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# Effects of Guaifenesin on Nasal Mucociliary Clearance and Ciliary Beat Frequency in Healthy Volunteers\*

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**Study objective:** Mucociliary clearance is an important host defense function of the upper respiratory tract that requires the coordinated beating of cilia and results in the transport of mucus to the oropharynx. Guaifenesin is a commonly prescribed drug that is reported to improve the clearance of respiratory secretions. We hypothesized that guaifenesin increases nasal mucociliary clearance related to increases in ciliary beat frequency (CBF) and that a direct relationship exists between nasal CBF and nasal mucociliary clearance.

**Design:** Double-blind placebo-controlled crossover study.

**Participants:** Ten healthy volunteers with a previous history of sinus disease.

**Interventions:** Subjects received guaifenesin or placebo on days 1 to 7 or days 14 to 21.

**Measurements and Results:** *In vivo* saccharine transit time (STT) was measured by noting the time in minutes required for the subject to taste a saccharin particle placed on the inferior turbinate of the nares. The CBF was determined by video microscopy on ten separate groups of beating ciliated nasal mucosal cells obtained by brushing immediately after each STT determination. We found that there was no significant change between

the guaifenesin- or placebo-treated groups from baseline values of STT ( $p=0.94$ ) or CBF ( $p=0.46$ ). Regression analysis demonstrated no relationship between STT and CBF for repeated measures within subjects (mean  $r^2=0.18$ ; mean  $p=0.66$ ) and between STT and CBF when all paired measurements were combined across subjects ( $r^2=0.47$ ;  $p=0.46$ ).

**Conclusion:** We conclude that guaifenesin exerts no measurable effect on *in vivo* nasal mucociliary clearance or *ex vivo* nasal ciliary motility in healthy volunteers with previous sinus disease. In addition, there appears to be no relationship between nasal STT measured *in vivo* and CBF measured *ex vivo*. The lack of correlation is most likely due to variations in CBF related to sampling artifacts introduced by the nasal brushing process. (Chest 1995; 107:747-51)

CBF=ciliary beat frequency; STT=saccharin transit time

**Key words:** ciliary motility; guaifenesin; mucociliary clearance; nasal mucus clearance

Mucociliary clearance is an important host defense function of the airways. This function requires the coordinated beating of cilia which results in the transport of mucus to the oropharynx. Although the motor activity of cilia is certainly responsible in large part for the propulsion of mucus out of the airway, the linkage between ciliary motility and mucociliary clearance is poorly understood with no direct relationship described between the frequency of beating cilia and mucus clearance rates in man. The clinical impact of a dysfunctional mucociliary clearance mechanism is clear, however, since individuals with genetically defective mucociliary clearance mechanisms are plagued with cough and recurrent upper respiratory tract infections.<sup>1</sup>

Guaifenesin is a compound reported to enhance airway mucus clearance and is commonly prescribed to patients with productive cough, nasal congestion, or excessive mucus production. While one recent study suggests that guaifenesin may improve nasal symptoms associated with impaired clearance,<sup>2</sup> few have shown any clear effect of guaifenesin on direct measures of mucociliary clearance,<sup>3</sup> and none have examined the drug's impact on nasal ciliary motility or mucus clearance in the nose.

The current study examines two hypotheses: (1) Does guaifenesin increase nasal mucociliary clearance *in vivo*, as assessed by the saccharin transit time (STT), or nasal ciliary beat frequency (CBF), as assessed by nasal brushing and *ex vivo* microscopy, or both? (2) Does a relationship exist between nasal CBF and nasal STT? We report the effect of guaifenesin on both *in vivo* STT and *ex vivo* CBF determined in the same individuals repeatedly over time and also examine the relationship between these two measures of nasal mucociliary function within and across individuals.

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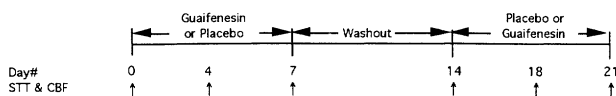


FIGURE 1 Representation of *in vivo* nasal STT and *ex vivo* CBF determinations for each subject carried out six times throughout the study.

## METHODS

### Clinical Data

**Subject Recruitment:** The study protocol was approved by the Institutional Review Board at the University of Nebraska Medical Center prior to subject accrual. Ten healthy volunteers with a history of previous sinus problems were recruited through an advertisement to participate in the study. All subjects had no active sinus infection, nasal or sinus discharge, fevers, nasal stuffiness, or other active symptoms at the time of the study. Originally 12 subjects started the study, but one subject was not able to complete the study for personal reasons and another subject dropped out due to an exacerbation of asthma requiring oral steroid therapy. The remaining ten subjects were able to complete the entire study. Informed consent was obtained for all individuals at the time of enrollment.

**Study Design:** The study was a double-blind, placebo-controlled crossover study in which subjects were given guaifenesin, 400 mg orally, 5 times a day (2,000 mg/d) for 7 days either in the first or third week of the study and were given placebo during the opposite week. Guaifenesin and placebo were coded and dispensed by the pharmacy such that the subjects and investigators were blind to the code until the study was completed. The middle week (day 8 through 14) was a washout period when the subjects received no drugs. *In vivo* nasal STT and *ex vivo* CBF was determined on each subject 6 times throughout the study as indicated in Figure 1.

Both tests were performed at the same time on each test day. In each case, the nasal STT was completed immediately prior to the nasal brushings. Out of 60 possible paired STT and CBF measurements, 48 were successfully completed. Difficulty in saccharin particle placement precluded STT determination in five instances, and inadequate nasal tissue obtained by brushing precluded CBF determination in eight instances. Eight of the ten subjects successfully completed paired measurements of STT and CBF, allowing analysis of both pre- and post-drug values of both parameters for the guaifenesin and placebo treatment periods.

**Nasal Saccharin Transit Time:** The nasal STT was measured using a standard protocol as described.<sup>4</sup> Briefly, the more patent naris was subjectively determined by the subject prior to the study, and the saccharin was placed in this naris for all subsequent determinations throughout the study. A 5-mg particle of saccharin measuring approximately 0.5 mm in diameter was placed on the inferior turbinate of the appropriate naris under direct visualization using a headlamp and a nasal speculum. After correct particle placement was visually confirmed, a stopwatch was started and the total time was recorded from initial particle placement until the subject was able to clearly taste sweetness. If the subject was unable to taste any sweetness after 30 min, an additional particle of saccharin was placed on the anterior aspect of the subject's tongue to exclude taste loss. In all determinations, the subjects had intact taste.

**Ex Vivo Ciliary Beat Frequency:** Immediately following completion of the STT determination, the right and left nares were brushed vigorously with a 2-mm diameter nylon cytology brush for approximately 5 s in each naris on the inferior turbinate.<sup>5</sup> The brush immediately was rinsed in medium 199 and the cells were maintained at a constant temperature of 37°C while being

transported to the laboratory. The cells were resuspended upon arrival at the laboratory; they were placed on a glass slide with a coverslip and examined by phase-contrast microscopy. The temperature of the microscope stage was maintained electronically at 37°C with a heated stage throughout the experiment. The sample was examined for ten separate groups of beating ciliated cells, and CBF was determined by recording the fields on videotape and performing frame-by-frame slow-motion video analysis as described.<sup>6</sup>

### Statistical Analysis

All pre- and post-drug comparisons were made using the paired Student's *t* test. The relationships between STT and CBF were determined using a linear regression statistic.

## RESULTS

### Effect of Guaifenesin and Placebo on Saccharin Transit Time

The effect of guaifenesin was examined by STT. The baseline STT for individuals prior to guaifenesin and following 7 days on 2,000 mg/d was not significantly different (pre,  $14.9 \pm 1.2$  min vs post,  $14.1 \pm 1.7$  min;  $p=0.31$ ; Fig 2, A). Similarly, there was no significant difference between the STT measured before and at the end of the placebo period of 7 days (pre,  $16.8 \pm 2.1$  min vs post,  $15.5 \pm 1.2$  min;  $p=0.28$ ; Fig 2, B). When the change over seven days of treatment for guaifenesin was compared with the change with placebo relative to the baseline STT, there also was no significant difference between guaifenesin and placebo (guaifenesin,  $-0.8 \pm 1.4$  min vs placebo,  $-1.3 \pm 1.6$  min;  $p=0.46$ ; Fig 2, C).

### Effect of Guaifenesin and Placebo on Ciliary Beat Frequency

The effect of guaifenesin on CBF also was examined. The mean CBF from each individual prior to guaifenesin (day 0 or 14) was compared with the mean CBF at the end of the 7 days of guaifenesin treatment (day 7 or 21). There was no significant change in CBF pre- to post-drug (pre,  $9.4 \pm 0.4$  Hz vs post,  $9.2 \pm 0.4$  Hz;  $p=0.39$ ; Fig 3, A). This was similar to the results obtained for placebo in which CBF also did not change significantly (pre,  $9.8 \pm 1.1$  Hz vs post,  $9.9 \pm 0.5$  Hz;  $p=0.87$ ; Fig 3, B). The change in CBF after 7 days on the drug compared with baseline also was not significantly different (guaifenesin,  $-0.3 \pm 0.4$  Hz vs placebo,  $0.1 \pm 0.9$  Hz;  $p=0.46$ ; Fig 3, C).

### Relationship Between Saccharin Transit Time and Ciliary Beat Frequency Within and Across Subjects

The relationship between CBF and STT was examined within each subject on repeated days using regression analysis. In all but one subject there was no relationship between STT and CBF (average  $r^2=0.18$ ; average  $p=0.66$ ; data not shown). The only exception

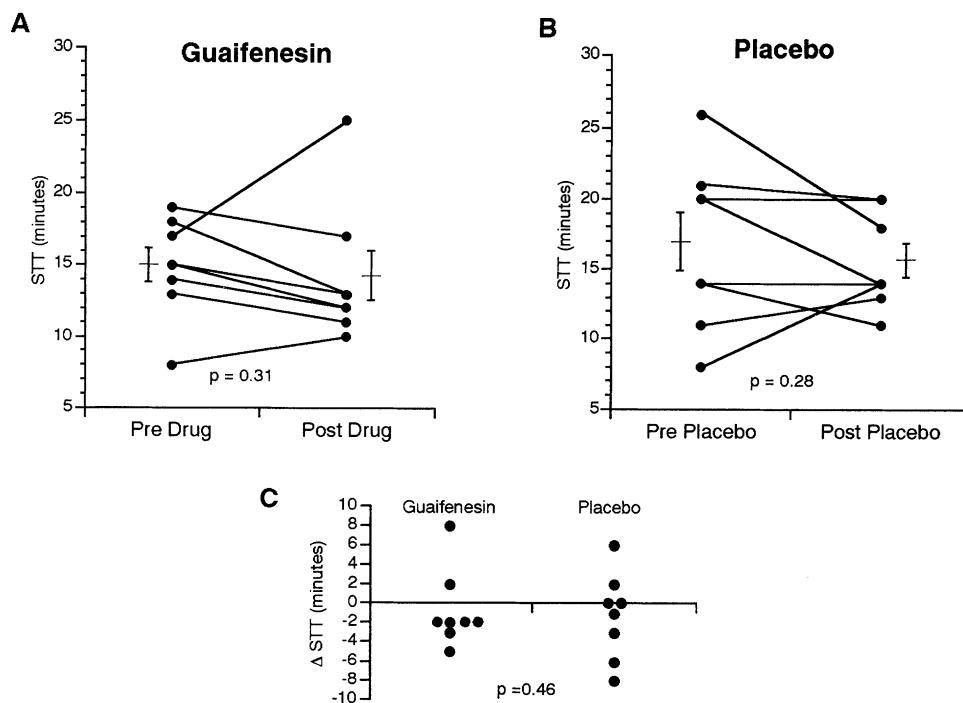


FIGURE 2. Effect of guaifenesin vs placebo on nasal STT. *Panel A* and *B*, The vertical axes represent the nasal STT expressed in minutes and the horizontal axes represent the pre-drug (day 0 or 14) and post-drug (day 7 or 21) STT determinations with paired samples for each subject connected by lines. *Panel A* demonstrates the values for all subjects receiving guaifenesin and *panel B* shows those for all subjects receiving placebo. The mean  $\pm$  1 SEM for the group of subjects is displayed next to the individual data points for each group. *Panel C*, The vertical axis represents the change in STT compared with pre-drug values and the horizontal axis represents the guaifenesin and placebo treatment groups. The *p* values were determined using the Student's paired *t* test.

in which a positive correlation was seen between the two variables was in one subject ( $r^2=0.84$ ;  $p=0.01$ ; data not shown). We also examined the relationship between CBF and STT across all subjects combining all data points. There was no significant relationship between these two variables in 10 subjects for 47 independent paired measurements ( $r^2=0.04$ ;  $p=0.18$ ; Fig 4). This lack of correlation existed regardless of how the data were examined with regard to measurements made while the subject was taking placebo or guaifenesin or was not receiving any drugs.

#### DISCUSSION

Our study examined the effect of guaifenesin on mucociliary clearance as measured *in vivo* by nasal STT and on ciliary motility as measured *ex vivo* by CBF. We found that guaifenesin had no significant effect on either of these measures of nasal mucociliary function. Our observation bolsters the experience in the literature in which few well designed studies have shown that guaifenesin promotes mucociliary clearance. Thomson and coworkers<sup>3</sup> found that guaifenesin had a small but positive effect on lung clearance of inhaled radiolabeled particles from bronchitic but not normal subjects. Unfortunately, all but one of the normal subjects in that study smoked

heavily, and the authors only examined the effect of a single 600-mg dose of guaifenesin. That study also differed from ours in that the authors examined lung clearance, while we examined nasal clearance. Wawrose and colleagues<sup>2</sup> found that guaifenesin was associated with symptomatic improvement in nasal congestion and a subjective decrease in nasal secretion thickness when given to a group of HIV-positive patients with sinonasal symptoms. They did not examine any objective measure of mucociliary function, however, and their study, while double-blinded, was not a crossover design.<sup>2</sup> For these reasons, our study is important because we examined the effects of guaifenesin in a healthy population, we examined objective measurements of nasal mucociliary function, and we used a double-blind crossover design to minimize investigator and subject bias.

There are several possible explanations why we could not measure an effect of guaifenesin on STT or CBF: (1) Guaifenesin may be ineffective in promoting nasal mucociliary clearance. (2) Guaifenesin may not penetrate the nasal mucosa. (3) Nasal STT only assesses clearance of the nares and may have no relationship to clearance of the lower respiratory tract. (4) Nasal STT may be insensitive to small drug effects such that the test may not be capable of detecting a

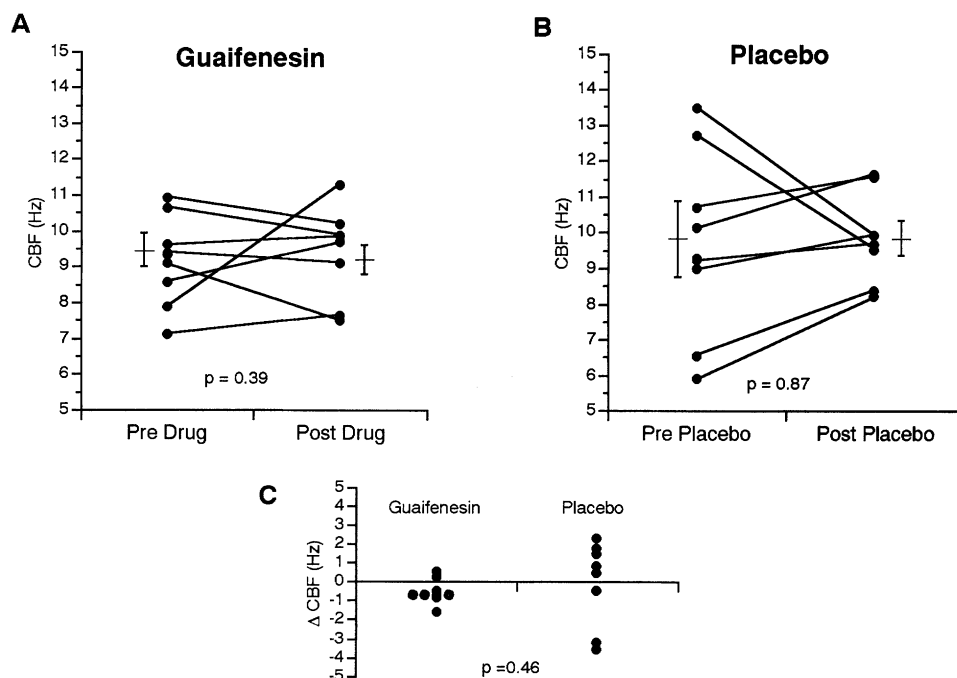


FIGURE 3. Effects of guaifenesin vs placebo on CBF. *Panel A* and *B*, The vertical axes represent CBF expressed in cycles per second (Hertz) and the horizontal axes represent the pre-drug (day 0 or 14) and post-drug (day 7 or 21) CBF determinations with paired samples for each subject connected by lines. *Panel A* demonstrates the values for all subjects receiving guaifenesin and *panel B* shows those for all subjects receiving placebo. Each data point represents the mean of ten separate CBF measurements made from different groups of ciliated cells obtained from a single nasal sample. The mean  $\pm$  1 SEM for the group of subjects is displayed next to the individual data points for each group. *Panel C*, The vertical axis represents the change in CBF compared with the pre-drug values, and the horizontal axis represents the guaifenesin and placebo treatments groups. The probability values were determined using the Student's paired *t* test.

small change in clearance. There also are several reasons why guaifenesin may not alter ciliary motility measured by *ex vivo* CBF including one that changes in *in vivo* CBF may have occurred; however, the *ex vivo* method used to determine CBF in this study introduces enough preparation artifact that this change cannot be detected. Mucus transit rates probably depend not just on CBF, but also on changes in the height and character of the periciliary fluid present on the surface of the ciliated epithelium. Our study did not examine changes in nasal mucus viscosity, which guaifenesin might have affected. Such an effect could impact on effective clearance without altering CBF or STT. Another limitation of our study is that it only examined healthy volunteers with no active nasal or sinus disease. It could well be that the drug is active in a sicker patient population, which has been suggested with regard to guaifenesin's effect on secretions in chronic bronchitic subjects,<sup>3</sup> but has no significant impact on well individuals. Lastly, our study only examined nasal effects on mucociliary function, which does not exclude possible effects that may have been beneficial in the sinuses or other parts of the respiratory tract.

Our second hypothesis proposed that there is a direct relationship between nasal mucociliary clear-

ance *in vivo*, as assessed by STT, and nasal ciliary motility, measured *ex vivo* as CBF. We found no relationship between these measures of mucociliary function. One might predict that if a relationship existed, it would be an inverse one in which faster CBF would result in shorter STT. We did not observe this relationship, however. The only statistically significant relationship between STT and CBF we observed was present in only one subject, and this relationship was the opposite of what our hypothesis suggested. There are several reasons why we may not have seen any relationship between these two variables: (1) They may be valid but independent measures of mucociliary function. (2) There is likely to be an important artifact introduced into the CBF determinations because these are measured *ex vivo* rather than *in vivo*. (3) Factors such as humidity, local inflammation, and the presence of irritants may influence clearance or ciliary motility, or both, on a given day. We suspect that removing nasal ciliated cells by the brushing technique and observing them *ex vivo* introduces significant changes in motility and represents the most likely explanation for the variance in CBF that we observed. This is somewhat supported by the fact that there was more variation in the *ex vivo* CBF measurements than there was in



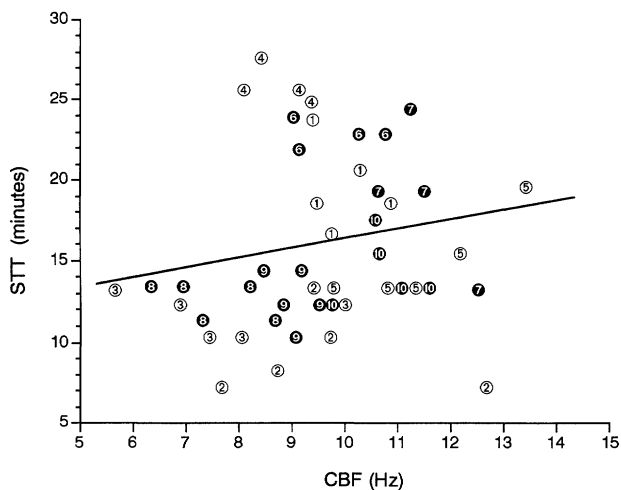


FIGURE 4. Relationship of STT to CBF. The vertical axis represents the STTs expressed in minutes, and the horizontal axis represents the CBF expressed in cycles per second (Hertz). Each data point represents the paired simultaneous STT and CBF determinations for a given subject. The subject numbers are displayed as open circles (for the group which received guaifenesin during the first week) and solid circles (for the group which received placebo during the first week). There was no statistically significant relationship between STT and CBF using linear regression analysis ( $r^2=0.04$ ;  $p=0.18$ ).

the STT measurements when repeated measurements were examined within each individual. An alternative explanation may be that there should be little change in either of these in a well, healthy outpatient population such that not enough variation is present to detect a relationship between these two variables using regression analysis. For this reason, we also examined the relationship of both of these variables for the group as a whole. When the across-subject relationship between CBF and STT was

examined, there also was no relationship between these two variables (Fig 4). Again, the same explanations could support this lack of a linear relationship.

In summary, we conclude that guaifenesin has no significant impact on either nasal STT or *ex vivo* CBF in healthy volunteers with a previous history of sinus disease. Nasal STT and *ex vivo* CBF appear to be independent measures of mucociliary function, which are most likely to be related to sampling artifacts introduced by the nasal brushing technique or the *ex vivo* nature of the CBF assay.

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