The Effect of Inhaled Tiotropium Bromide on Lung Mucociliary Clearance in Patients With COPD*

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Study objective: To assess the effects of tiotropium on lung mucociliary clearance in COPD.
Design: Randomized, double-blind, placebo-controlled, parallel-group study.
Setting: Outpatients of an urban-area university teaching hospital.
Patients: Thirty-four patients with COPD aged 40 to 75 years classified equally into two groups.
Intervention: Single (18 μg) daily dose of tiotropium inhalation capsules or of placebo for 21 days.
Methods: Six-hour tracheobronchial clearance of inhaled 99mTc-labeled polystyrene particles using a 48-h retention measurement to determine the “nontracheobronchial” deposition fraction.
Results: Test radioaerosol penetration into the lungs increased significantly (p < 0.003) as did FEV1 (p < 0.006) in the tiotropium-treated patients, but measured mucociliary clearance was not significantly changed despite the increased pathway length for clearance (mean ± SE area under the tracheobronchial retention curve changed from 442 ± 22 to 453 ± 20%/h). Smaller (nonsignificant) decreases of radioaerosol penetration and FEV1 occurred in the placebo group together with a small (nonsignificant) decrease in the area under the retention curve.
Conclusion: Twenty-one days of inhaled tiotropium, 18 μg/d, as a dry powder does not retard mucus clearance from the lungs.

Key words: anticholinergic; COPD; mucociliary clearance; radioaerosol; tiotropium

Abbreviations: AD = alveolar deposition; AUC0–6 = area under the curve for the entire 6-h observation period; PEFR = peak expiratory flow rate; PI = penetration index

COPD is characterized by reduced expiratory airflow and by symptoms of cough, sputum production, and dyspnea. Cholinergic vagal tone has been claimed to be the major reversible component of airway narrowing in patients with COPD. Cholinergic mechanisms are also important in regulation of submucosal gland secretion, which is increased in COPD. Anticholinergics block muscarinic receptors on airway smooth muscle and possibly on submucosal gland cells. By blocking the activity of the receptors, the level of bronchoconstriction and mucus production is lessened. Anticholinergic agents have proved to be of particular value in the treatment of COPD, and have been recommended as first-line maintenance bronchodilator medication.

Tiotropium is a quaternary ammonium structure that is derived from that of ipratropium. This compound is a once-daily inhaled anticholinergic bronchodilator that exhibits long duration of action due to prolonged muscarinic receptor antagonism. Both single-dose and multiple-dose studies using 18 μg qd have confirmed a 24-h duration of action as assessed by spirometry. Studies on long-term effect of tiotropium have demonstrated maintenance of the bronchodilator benefits in patients with COPD.

Mucociliary clearance is a vital host defense mechanism of the airways that, together with cough, helps to keep the lungs clean even when exposed to a polluted environment. It is not clear what mechanisms regulate mucociliary clearance in response to airway stresses. However, data indicate that regulation of airway surface liquid by airway epithelia involves the reciprocal regulation of active Na+ absorption and Cl− secretion. Clearance is...
affected by a variety of factors, including lung diseases and pharmacologic agents. Historical evidence has suggested the possibility of clearance impairment from anticholinergic drugs, but this is not borne out by studies on newer compounds such as ipratropium and oxicromium bromide. These studies have agreed that there was no adverse effect on lung mucociliary clearance, and there was either direct or indirect possible evidence of stimulatory effect, which could be caused by changes in the volume of airway surface liquid. The purpose of the present study was to investigate what effects, if any, the administration of a long-acting anticholinergic compound such as tiotropium bromide may have on mucociliary clearance in patients with COPD.

MATERIALS AND METHODS

Study Design

This was a single-center, randomized, double-blind, placebo-controlled, and parallel-group study. Patients were asked to attend a screening visit to assess eligibility, at which time informed consent and blood samples were obtained, and a complete medical history and physical examination, which included BP and pulse rate, 12-lead ECG, and lung function, were assessed. Eligible patients entered a run-in period (2 to 7 days) during which patients measured their peak expiratory flow rate (PEFR) twice daily and recorded the use of rescue medication. Following this period, patients underwent a baseline mucociliary clearance assessment prior to randomization to treatment. Patients were randomly assigned to receive a single dose of either tiotropium (18 mg) dry-powder inhalation capsules or placebo lactose capsules once daily in the morning for a period of 21 ± 3 days. Capsules were packed in blister strips and administered using a dry-powder inhaler device (Handihaler; Boehringer Ingelheim; Germany). A final mucociliary clearance assessment was performed at the end of treatment period followed by another physical examination, ECG, and blood evaluation.

Throughout the study, patients completed a daily diary card to record intake of rescue medication together with their morning and evening PEFR (Personal Best Peak Flow Meter; Healthscan Products; Cedar Grove, NJ) and the time of inhalation of the study drug. Compliance was assessed from diary cards and number of treatment capsules being used. In order to obtain a subjective assessment of any possible adverse events, patients were asked on all visits how they had been since the previous visit. Patients were asked to count the number of rescue medication. The use of antibiotics, bronchodilators if taken at a stable dosage for at least 6 weeks prior to the screening visit and throughout the study, and beta-agonists was discontinued from at least 6 h and 48 h respectively prior to mucociliary clearance assessments. The use of short- and long-acting theophylline preparations were discontinued from at least 24 h and 48 h, respectively, prior to mucociliary clearance assessments. The study was approved by the Ethics Committee of the Royal Free Hospital, and all patients gave informed written consent.

Patients

We studied male and female patients between 40 years and 75 years of age with the diagnosis of COPD according to the definition of the American Thoracic Society. Patients were required to have relatively stable airway obstruction with FEV1 ≤ 30% and ≤ 65% of predicted normal and FEV1 ≤ 70% of FVC. Patients were also required to be smokers or ex-smokers with a history of > 1 pack-years, current smokers refrained from smoking for 1 h before and 6 h after radioaerosol inhalation. Patients with a history of bronchiectasis, cystic fibrosis, asthma, allergic rhinitis, or atopy, an elevated total eosinophil count, or a recent respiratory tract infection were excluded. Patients receiving regular daytime oxygen therapy or who had a significant disease other than COPD were also excluded.

Mucociliary Clearance

A noninvasive radioaerosol technique was used to provide objective measurements of lung mucociliary clearance before the first dose of treatment and immediately following the last dose of treatment. Using a spinning top generator, located within an airtight tank, polystyrene particles were generated at 5 μm diameter labeled firmly with the gamma-emitting radionuclide 99mTe. Patients wore a nose-clip and inhaled the radioactive aerosol particles through a mouthpiece, from a seated position, under strictly controlled conditions. Inhalation involved taking discrete breaths of 0.45 L from resting level of the lungs, followed by a 3-s breath-holding to enhance peripheral deposition of the radioaerosol particles by sedimentation within the lungs. Patients were not allowed to smoke for at least 1 h before radioaerosol administration, nor in the following 6 h.

Initial radioaerosol particle deposition in the lung and its subsequent clearance were measured by two scintillation detectors. The detectors were positioned, posteriorly and anteriorly to the chest, midway along the sternum. Gamma-radiation emitted by the inhaled particles, from most of both lungs, was measured by the collimated detectors and counts were recorded at 30-min intervals up to 6 h and then at 48 h. The residual background radioactivity in the lungs at 48 h (corrected for radioactive decay) was used to estimate alveolar deposition (AD), which was taken as the proportion of particles deposited in the nonciliated airways and therefore not available for mucociliary clearance. A tracheobronchial retention curve (also background and decay corrected) was generated by the subtraction of the alveolar deposition from the total lung burden.

The initial distribution of radioaerosol particles within the lungs was expressed as a penetration index (PI), which is the ratio of the amount of radioaerosol particles in an outer to inner region of the lungs divided by the same ratio of krypton gas (113mKr).

Data for PI measurement were acquired immediately after inhalation of radioaerosol particles, by using a large-field-of-view gamma camera.

During the 6-h observation period, patients were encouraged to avoid coughing, but in most instances they were unable to do so. Therefore, the patients were instructed to count the number
of involuntary coughs and collect any sputum sample produced in a separate pot. The sputum samples were weighed, and the radioactive content of each was determined. This radioactive content was expressed as a percentage of the initial tracheobronchial deposition and added back to the retention curves at the appropriate times of expectoration to account for the effect of productive coughing on mucus transport.36

Lung Function

The lung function of each patient was assessed during the screening visit and on the two mucociliary clearance assessment visits before inhalation of the radioaerosol. FEV₁, FVC, and PEFR were measured for each patient using a compact spirometer (Vitalograph; Buckingham, UK). For each lung function index, the highest of three technically acceptable measurements was recorded and expressed as a percentage of predicted normal value.37

Data Analysis

The data were not normally distributed, and statistical analysis was assessed using the nonparametric paired and unpaired Wilcoxon test. GB-STAT software (Dynamic Microsystems; Silver Spring, MD) was used for these analyses. Unless otherwise specified, data are presented as mean ± SE. The level of significance was taken as p ≤ 0.05.

Results

Patient Demographics

A total of 38 patients were randomized into the study, of whom 34 completed the study. One patient from the tiotropium group failed to complete due to an adverse event, shortness of breath. The other three patients had incomplete data acquisition (unable to attend for 48-h postinhalation radioaerosol assessment), two from the placebo group. The two treatment groups had reasonably matched demographics and baseline characteristics (Table 1), with the exception of tobacco consumption, which was higher (p < 0.07) in the tiotropium group.

The use of concomitant respiratory medication was higher in the placebo group (100%) than the tiotropium group (71%). Five patients in the tiotropium group were receiving no medication for their respiratory symptoms, while the rest of the group and those in the placebo group were receiving more than one therapeutic agent (Table 2). During the treatment period, the patients in the tiotropium group received a mean total of 2 puffs (range, 0 to 9 puffs) of rescue medication per day, compared to 4 puffs (range, 0 to 12 puffs) per day for the patients in the placebo group.

Both treatment groups recorded good compliance. All patients in both groups received study drug between 20 days and 23 days, except from two patients in the tiotropium group who received study drug for 25 days and 26 days, respectively. Patients in both groups reported receiving a mean of 21 capsules of study drug.

Mucociliary Clearance

AD was significantly increased (p < 0.008) in the group treated with tiotropium. The increase was observed in 14 of 17 patients. AD, although not significantly different, decreased in 11 of 17 patients in the placebo group (Fig 1). Posttreatment AD was significantly increased (p < 0.025) in the tiotropium group compared to the placebo group. PI was changed in both groups in a similar manner to AD. PI was significantly increased (p < 0.003) in the tiotropium treatment group compared to the placebo group (Table 3). Eleven of 17 patients showed an increased PI following treatment with tiotropium, compared to a decrease in 11 of 17 patients after receiving placebo.

Prior to treatment, the number of coughs during the 6-h observation period was significantly higher (p < 0.01) in the tiotropium group (mean, 27 ± 6; range, 0 to 80) compared with the placebo group (mean, 9 ± 2; range, 0 to 24). This difference per-

Table 1—Patient Characteristics and Baseline Lung Function*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Tiotropium (n = 17)</th>
<th>Placebo (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>67 ± 1</td>
<td>65 ± 1</td>
</tr>
<tr>
<td>Gender, No.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>Female</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Height, cm</td>
<td>167 ± 2</td>
<td>169 ± 2</td>
</tr>
<tr>
<td>Duration of COPD, yr</td>
<td>6.6 ± 1.7</td>
<td>4.5 ± 0.7</td>
</tr>
<tr>
<td>Smoking, pack-yr†</td>
<td>60 ± 10</td>
<td>44 ± 5</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>1.19 ± 0.11 (43 ± 2% predicted)</td>
<td>1.25 ± 0.10 (45 ± 3% predicted)</td>
</tr>
<tr>
<td>FVC, L</td>
<td>2.49 ± 0.20 (72 ± 4% predicted)</td>
<td>2.50 ± 0.18 (72 ± 5% predicted)</td>
</tr>
<tr>
<td>PEFR, L/min</td>
<td>203 ± 17 (46 ± 3% predicted)</td>
<td>217 ± 18 (49 ± 4% predicted)</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SE unless otherwise indicated.
†Seven ex-smokers in each group.
sisted after 21 days of treatment despite a nonsignificant decrease (19 ± 5; range, 0 to 80) in cough frequency in the tiotropium group and a nonsignificant increase (13 ± 3; range, 0 to 30) in the placebo group (Fig 2). The change in radioactive content of the expectorated sputum samples, which represents productive coughing, during the 6-h observation period was also not significant in both groups (Fig 3).

Figure 4 shows the mean tracheobronchial retention curves, corrected for productive coughing, for the tiotropium and placebo groups before and after treatment. Baseline clearance was significantly slower (p < 0.03) at 1 h after radioaerosol inhalation in the group who were subsequently treated with tiotropium compared with the group who were treated with placebo. Assessed in terms of AUC₀⁻₆, pretreatment and posttreatment mucociliary clearance was not statistically significant in both groups (Table 3).

Tracheobronchial retention curves uncorrected for cough were generally similar to the corrected curves; in particular, the uncorrected data also showed significantly slower (p < 0.04) baseline clearance at 1 h for the tiotropium as opposed to the placebo group together with no significant within-group changes when quantitated in terms of AUC₀⁻₆.

Table 3 also gives data for tracheobronchial retention at 6 h (both corrected and uncorrected for productive cough), again showing no significant changes within either the tiotropium or the placebo group. A between-group comparison of the changes relative to baseline, however, suggested a significant (p < 0.05) difference between the mean increase of 6-h uncorrected tracheobronchial retention in the tiotropium group and the mean decrease in the placebo group. This finding was not supported by any significant between-group differences for 6-h cough-corrected tracheobronchial retention or for AUC₀⁻₆ (corrected or not corrected for cough). Figure 3 demonstrates a further analysis of the 6-h retention clearance data; this is expressed in terms of clearance (100% – retention) terms rather than retention terms to facilitate comparison with the amount of clearance achieved (over the 6-h period) by productive cough. Because of the skewed distribution of the productive cough data (percentage of

Table 2—Pulmonary Medication Used by Patients in Both Groups*

<table>
<thead>
<tr>
<th>Concomitant Therapy</th>
<th>Tiotropium Group</th>
<th>Placebo Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salbutamol</td>
<td>7 (41)</td>
<td>14 (82)</td>
</tr>
<tr>
<td>Terbutaline</td>
<td>5 (29)</td>
<td>4 (24)</td>
</tr>
<tr>
<td>Ipratropium bromide†</td>
<td>6 (35)</td>
<td>8 (47)</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>3 (18)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Beclomethasone</td>
<td>3 (18)</td>
<td>9 (53)</td>
</tr>
<tr>
<td>Ipratropium bromide†</td>
<td>6 (35)</td>
<td>2 (12)</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>2 (12)</td>
<td>3 (18)</td>
</tr>
<tr>
<td>Aminophylline</td>
<td>4 (24)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Theophylline</td>
<td>1 (6)</td>
<td>1 (6)</td>
</tr>
</tbody>
</table>

*Data are presented as No. (%).
†Discontinued from 24 h prior to baseline mucociliary assessment until the end of study period.
tracheobronchial deposition recovered in sputum produced over the 0–6 h period), this figure is presented in box-plot form and a nonparametric statistical test (the Mann-Whitney test) was used. The between-group difference tested this way is statistically significant (p < 0.05). When, however, the data are split into cough-corrected ("mucociliary") clearance changes and cough-clearance (activity measured in sputum) clearance terms, no statistically significant between-group changes were detected.

In view of the significant effect of tiotropium in changing radioaerosol deposition, changes in the retention and clearance measurements were evalu-

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Tiotropium</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD, %</td>
<td>33 ± 3</td>
<td>29 ± 3</td>
</tr>
<tr>
<td>PI</td>
<td>0.61 ± 0.05</td>
<td>0.57 ± 0.03</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0&lt;/sub&gt;–&lt;sub&gt;6&lt;/sub&gt;, %/h (cough corrected)</td>
<td>442 ± 22</td>
<td>382 ± 29</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0&lt;/sub&gt;–&lt;sub&gt;6&lt;/sub&gt;, %/h (uncorrected)</td>
<td>412 ± 23</td>
<td>373 ± 28</td>
</tr>
<tr>
<td>Retention at 6 h, % (cough corrected)</td>
<td>63 ± 5</td>
<td>49 ± 6</td>
</tr>
<tr>
<td>Retention at 6 h, % (uncorrected)</td>
<td>53 ± 6</td>
<td>46 ± 2</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>1.14 ± 0.11</td>
<td>1.26 ± 0.10</td>
</tr>
<tr>
<td>FVC, L</td>
<td>2.49 ± 0.20</td>
<td>2.59 ± 0.18</td>
</tr>
<tr>
<td>Morning PEFR, L/min</td>
<td>208 ± 18</td>
<td>213 ± 15</td>
</tr>
<tr>
<td>Evening PEFR, L/min</td>
<td>207 ± 18</td>
<td>226 ± 18</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SE.

![Figure 2](image-url)  
**Figure 2.** Mean ± SE number of coughs during the 6-h observation period for both groups before and after treatment.
ated in relationship to deposition distribution (AD) changes. No significant relationship was detectable for the AUC₀–₆ data or for the cough-corrected data. However, taking both tiotropium and placebo groups together, a significant linear regression relationship (p < 0.05) was found—for uncorrected tracheobronchial retention changes—between the 6-h retention changes and AD changes (Fig 5). No significant relationship was detected within either the tiotropium or the placebo group on its own.

**Lung Function**

Pretreatment FEV₁ and FVC values did not differ significantly between the tiotropium and placebo groups. FEV₁ significantly increased (p < 0.006) fol-

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**Figure 3.** The change in tracheobronchial clearance at 6 h after radioaerosol inhalation and in productive coughing (represented by radioactivity of expectorated sputum) together with their difference (mucociliary).

**Figure 4.** Mean ± SE cough-corrected tracheobronchial retention curves for the two groups of patients who were treated with either tiotropium or placebo.
following treatment with tiotropium (Table 3). The evening PEFR was also significantly improved (p < 0.001) in the tiotropium group.

DISCUSSION

Bronchodilators are the mainstay of drug therapy for patients with COPD, with an increasing reliance on the effectiveness and convenience of long-acting formulations. A recent study has strongly argued that the potential benefit from a bronchodilator maintenance regime should be evaluated not just in terms of lung function but in terms of a more rounded assessment of health status. Relevant factors include symptoms of breathlessness and limitation of daily activities. We would argue that attention should also be paid to the lung defense mechanisms of cough and mucociliary clearance. It is generally accepted that maintenance of an adequate, albeit impaired, mucociliary defense can be important to the health status of patients with COPD. Excess mucus retention must be undesirable in the context of patients whose mucociliary transport system is already compromised. In addition, a badly impaired lung defense system may heighten the risks of infective exacerbations.

The combined effectiveness of mucociliary clearance and cough in maintaining relatively adequate airway patency depends on a complexity of interacting factors. Important among these are the volume and composition of the airway surface liquid and the effectiveness of the driving forces available to propel the mucus component of this liquid toward the trachea. Given this complexity and the need for successful interaction between driving forces and the airway mucus, consideration of the long-term implications of new pharmacotherapies for the mucus transport system should contribute to achieving a comprehensive profile of the effects of a new drug. Not least among the issues to be considered should be the relative roles of cough and of mucociliary transport per se.

Cough plays an important role in patients with COPD by clearing the excess mucus they so often produce and which exceeds the capacity of mucociliary transport on its own to clear. In this study, the number of coughs at baseline in the group of patients subsequently treated with tiotropium was markedly higher than in the patient group subsequently receiving placebo treatment. This indicates that patients in the tiotropium group were likely relying more on cough to get rid of excess mucus than were the patients in the placebo group. Although we attempt to draw a distinction between “mucociliary clearance” and “clearance-by-cough” (Fig 3), the data we rely on for assessing the contribution of cough (based on sputum radioactivity over the 0–6 h observation period) are essentially a surrogate for the true contribution of cough. Many cough events can help to propel mucus proximally within the airways without

![Figure 5. Relationship between the change in radioaerosol retention at 6 h after inhalation and the change in AD.](http://journal.publications.chestnet.org/pd fissu raccess.ashx?url=/data/journals/chest/22008/)
necessarily leading to any expectorated radioactivity. Nevertheless, we believe measured sputum radioactivity provides a useful demonstration of demonstrable clearance by the cough mechanism and can indicate when reliance on cough as a clearance mechanism seems to play a major mucus transport role. Our data are, we believe, consistent with the possibility of tiotropium treatment producing a relative shift from cough to mucociliary action. There was an encouraging decrease in cough frequency (a mean 27 coughs per 6 h falling to 19, a decrease of 30%) in the tiotropium group, when compared to the increase in the placebo group (a mean 9 coughs per 6 h rising to 13, an increase of 44%). We might speculate that a diminution of cough frequency, however small, may reduce reliance on cough as a clearance mechanism, perhaps reducing damage to airway ciliated epithelium. However, a much larger study with groups more closely matched for cough frequency will be required to confirm or deny this contention.

Current recommendations favor the use of anticholinergic drugs as opposed to sympathomimetics in the maintenance therapy of patients with COPD. Some evidence supporting this comes from a study comparing (over a 6-month period) the relative effectiveness of tiotropium and salmeterol. Given the general ability of anticholinergic drugs to affect cellular secretions, what relevant evidence is available as to the effects of present-day anticholinergic bronchodilators on lung mucociliary defense? The data on the whole are encouraging. Studies with ipratropium on the clearance of secretions from the lungs of healthy subjects and patients with airways obstruction have shown no evidence of mucus retention or retardation of mucociliary clearance. Similarly oxitropium has been reported to show no adverse effect on mucociliary clearance in patients with COPD. The present study extends this work by investigating the effect on mucociliary transport and cough of a long-acting anticholinergic tiotropium at a dosage appropriate to long-term therapy. A key factor to evaluate in analyzing our data on tiotropium is the relationship between test particle deposition and the subsequent time course of clearance. Any measure of the tracheobronchial clearance of deposited radioaerosol particles (AUC–6 or retention at 6 h, for example) inevitably depends on the sites of initial particle deposition in the lungs. The pattern of initial deposition is affected by the physical properties of the aerosol particles, the mode of aerosol inhalation and the patience of the patient’s airways. In this study, the physical properties and mode of inhalation of the aerosol particles were kept closely similar between the two groups. Airway patency, however, as indicated by the lung function data, was distinctly increased after tiotropium treatment. This caused a significantly increased proportion of radioaerosol particles to be deposited in more peripheral airways as shown by the increases in PI and AD. This should have resulted post tiotropium treatment in a substantial slowing of measured tracheobronchial clearance because of the longer average transit path along the ciliated airways for the deposited radioaerosol to be transported to the trachea. The effect of this increased transit path will have been further amplified by the fact that clearance through individual peripheral airway units is much shorter than through more proximal units. It is however admittedly difficult to express the deposition-clearance relationship in quantitative terms. Nevertheless, Figure 5 gives, semiquantitatively, an indication of the average trend for measured clearance to increase with increased peripheral deposition of the radioaerosol particles. It suggests that an increase of AD from, for example, 33% to 38% might be associated with an increase in 6-h retention from 53 to 59%.

Our study confirms the prolonged bronchodilator effect of tiotropium. Because effective bronchodilation led to deeper penetration of the radioaerosol, we conclude that the transit pathway for (labeled) mucus was lengthened, strongly suggesting that tiotropium does not adversely affect mucus transport, and may marginally enhance mucociliary transport efficiency.

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