Effects of S-carboxymethylcysteine on Tracheal Mucus Velocity*

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The effects of S-carboxymethylcysteine on tracheal mucus velocity were assessed in a double blind crossover study between 2 grams S-carboxymethylcysteine and placebo. Subjects included six healthy non-smokers, eight smokers with small airway disease and chronic simple bronchitis, and eight subjects with chronic obstructive bronchitis. Tracheal mucus velocity was measured prior to and two and three hours after each subject had ingested S-carboxymethylcysteine or placebo. No significant change in tracheal mucus velocity occurred after placebo or S-carboxymethylcysteine in any of the groups, indicating that the drug has no acute effect on mucus transport.

S-carboxymethylcysteine is an oral agent related to acetylcysteine. Its free sulfhydryl groups are purported to split the disulfide bonds of long chain glycoproteins found in mucus, thereby reducing its viscosity. It has been promoted in the United Kingdom and Europe as an effective oral mucolytic agent in patients with chronic bronchitis. Theoretically, it should facilitate the ease of raising sputum by expectoration and could improve mucociliary transport because of a favorable change in mucus rheology. However, if cilia are destroyed, beating slowly or dysynchronously, mucus transport might not be improved. Thompson and associates,1 using a radioactive scanning technique, found no alteration in pulmonary clearance after four to seven days of treatment with S-carboxymethylcysteine of patients with chronic bronchitis. The purpose of our study was to examine whether this agent has an effect upon mucus transport in the trachea of subjects who would be expected to have normal mucociliary function and those with varying degrees of abnormalities. These included normal nonsmokers, smokers with small airway disease, and patients with chronic simple and obstructive bronchitis.2

Materials and Methods

The characteristics of the volunteers are listed in Table 1. All gave informed consent and received financial remuneration for their participation in the study. The subjects were grouped into three categories by clinical examination and pulmonary function tests: 1) healthy nonsmokers, 2) smokers with small airway disease and patients with chronic simple bronchitis and, 3) patients with chronic obstructive bronchitis. Spirometric results, body plethysmography, single breath nitrogen test with closing volume, nitrogen clearance delay by multiple breath nitrogen washout at respiratory frequencies of 20 and 40/min and flow-volume loops using air and helium-oxygen mixtures were measured.3

The healthy young smokers denied a history of recent respiratory infections, cough or dyspnea. They had a vital capacity greater than 80 percent of predicted, residual volume less than 120 percent of predicted, slope of phase III on the single breath nitrogen test within normal limits, nitrogen clearance delay at respiratory frequencies of 20 and 40 of zero, forced expiratory volume in one second greater than 80 percent of predicted, airway resistance less than maximal normal predicted value, normal closing volume, and volume of isoflow expressed as a percentage of vital capacity less than the maximal normal predicted value.

Smokers with small airway disease had no cough or only an occasional productive cough. They were designated as having small airway disease if vital capacity was greater than 80 percent of predicted, residual volume less than 120 percent of predicted, FEV1 greater than 75 percent of predicted and airway resistance less than normal maximal predicted value, but at least two abnormal tests of the following were present: closing volume, volume of isoflow and nitrogen clearance delay. Patients with chronic simple bronchitis differed from the smokers with small airway disease in that they had chronic productive morning cough, but no significant major airway obstruction as defined by absence of wheezing, an FEV1 greater than 75 percent predicted, and an airway resistance less or minimally greater than the maximal normal predicted value.

Patients with chronic obstructive bronchitis had chronic productive morning cough and dyspnea on exertion. All had major airway obstruction as defined by an FEV1 less than 70 percent of predicted and/or an airway resistance greater than the maximal normal predicted value.

Tracheal Mucus Velocity

This was measured by a previously described roentgeno-
**Table 1—Characteristics of Subjects**

<table>
<thead>
<tr>
<th>Category</th>
<th>Age*</th>
<th>Sex</th>
<th>Vital Capacity † % Predicted</th>
<th>FEV † % Predicted</th>
<th>Airway Resistance † % Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonsmokers</td>
<td>24 (2)</td>
<td>1M</td>
<td>5F</td>
<td>93 (85-107)</td>
<td>91 (80-109)</td>
</tr>
<tr>
<td>Smokers with small airway disease and chronic simple bronchitis</td>
<td>45 (18)</td>
<td>7M</td>
<td>1F</td>
<td>88 (74-109)</td>
<td>82 (75-90)</td>
</tr>
<tr>
<td>Chronic obstructive bronchitis</td>
<td>63 (5)</td>
<td>4M</td>
<td>4F</td>
<td>67 (45-103)</td>
<td>46 (20-78)</td>
</tr>
</tbody>
</table>

*Mean and SD in parentheses
†Mean and range

graphic technique. Briefly, radiopaque Teflon discs are deposited in the trachea through the vocal cords via the inner channel of a fiberoptic bronchoscope with the subject seated. The discs measure 1 × 0.8 mm and weigh 1.8 mg. In an isolated tracheal preparation, we have shown that these discs move at the same rate as methylene and alcin blue solutions. The axial cephalad motion in the trachea over one minute is measured from a videotape recording of the trachea obtained from a fluoroscopic image intensifier. Discs which move traversely or caudally are counted as zero motion. The mean value of tracheal mucus velocity is computed from the transit of 17 to 23 individual discs in the fluoroscopic image field selected prior to knowledge as to the direction of motion. Zero motion discs are averaged in the mean.

**Procedure**

The study was designed as a double-blind crossover between 2 gm of S-carboxymethylcysteine and a placebo. After baseline value of tracheal mucus velocity was obtained, the subject swallowed four 0.5 gm capsules of S-carboxymethylcysteine or placebo, each study being separated by at least one day, and measurements of tracheal mucus velocity were repeated two and three hours later. Samples of venous blood were obtained for assay of S-carboxymethylcysteine at each tracheal mucus velocity measurement. The principle of drug analysis was as follows: plasma containing S-carboxymethylcysteine was saturated with sodium bicarbonate in slight excess, acetic anhydride was added to this solution and allowed to react with the sodium bicarbonate to acetylate the amino group on S-carboxymethylcysteine. The solution was then made acid with hydrochloric acid. The acetylated compound was extracted with ethyl acetate and the ethyl acetate evaporated to dryness. Diazomethane was added to the dry residue to form the methyl ester. The acetylated methyl ester was injected into a gas chromatograph with a sulfur detector and the concentration then determined with the aid of an internal standard.

Data were analyzed for statistical significance by means of the paired Student t-test.

**RESULTS**

The baseline pulmonary function tests are listed in Table 1. Values of tracheal mucus velocity and corresponding plasma levels of S-carboxymethylcysteine are listed in Table 2. Baseline values of tracheal mucus velocity were significantly higher in nonsmokers than smokers with small airway disease or chronic bronchitis. The majority of the latter showed a mean tracheal mucus velocity of zero. In those that had a positive value of mean tracheal mucus velocity, up to 80 percent of discs measured had zero motion. There was no change in tracheal mucus velocity after placebo or S-carboxymethylcysteine in any of the groups which were divided according to pulmonary dysfunction. There was no significant conversion to motion by drug in those patients who had zero baseline motion whether the discs remained in one position or moved caudally. S-

**Table 2—Tracheal Mucus Velocity and Plasma Levels of S-Carboxymethylcysteine**

<table>
<thead>
<tr>
<th>Category</th>
<th>Placebo Baseline</th>
<th>2 Hours Post Drug</th>
<th>3 Hours Post Drug</th>
<th>S-Carboxymethylcysteine Baseline</th>
<th>2 Hours Post Drug</th>
<th>3 Hours Post Drug</th>
<th>Drug Level 2 Hours</th>
<th>Drug Level 3 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonsmokers</td>
<td>8.3 (1.8)</td>
<td>6.7 (2.2)</td>
<td>7.6 (3.6)</td>
<td>9.6 (1.8)</td>
<td>8.1 (1.8)</td>
<td>9.3 (3.7)</td>
<td>22.2 (1.6)</td>
<td>13.1 (3.9)</td>
</tr>
<tr>
<td>Smokers with small airway disease or chronic simple bronchitis</td>
<td>2.8 (2.7)</td>
<td>3.0 (4.0)</td>
<td>2.2 (1.7)</td>
<td>2.4 (3.0)</td>
<td>4.0 (2.1)</td>
<td>2.2 (2.1)</td>
<td>18.1 (3.5)</td>
<td>14.3 (2.1)</td>
</tr>
<tr>
<td>Chronic obstructive bronchitis</td>
<td>2.8 (2.8)</td>
<td>5.0 (3.0)</td>
<td>2.3 (2.3)</td>
<td>4.5 (3.6)</td>
<td>6.0 (3.0)</td>
<td>1.1 (2.5)</td>
<td>20.3 (4.0)</td>
<td>16.9 (4.8)</td>
</tr>
</tbody>
</table>

*Mean and standard deviation in parentheses; zero indicates number of patients with mean tracheal mucus velocity of 0 mm/min (no discs moved in a cranial axial motion) and motion those patients that had a mean value greater than 0 (all patients had some discs with no motion).
carboxymethylcysteine levels were similar among the three groups and were higher at two than three hours.

Discussion

In patients with chronic bronchitis, Edwards et al. reported that eight days and three months of treatment with S-carboxymethylcysteine in two separate trials effected a reduction in viscosity of morning sputum aliquots, improvement in the ability and ease of coughing up secretions, increase in sputum volume output, reduction in cough frequency, improvement of FEV₁, and lessening of dyspnea. The short-term results could not be confirmed by Thomson et al. who employed a similar experimental design. These authors found that mucociliary clearance measured by a radioisotopic scanning technique was not altered by S-carboxymethylcysteine. They further failed to demonstrate deeper penetration of the radioactive aerosol into the lung after treatment with S-carboxymethylcysteine, suggesting that the drug did not clear the smaller airways during the short treatment period. Finally, there was no significant difference between drug and placebo trials in the number of coughs or the weight of sputum raised at the end of the trial by chest percussion and postural drainage. The present study extends the observations of Thomson et al. in that we found the drug also failed to improve tracheal mucus transport in subjects in whom mucociliary clearance would be expected to be normal or minimally to moderately depressed, viz., normal subjects and smokers with small airway disease or patients with chronic simple bronchitis.

The roentgenographic method for following the velocity of radiopaque Teflon discs in the trachea does not depend upon distribution of particle deposition as does the rectilinear scanning of inhaled radioactive tracers. This ensures comparable baseline and test runs of mucus velocity. We measured tracheal mucus velocity two and three hours after drug administration; the plasma levels of the drug at two hours were higher than at three hours, which is in agreement with the manufacturer who observed similar results. Mucolytic agents fail to improve mucus transport in the airways of patients with chronic simple or obstructive bronchitis and in smokers with small airway disease who previously had zero mucus transport in the trachea measured by the movement of radiopaque Teflon discs when measurements were repeated every two to three minutes over a ten-minute period and hourly over a three-hour period on different days. Camner et al. also demonstrated a 50 percent incidence of zero or near zero clearance of radioactive aerosol over a two-hour period from the lungs of patients with chronic bronchitis. In the present study, observations of the trachea through the vocal chords revealed that discs deposited in both secretions on the mucosa of the trachea, as well as in areas that appeared devoid of excessive secretions, yet neither region showed transport of discs. Indeed, some discs deposited in the secretions slid down the trachea in our upright subjects and were considered to have zero motion. Such gravity-dependence of secretions has been noted previously in patients with cystic fibrosis.

Mucus transport is dependent upon optimum rheology and quantity of mucus and preservation of the ciliary apparatus. Absent particle transport could occur if any of these factors were impaired, but if ciliary activity were lost, improvement in characteristics of mucus would not be expected to increase transport. There have been no measurements of ciliary structure and function of the large airways simultaneously with measurements of transport, but destroyed or improperly functioning cilia together with stagnation of secretions have been observed in rats with chronic bronchitis.

Other oral agents purported to have a mucolytic or expectorant action have been studied for their effects upon mucociliary clearance by radioisotopic scanning techniques. Bromhexine (Bisolvon), a mucolytic agent administered for two weeks to smokers with chronic bronchitis, produced a slight but significant improvement in clearance, but the authors cautioned that clinical changes and smoking during the treatment period might have influenced the data between baseline and test runs. Guaiaphenesin (Robitussin), which is said to reduce tenaciously of sputum and diminish frequency of coughing, was administered as a single dose to both normal volunteers and patients with chronic bronchitis. There was no change in mucociliary clearance in normal subjects, but there was slight improvement noted in the patients. Initial particle penetration into the lung with placebo or guaiaphenesin was similar and bulk movement of mucus caused by coughing was less with guaiaphenesin since cough frequency decreased. However, no measurement was made of the effectiveness of cough.

We believe that tests should be designed for long-term objective measurement of effectiveness and frequency of cough in patients with abnormal bronchopulmonary secretions, since studies of mucociliary transport might not detect potentially beneficial effects of mucolytic agents, i.e. facilitation of expectoration of secretions.

References

1. Thomson ML, Pavia D, Jones CJ, et al: No demonstrable
4 A. H. Robins Company; Personal communication, 1977

Symposium on Hypoxia

The Arctic Institute of North America will present the Symposium on Hypoxia at Banff, Alberta, Canada, February 21-23. For information, contact Charles S. Houston, M.D., Chairman of the Symposium, at the Arctic Institute of North America, University Library Tower, 2920 24th Avenue, NW, Calgary, Alberta, Canada T2N 1N4.

25th New York Trudeau Society Annual Scientific Meeting

The 25th Annual Scientific Meeting of the New York Trudeau Society will take place in West Point, New York, February 3-4. For information, write Mr. W. Ray Williams, Executive Secretary, 8 Mountain View Avenue, Albany, New York 12205.

Clinical Cytopathology for Pathologists

The 20th Postgraduate Institute for Pathologists in Clinical Cytopathology will be given at The Johns Hopkins University School of Medicine and The Johns Hopkins Hospital, Baltimore, April 23-May 4. Application should be made before February 28. For details write: John K. Frost, M.D., 610 Pathology Building, The Johns Hopkins Hospital, Baltimore 21205.