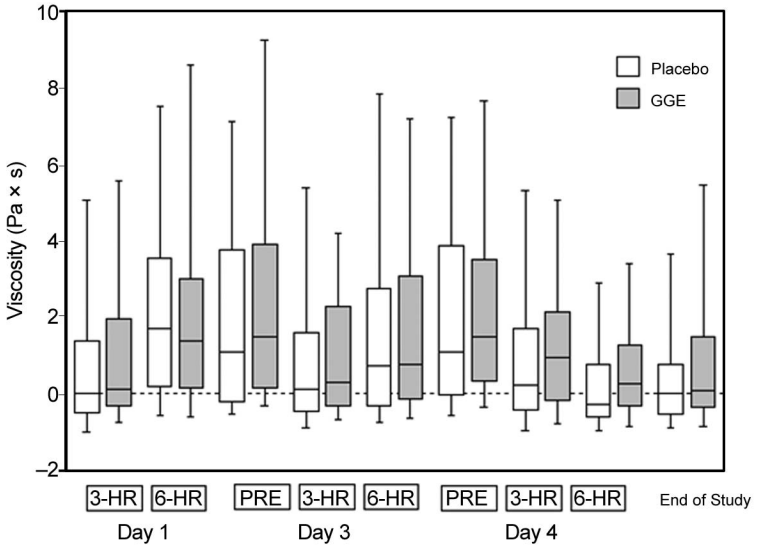

Fig. 2. Changes in viscosity from baseline in the placebo and GGE (glyceryl guaiacolate) groups over the course of the study. There were no significant differences in the change from baseline between the two groups by ANOVA. Whiskers represent 95% CI.

wise healthy and had symptomatic RTI for up to 5 d before enrollment. There were 295 subjects (151 GGE and 144 control) who completed the full protocol. There were no significant differences between groups for demographics (Table 2).

Rheology

As determined by two-way ANOVA, there were no significant differences with respect to changes from baseline in the study between the GGE and placebo subjects for elasticity (G′, $P = .71$) (Fig. 1), viscosity (G″, $P = .45$ (Fig. 2), and mechanical impedance (G*, $P = .75$).

Interfacial Tension

There were no significant treatment differences between groups concerning interfacial tension at any time point ($P = .88$) (Fig. 3).

Mucus Hydration and Volume

There were no significant differences in the wet weight between groups at the first collection (GGE, 4.70 ± 0.471 g;

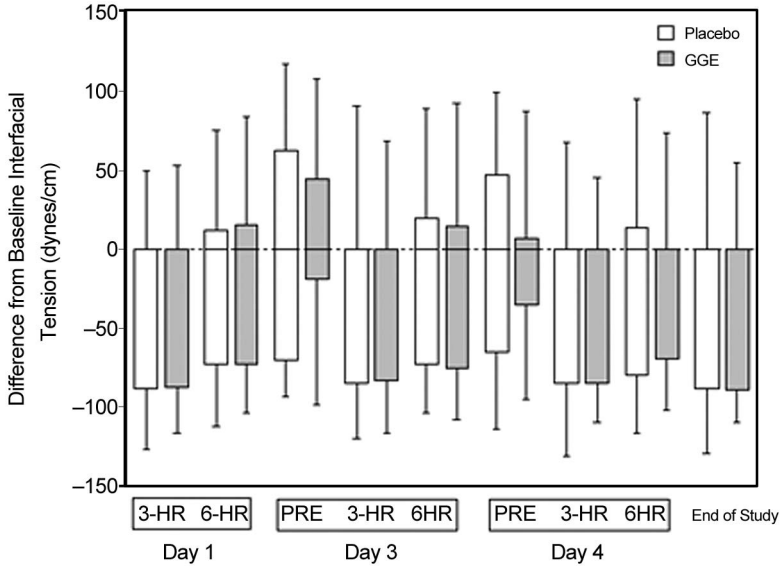

Fig. 3. Changes in interfacial tension from baseline in the placebo and GGE (glyceryl guaiacolate) groups over the course of the study. There were no significant differences in the change from baseline between the two groups by ANOVA. Whiskers represent 95% CI.

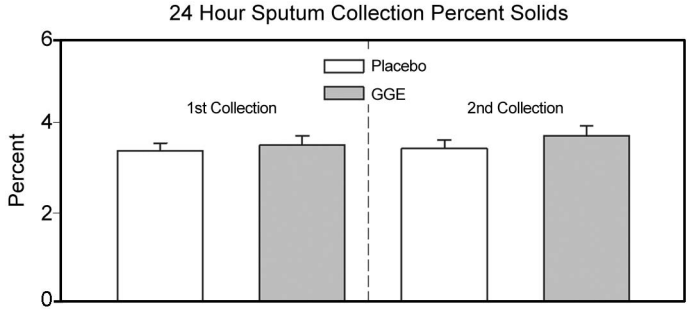

Fig. 4. Sputum percent solids for the first collection (days 1 and 2) and the second collection (days 4 and 5) in the control and GGE (glyceryl guaiacolate) groups. By *t* test, there were no significant differences between the two groups in either the first collection ($P = .69$) or the second collection ($P = .33$).

placebo, 6.083 ± 0.754 g; $P = .12$) or second collection (GGE, 4.292 ± 0.460 g; placebo, 4.718 ± 0.518 g; $P = .54$) or in the change between the two collections (GGE, −0.981 ± 0.593 g; placebo, −2.081 ± 0.821 g; $P = .14$). Similarly, there were no significant differences in the percent solids between the groups (Fig. 4) in the two collections or in the change between the collections (GGE, 0.191 ± 0.223%; placebo, 0.042 ± 0.236%; $P = .65$).

Discussion

In this large randomized clinical trial, there were no consistent statistically significant changes in sputum properties comparing placebo with GGE for therapy of acute symptoms of RTI in subjects without underlying chronic pulmonary disease. The absence of changes in sputum rheology and interfacial tension, independent of within-group symptom decrease over time, makes it unlikely that GGE is a mucolytic or that GGE therapy would improve mucociliary or cough clearance. Similarly, the lack of difference in sputum wet volume or dry weight makes it unlikely that GGE has significant expectorant properties in healthy subjects with an acute upper RTI. Although the upper respiratory quality of life improved over the course of the study in both the GGE and placebo groups, this improvement was not accompanied by changes in sputum properties.

We conclude that extended-release GGE (Mucinex) administered at the recommended dose is no more effective than a placebo in changing sputum properties. Although it is possible that the negative results could be due to an inadequate dose, the drug dosage studied here is consistent with current dosing recommendations for GGE as an over-the-counter medication to ease cold symptoms. It is also possible that the drop off in sample number over the course of the study could confound the results because those sub-

jects with improvement in their productive cough or sputum production may have been omitted from the sampling. Another possible limitation is that the diagnosis of RTI was made clinically and not confirmed by microbiological testing. However, the clinical assessment was performed by experienced clinicians, and the clinical conditions matched those for which GGE is most commonly used.

It has been suggested that GGE is either an expectorant or a mucolytic (requiring very different mechanisms of action) and that changes in sputum properties are responsible for clinical effectiveness. If GGE were an expectorant,[4,12,13] we would expect to see increased sputum volume and hydration. This was not supported by the results of sputum volume or percent solid measurements in our study. If GGE were a mucolytic,[14,15] we would expect to see decreased viscoelasticity. In our study, we saw no evidence of either expectorant or mucolytic properties either for GGE or for the placebo. Furthermore, there were no changes in sputum properties that would be expected to improve mucociliary or cough clearance. In contrast to an earlier in vitro study showing that GGE decreased mucociliary transport when applied directly to a ciliated epithelium,[14] a more recent study showed a dose-dependent increase in mucus transport when GGE was introduced into airway cell culture.[15] These data from a clinical study in subjects with an acute upper RTI clearly show no evidence of mucolytic properties and no temporal or drug-associated changes in viscoelasticity or sputum volume.

The results of this study, which focused on the properties of mucus during RTIs, are consistent with published studies showing that GGE is not an effective medication for treating acute RTIs.[1-5] The placebo effect has been reported to be as high as 85% in studies of cough therapy,[16] and given the absence of biophysical findings, this may be the best explanation for any perceived benefits for GGE.

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