Effect of inhalation of salbutamol, beclometasone dipropionate & ipratropium bromide on mucociliary clearance in some patients with chronic stable bronchial asthma


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Background & objectives: Asthma is now regarded as an inflammatory disease and bronchial inflammation may disrupt mucociliary function. Inhaled drugs may act by improving mucociliary function. The aim of the study was to investigate the effect of salbutamol, ipratropium bromide and beclometasone on mucociliary clearance in patients with chronic stable asthma and to compare the efficacy of these drugs on mucociliary clearance.

Methods: Ten patients with chronic stable asthma were enrolled in the study, but two patients did not complete the study. Patients with bronchial asthma were chosen on clinical grounds. 99mTc phytate radioaerosol generated through a nebulizer, was given to each patient on four days. After each administration the radioactivity over the thorax was constantly measured in sequential frame mode for 120 min. Radioactivity in the thorax was also measured after 24 h. A base-line pulmonary function test with reversibility was obtained. Salbutamol, ipratropium bromide, beclometasone dipropionate and placebo inhalation were given randomly to each patient on four days.

Results: The mean age of patients (n=8) was 36±9.3 yr and mean duration of symptoms was 5±6.6 yr. There was no visual impression that mucociliary clearance was enhanced with any of the drugs. The time activity curves did not show any visually recognisable change in slope. In only one patient the curve tended to show a steeper slope with ipratropium inhalation. In the rest of the patients the curves showed no difference at all with medication when compared with placebo. All the quantitative indices analyzed by two-way ANOVA at the end of one and two hours were comparable for the three test drugs and placebo. None of the three test drugs demonstrated statistically significant mucociliary clearance effect compared with placebo. However, the temporal difference in airways clearance efficiency (ACE) was significant with beclometasone and ipratropium bromide.

Interpretation & conclusion: Inhalation of any of the three drugs tested did not produce any immediate improvement in mucociliary clearance as compared to placebo in patients with stable bronchial asthma suggesting the need for further studies using higher doses of drugs for longer duration in a large sample.

Key words Beclometasone dipropionate - bronchial asthma - ipratropium bromide - mucociliary clearance - radioaerosol - salbutamol

Mucociliary clearance is one of the most important defenses of the respiratory tract for the removal of inhaled particles, endogenous cellular debris, and excess secretions from the
The effect of pharmacological agents on the clearance of airways secretions has been debatable. Whether $\beta_2$ agonists increase mucociliary clearance in the lungs in vivo is still an unanswered question as studies undertaken are few and the results are conflicting\textsuperscript{2-4}.

Similarly the effect of anti-inflammatory agent on mucociliary clearance is not known. It is presumed that bronchial inflammation may disrupt mucociliary function. It is also possible that increased bronchial inflammation and decreased mucociliary clearance may interact and be mutually exacerbating. Steroid therapy in bronchial asthma helps in recovery by bringing about the resolution of airway inflammation. Oral glucocorticoid therapy has been documented to improve peripheral airways mucus clearance in stable asthma\textsuperscript{5}. The effect of inhaled steroids on mucociliary clearance is unclear and needs evaluation.

Ipratropium bromide, an anticholingergic drug, has been used effectively in the treatment of stable bronchial asthma. One study\textsuperscript{6} has demonstrated facilitated clearance following the administration of the drug in healthy subjects. Its effect on mucociliary clearance in bronchial asthma has also been investigated\textsuperscript{7,8}. The present study was undertaken to evaluate the effect of $\beta_2$ agonist (salbutamol), anticholinergic drug (ipratropium bromide) and steroid (beclomethasone) inhalation on mucociliary clearance in patients of stable bronchial asthma.

**Material & Methods**

Ten patients with chronic stable asthma attending the Medicine outpatients Department and Chest Clinic of the All India Institute of Medical Sciences (AIIMS), New Delhi were enrolled for the study; two patients did not complete the study. The sample was a sample of convenience. Each patient underwent 4 studies on 4 days with a 24h follow up recording. A total of 36 studies was done. As there were resource constraints and each patient work up was quite exhaustive only 10 patients were studied. The study was conducted during 1995 to 1997. Patients with bronchial asthma were chosen on clinical grounds. They included non smoking adults with paroxysms of dyspnoea, wheezing and cough, who improved with drug therapy. Chronic stable asthma was defined as patients who were symptom free, had not had a paroxysmal dyspnoic attack for at least 6 wk prior to the study and were on minimum maintenance bronchodilators. Patients with associated right ventricular failure, arrhythmia, valvular disease \textit{etc.}, and those with respiratory failure and associated acute illness such as febrile illness and acute respiratory tract infection were excluded from the study.

Written informed consent for participation in the study was obtained from all the patients. Details of the patients including age, sex, weight, height, history of dyspnoea, cough, wheezing and smoking habits and treatment were recorded. The findings of physical examination were also recorded in a proforma. A chest X-ray was obtained. Patients were advised to stop all the drugs 12 h before the study which was carried out on outpatient basis. Routine spirometry was done with an electronic rolling seal spirometer (PK Morgan, UK). Salbutamol (100 µg/puff), ipratropium bromide (20 µg/puff), beclomethasone dipropionate (100 µg/puff) and placebo inhalation were given to each patient at random on four separate days.

**Radioaerosol inhalation lung cine-scintigraphy:** This was done in the Department of Nuclear Medicine as follows. After a preliminary physical examination on day one to make sure that the patient did not have symptomatic bronchospasm, the patient was made to sit comfortably in a chair and relax for 10 min. $^{99m}$Tc phytate radioaerosol generated through BARC (Bhaba Atomic Research Centre, Mumbai) nebuliser was given through a mouth piece during resting tidal volume breathing. The radioaerosol solution used contained 20 mci of radioactivity (half life of $^{99m}$Tc is 6 h). The size of aerosol produced by the BARC nebuliser was 0.84 micron in activity median aerodynamic diameter (AMAD) with a geometric standard deviation of 1.73. Patients were asked to inhale the aerosol for about 3 min so that about 2 mci \textit{i.e.}, one-tenth of the total preparation was deposited inside the thorax. Immediately after this, the patient was given a puff of the test medication from a meter dose inhaler.
approximately at mid lung volume while performing a slow inspiration from functional residual capacity to total lung capacity in the same sitting position. About 10 sec of breath holding was observed after complete inhalation. The manoeuvre was repeated twice over one minute or so with some quiet breath intervals. Care was taken to see that the proper technique was used while the inhaler was used. Placebo inhaler was used before the procedure to ensure adequate inhalation technique.

The patient was then immediately made to lie comfortably in the supine position on the examination table under the Gamma camera. Radioactivity in the thorax was continuously measured in sequential frame mode from anteriorly for 120 min. A total of 120, 60-second frames were stored in the computer. At the end of the recording period, a static emission image was obtained. During the procedure aerosol deposition patterns in the lungs were inspected and, for quantitative analysis the 120 frames were sequentially divided into 8 parts, each representing a sequential 15 min process consisting of 15 original frames. These sequential 15 frames were combined to make one frame. Thus eight new frames were made out of 120 frames in all. Radioactivity in the first new frame covering the initial 15 min after radioaerosol inhalation was the basis for the subsequent calculation and comparison. The patient was called the next day to measure the radioactivity that remained in the thorax at the end of 24 h to find the alveolar deposition ratio.

**Data analysis**: Following correction for background radioactivity and after obtaining a physically half-life corrected time activity curve from the right lung, visual inspection of the time activity curve was done and the following quantitative parameters to assess mucociliary clearance were calculated for each 15 min period for the ciliated airways in the right lung. The left lung was excluded because of possible contamination of radioactivity from the stomach. Considering

\[
A = \text{Radioactivity in the extrapulmonary ciliated airway at time } t.
\]

\[
B = \text{Radioactivity in the intrapulmonary ciliated airways at time } t.
\]

\[
C = \text{Radioactivity in the poorly ciliated or non ciliated airways and/or the alveoli.}
\]

\[
T = \text{Total radioactivity.}
\]

Total radioactivity at ‘o’ time, \(To = A_0 + B_0 + C_0\)

In actual calculation the radioactivity in the compartment A was not taken into consideration by obviating measurement of radioactivity in the mediastinal portion. In this case, \(To = B_0 + C_0\).

Because the radioactivity in the alveolar compartment is not cleared, the radioactivity remaining in the lungs at 24 h is defined as the alveolar deposition, \(C_0\) should be equal to \(C_t\) at 24 h.

Hence, the equation is \(To = B_0 + C_0 = B_0 + C_t\)

The various parameters to evaluate intrapulmonary mucociliary clearance are shown in Table I.

**Statistical methods**: The data were recorded in a pre designed proforma and managed on an excel worksheet. All the entries were checked for any error. The quantitative variables were assessed for approximate normality and these were summarized by mean and standard deviation in each group. After checking the variance stability and normality, two-way analysis of variance (ANOVA) was used to compare mean values of quantitative variables between the main effects of drug groups and the time and drug interaction. Since the change in the cine-scintigraphic quantitative parameters was not normally distributed, Kruskal wallis one-way ANOVA followed by Wilcoxon rank sum test with Bonferroni correction were used to compare the various parameters in groups. In this study, \(P < 0.05\) was considered as statistically significant.

**Results**

**Demographic profile**: Of the 10 patients included, 8 (5 males and 3 females) completed the study. The mean age was 36±9.3 yr; all were non smokers, and mean duration of symptoms were 5±6.6 yr. The pulmonary function test showed mean FVC 83±19.8 per cent of predicted, mean FEV\(_1\) 66.2±25.3 per cent of predicted and FEV\(_1\)/FVC per cent was 79.3±20.2.
There was no visual impression that mucociliary clearance was enhanced with any of the drugs. Time activity curves – The time activity curves did not show any visually recognisable change in slope. In one patient the curve tended to show a steeper slope with ipratropium. In the rest of the patients the curves showed no difference when compared with those of placebo or the other drugs.

Quantitative indices – All the quantitative indices analysed by two-way ANOVA at the end of one and 2 h in asthmatic patients were comparable for placebo and the three test-drug (Table II). However, the temporal differences in all parameters were significant with beclomethasone and ipratropium bromide (Table III).

Discussion

The study is largely comparable in methodology to those by Isawa et al\cite{9,10} and Lafortuna et al\cite{4}. We did continuous recording of radioaerosol clearance for the test period to alleviate any discrepancies in the result that might arise from repositioning of the patients before the Gamma camera. Also, unlike the previous workers\cite{4,9,10} we examined the clearance effect on a separate day with the placebo. This was based on the assumption that giving placebo and test drug on the same day would take a longer time and hence there was a greater chance of getting an error due to inadvertent movement of the patient. Secondly, as there were three test drugs the whole study consisting of the combination of test drug and placebo would have become more cumbersome.

Mossberg et al\cite{11} found that tracheobronchial clearance of rapidly inhaled 99m Tc-labelled Teflon particles in patients with asthma was the same as that in healthy non smokers. Foster et al\cite{12} however noted considerable reduction in the mucus clearance and tracheal mucus velocity in asthmatic patients with symptoms; while Bateman et al\cite{13} showed that mucociliary clearance was significantly poor in asthmatics than in the healthy control groups. Pavia et al\cite{14} and Pakes et al\cite{15} also found impaired mucociliary clearance in asthmatics both in mild, stable disease and in remission, relative to normal volunteers. The degree of impairment of the mucociliary clearance may be related to the degree of severity of the asthmatic attack although cause or effect could not be established. These studies suggest that impairment of mucociliary clearance occurs in stable asthmatics and it possibly increases as the disease worsens.

Table I: Various parameters to evaluate intrapulmonary mucociliary clearance

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>LRR (%)</td>
<td>( \text{LRR} = \frac{\text{To} - \text{Tt}}{\text{To}} \times 100 )</td>
</tr>
<tr>
<td>ADR (%)</td>
<td>( \text{ADR} = \frac{\text{Bt} - \text{Co}}{\text{To}} \times 100 )</td>
</tr>
<tr>
<td>ARR (%)</td>
<td>( \text{ARR} = \frac{\text{Bo} - \text{Bt}}{\text{Bo}} \times 100 )</td>
</tr>
<tr>
<td>ACE (%)</td>
<td>( \text{ACE} = \frac{\text{Bo} - \text{Bt}}{\text{Bo}} \times 100 )</td>
</tr>
<tr>
<td>AIDR (%)</td>
<td>( \text{AIDR} = \frac{\text{Co}}{\text{To}} \times 100 )</td>
</tr>
</tbody>
</table>

LRR, lung retention ratio; ADR, airway deposition ratio; ARR, airway retention ratio; ACE, airways clearance efficiency; AIDR, alveolar deposition; Tt, amount of radioactivity in the lung at time 't'; To, total amount of radioactivity initially deposited in lung; Bt, amount of radioactivity present in pulmonary ciliated airways i.e., at time t; Bo, amount of radioactivity initially deposited in pulmonary ciliated airways i.e., at time O; Co, amount of radioactivity initially deposited in non ciliated alveolar space i.e., at time O.

Radioaerosol inhalation lung cine scintigraphy: There was no visual impression that mucociliary clearance was enhanced with any of the drugs.

Time activity curves – The time activity curves did not show any visually recognisable change in slope. In one patient the curve tended to show a steeper slope with ipratropium. In the rest of the
It is unclear from the literature whether mucociliary clearance increases with inhaled medication. Studies of the effect of salbutamol on mucociliary clearance in bronchial asthma are limited. In 1986 Isawa et al demonstrated a minimal but significant bronchodilatation followed 7 days treatment with oral salbutamol, but the treatment did not induce any recognisable changes either in the deposition pattern of inhaled aerosol or in mucociliary clearance. Mortensen et al demonstrated significantly increased mucociliary clearance in asthmatics and healthy subjects. They however found no benefit with a dry powder inhaler. We did not find any significant improvement with salbutamol inhalation in the present study.

Previous studies on the effect of the ipratropium bromide on mucociliary clearance in healthy subjects and in patients with bronchial asthma have also not shown any significant change. In humans ipratropium is believed not to alter the volumetric and rheologic properties of secretions and it is believed that it does not adversely affect their clearance from the lungs. In our study we failed to show improved mucociliary clearance with 40 µg of ipratropium. In only one patient was a steep slope in the time activity curve observed which may not be considered significant because none of the other patients showed any difference in the curves when compared with those of placebo and the other drugs. Perhaps studies on larger number of patients with higher dose of ipratropium might be more indicative.

Corticosteroids, by virtue of their ability to suppress inflammation, are acknowledged to play a major role in the management of asthma. It has been suggested that the steroids may improve the mucociliary clearance in patients with airway disease. However, studies are very limited. The

<p>| Table II. Radioaerosol lung cine scintigraphic quantitative parameters in bronchial asthma of patients at 1 and 2 h |</p>
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Salbutamol</th>
<th>Beclomethosone</th>
<th>Ipratropium</th>
</tr>
</thead>
<tbody>
<tr>
<td>LRR 1st h</td>
<td>87.16±11.00</td>
<td>82.4±11.89</td>
<td>85.08±11.75</td>
<td>86.6±9.94</td>
</tr>
<tr>
<td>2nd h</td>
<td>75.66±17.54</td>
<td>69.57±18.63</td>
<td>74.98±15.49</td>
<td>76.95±13.08</td>
</tr>
<tr>
<td>ADR 1st h</td>
<td>50.66±20.30</td>
<td>42.87±24.30</td>
<td>52.66±17.36</td>
<td>51.72±23.19</td>
</tr>
<tr>
<td>2nd h</td>
<td>39.4±18.27</td>
<td>29.9±21.60</td>
<td>39.88±15.42</td>
<td>44.88±23.05</td>
</tr>
<tr>
<td>ARR 1st h</td>
<td>78.58±6.21</td>
<td>69.08±25.75</td>
<td>80.38±10.90</td>
<td>79.6±9.77</td>
</tr>
<tr>
<td>2nd h</td>
<td>63.97±20.74</td>
<td>47.75±26.51</td>
<td>63.47±13.93</td>
<td>65.68±13.30</td>
</tr>
<tr>
<td>ACE 1st h</td>
<td>21.42±16.22</td>
<td>34.61±25.65</td>
<td>19.61±10.90</td>
<td>20.38±9.77</td>
</tr>
<tr>
<td>2nd h</td>
<td>35.92±20.86</td>
<td>51.00±24.55</td>
<td>36.52±13.93</td>
<td>34.43±13.29</td>
</tr>
</tbody>
</table>

LRR, lung retention ratio; ADR, airway deposition ratio; ARR, airway retention ratio; ACE, airway clearance efficiency
All values are in percentage. Values are shown as mean±SD (n=8)

<p>| Table III. Change in radioaerosol lung cine scintigraphic quantitative parameters from 1st to 2nd h |</p>
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Salbutamol</th>
<th>Beclomethosone</th>
<th>Ipratropium</th>
</tr>
</thead>
<tbody>
<tr>
<td>LRR 1st h</td>
<td>11.5±15.8</td>
<td>12.8±17.1</td>
<td>10.1±12.4*</td>
<td>9.6±12.2*</td>
</tr>
<tr>
<td>2nd h</td>
<td>11.2±15.3</td>
<td>12.8±32.3</td>
<td>6.8±11.6*</td>
<td>6.8±11.6*</td>
</tr>
<tr>
<td>ADR 1st h</td>
<td>-4.7±23.1</td>
<td>21.3±33.3</td>
<td>16.9±11.7*</td>
<td>13.2±10.1*</td>
</tr>
<tr>
<td>2nd h</td>
<td>-14.5±23.1</td>
<td>-16.3±29.9</td>
<td>-16.9±11.7*</td>
<td>-14.1±10.2*</td>
</tr>
</tbody>
</table>

*P<0.05; LRR, lung retention ratio; ADR, airway deposition ratio; ARR, airway retention ratio; ACE, airway clearance efficiency
Values are shown as mean±SD (n=8)
antigen induced fall in tracheal mucus velocity was prevented when budesonide was given in experimental animals. It has also been suggested that a delayed improvement in mucociliary clearance in response to oral glucocorticoid therapy may occur. This is supported by the study of Agnew et al.

In conclusion, salbutamol, ipratropium bromide and beclomethasone inhalation did not show any immediate improvement in mucociliary clearance over placebo in patients with stable bronchial asthma. It is possible that long-term use may improve mucociliary clearance. Further studies using higher doses of drug for longer durations and on a larger number of patients are required.

References


