Effect of ipratropium bromide on mucociliary clearance and pulmonary function in reversible airways obstruction

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ABSTRACT The effects of (a) regular use for one week and (b) a single dose of a synthetic anticholinergic (ipratropium bromide) on lung mucociliary clearance and as a bronchodilator was ascertained in a controlled, double-blind, cross-over study in 12 patients with reversible airways obstruction (mean increase in FEV₁, after isoprenaline: 17%, range 10–50%). Two puffs from a metered dose inhaler of either placebo (propellants only) or drug (40 ,ug) were administered four times a day for one week (regular use), and mucociliary clearance was measured, by radioaerosol tracer, at the end of each treatment period and after a control period in which no treatment was given. On the mornings of the measurements after the placebo and drug periods one final dose (single dose) of ipratropium (40 ,ug) or placebo was given 2-5 hours before the start of the test. There was no statistically significant difference between the three mean mucociliary clearance curves (control, placebo, and drug) for the group; however, there was a significantly greater penetration towards the periphery of the lung of the tracer in the test after drug administration compared with the other two. This increased penetration was attributed to bronchodilatation caused by the drug. Ipratropium bromide does not appear to impair mucociliary clearance, and it acts as an effective bronchodilator.

Impairment of lung mucociliary clearance has been observed in man after administration of the anticholinergic drugs hyoscine (Pavia and Thomson, 1971) and atropine (Foster et al, 1976). Ipratropium bromide, chemically a quarternary ammonium compound, is a synthetic anticholinergic agent. It is known to be an effective bronchodilator (Poppius et al, 1972). In healthy volunteers Francis et al (1977) have shown that this agent did not impair mucociliary clearance for inhaled doses up to four times the recommended therapeutic dose (40 ,ug). We report a controlled, double-blind cross-over study to ascertain the effect of (a) regular use (40 ,ug four times daily for seven days) and (b) a single dose (40 ,ug) of ipratropium bromide (and of the propellants) on lung mucociliary clearance and on bronchodilatation in 12 patients with reversible airways obstruction of 10% of baseline FEV₁ or greater were studied. Table 1 summarises their physical characteristics, tobacco consumption, and ventilatory function. Informed, written consent was obtained from each patient. Ten had chronic obstructive bronchitis and two had in addition clinical features of asthma. Six of the patients were current smokers and the remaining six ex-

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Results (mean ± SD)</th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>63±8</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1·68±0·09</td>
</tr>
<tr>
<td>Tobacco consumption (pack years)</td>
<td>64±30</td>
</tr>
<tr>
<td>FEV₁ observed (l)</td>
<td>1·14±0·50</td>
</tr>
<tr>
<td>FEV₁% predicted*</td>
<td>42±15</td>
</tr>
<tr>
<td>FVC observed (l)</td>
<td>2·70±0·62</td>
</tr>
<tr>
<td>FVC% predicted*</td>
<td>76±22</td>
</tr>
<tr>
<td>FEV₁/FVC observed (%)</td>
<td>41±11</td>
</tr>
<tr>
<td>PEFR observed (l/min⁻¹)</td>
<td>163±70</td>
</tr>
<tr>
<td>PEFR% predicted*</td>
<td>34±16</td>
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</table>

*Cotes (1975).
smokers. The diary cards showed that the level of tobacco consumption of the current smokers remained constant throughout the study.

The type of sputum produced by the patients during the clearance measurements was graded macroscopically according to the Medical Research Council (1965) criteria as follows: M1 (mucoid, white) in two patients; M2 (mucoid, white with a hint of yellow) in six patients; P1 (purulent, less than one-third yellow) in two patients; and P3, (purulent, more than two-thirds yellow) in the remaining two patients. The patients' mean (±SD) percentage changes in forced expiratory volume in 1 sec (FEV₁) from baseline values after inhaling two puffs of isoprenaline (1 mg) was 17 (±15%).

**EXPERIMENTAL DESIGN**

All treatment was discontinued for one week (washout period) before the first mucociliary clearance measurements and throughout the three weeks' trial period. Control measurements were performed after the washout period and then, in a random, double-blind manner, each of the patients was allotted placebo or drug treatment, half receiving each treatment first. The placebo consisted of propellants only; Freon 11, 12, and 114 in proportions 1 : 2 : 1, plus soya lecithin surfactant. During the next seven days the treatment aerosols were self-administered from metered dose inhalers (dose: two puffs=40 μg of ipratropium bromide) four times a day at 0800, 1200, 1600, and 2000.

The clearance measurements after placebo and drug were identical to the control determination, with the exception that final doses of both aerosols were inhaled about 2-5 hours before the inhalation of the radioaerosol.

The daily tobacco consumption (cigarettes a day) and the graded degree of shortness of breath and sputum production were recorded on a diary card by each patient daily for each of the three weeks. Peak expiratory flow rates (PEFR) on awakening (before treatment) and on retiring at night (two hours after last treatment) were also recorded on the cards.

Before the trial began patients underwent a two-day pilot study to ascertain that they responded to the bronchodilator action of the drug. In a double-blind, cross-over manner each of the 12 patients was allotted two puffs of placebo (propellants only) or drug at the same time of the day on two successive days. Their FEV₁, FVC, and PEFR were ascertained immediately before and after administration of the two puffs, and then at 15, 30, 60, and 120 minutes. After this period the patients were administered two puffs of isoprenaline (1 mg), irrespective of whether they were on placebo or drug, and its effect on the above lung function tests was measured. This established whether, at this time, their airways obstruction was maximally reversed by the ipratropium bromide.

**MEASUREMENT OF LUNG CLEARANCE BY RADIOAEROSOL**

The method has been fully described by Thomson and Short (1969) and Thomson et al (1973). Uniform 5 μm polystyrene particles were generated by a spinning disc (May, 1949) in an airtight tank, from which they were inhaled through the mouth by the seated patients. Inhalation (from the normal resting level of the lung) was automatically interrupted after a preset volume (here 0·45 l) and was followed by an obligatory three-second breath holding pause. The mean of the individual average inhalation flow rates, recorded by a pneumotachograph, were 33, 32, and 35 l/min for the control, placebo, and drug runs respectively. There were no statistically significant differences in this variable between any of the three runs. The particles were firmly labelled with 99m-technetium (Few et al, 1970), a gamma emitter of 6 h half-life, as tetraphenylarsonium pertechnetate. The initial lung burden did not exceed 30 μCi of 99mTc in any one run. The patients rinsed their mouths three times, and drank half a cup of water immediately after inhalation of the radioaerosol to remove any particles present in the oropharyngeal region and oesophagus. Clearance of the radioaerosol from the lungs was monitored by two opposing scintillation detectors (NaI(Tl) crystals) suitably collimated (Thomson and Pavia, 1973). The anterior detector was applied closely to the midpoint of the sternum, and the posterior one to the spine axially opposite. Counts were taken for 100 s immediately after inhalation and at half-hourly intervals over six hours, and were corrected for radioactive background and decay.

The initial distribution of the deposited radioaerosol across the right lung was determined by means of a rectilinear gamma scanner (Dawson et al, 1971). The detector traversed vertical columns at 2·5 cm intervals from the chest midline to the periphery. The detector was collimated by a cylindrical lead shield (2·5 cm internal diameter), which was extended 5 cm beyond the crystal face. The radioactive count for each traverse was displayed on a printer.

The times of all coughs were noted, all sputum was collected as separate samples, and the total weight and radioactive content of the samples was ascertained for each clearance measurement.
The patients did not smoke during the six-hour observation period, or for one hour before.

PULMONARY FUNCTION TESTS
The FEV₁ and FVC were measured by a dry bellows spirometer (Vitalograph) and the PEFR by a Wright peak flow meter. Throughout this study the highest reading was recorded out of three attempts for any one variable.

STATISTICAL ANALYSIS
The data of the variables measured in this study were not normally distributed, so the Wilcoxon test for pair differences (Snedecor and Cochran, 1968) has been used.

Results

PULMONARY FUNCTION TESTS
Figure 1 summarises the changes of the pulmonary function tests in the pilot study. The figure illustrates the mean values over a 120-min observation period of (a) PEFR, (b) FVC, and (c) FEV₁ after two puffs of ipratropium bromide (40 µg) or placebo and after two puffs of isoprenaline (1 mg) given at 123 min. There was no statistically significant difference between the mean baseline values for any of the three variables. From 15 min after inhalation onwards, however, all three variables were significantly higher (P<0-01) after ipratropium bromide compared with placebo. Administration of isoprenaline resulted in a striking increase in all three variables after placebo, but no change was noted after ipratropium.

From the diary cards it was ascertained that the mean (± SD) PEFRs in the mornings were 152 (±49), 148 (±49), and 161 (±61) l/min in the control, placebo, and drug treatment periods (seven days) respectively. The mean PEFR in the drug period was significantly higher than that during administration of placebo (P<0-05). The mean (± SD) late evening PEFRs were 162 (±60), 156 (±47), and 186 (±84) l/min for the control, placebo, and drug periods respectively. Here the PEFRs in the drug treatment period were statistically significantly higher than those in both the control (P<0-01) and placebo (P<0-05) periods.

Pulmonary function was assessed about 1-5 hours before inhaling the radioaerosol in each of the three administrations (table 2), that is, about one hour after the final dose of aerosol was inhaled after drug and placebo administration.

Both the FEV₁ and FVCs were significantly higher on the days after administration of the drug compared with either the control or placebo days. The PEFRs, however, were only significantly higher on the drug days compared with the control days.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Mean ± SD, FEV₁ and PEFR for 12 patients on the control, placebo, and drug mucociliary clearance measurements days</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁ (l)</td>
<td>FVC (l)</td>
</tr>
<tr>
<td>Control</td>
<td>1-14±0-50*</td>
</tr>
<tr>
<td>Placebo</td>
<td>1-16±0-64‡</td>
</tr>
<tr>
<td>Drug</td>
<td>1-40±0-70*‡</td>
</tr>
</tbody>
</table>

Paired differences statistically significant at the 5%*, 2%†, and 1%‡ levels.
LUNG SCANS
Figure 2 shows the initial lateral distribution of the radioaerosol across the right lung for the 12 patients on the control, placebo, and drug clearance measurement days. The counts in each traverse have been expressed as a percentage of the total scan count for each individual, and the mean percentage of all patients are shown as the height of the columns in fig 2. An index of penetration (Thomson and Pavia, 1974) has been used as a quantitative measure of the initial topographical distribution of the radioaerosol. This is obtained from the ratio of the sums of the counts of the outermost two traverses (nearest to the periphery) to those of the two innermost. The mean ± SD ratio for the drug runs, 0·75 ± 0·41, was significantly higher than that for the control runs, 0·41 ± 0·23 (p<0·01) and placebo runs, 0·55 ± 0·23 (p<0·05).

LUNG CLEARANCE
Figure 3 shows the mean (n=12) clearance curves from whole lung counts at half-hourly intervals for the control, placebo, and drug runs. The mean six-hour retention values are in accord with the mean penetration indices—that is, the greater the penetration index (0·75 for the drug) the greater the six-hour retention value and vice versa, the smaller the penetration index (0·41 for the control) the smaller the six-hour retention value.

Figure 4 shows the 12 individual paired differences for the amount of radioaerosol retained at six hours as a percentage of that initially deposited in the lungs between (a) control and drug runs and (b) placebo and drug runs. The mean (± SD) retentions were 62 (±21) %, 65 (±22) %, and 68 (±17) % for the control, placebo, and drug runs respectively. There was no statistically significant difference (p>0·10) between any of the three runs. A comparable analysis at two and four hours showed the same result.

SUBJECTIVE ASSESSMENT, COUGH, AND SPITUM DATA
The diary cards kept by the patients showed no difference in the severity of breathlessness during
Effect of ipratropium bromide in mucociliary clearance pulmonary function

While one recent study (Chopra and Elam, 1978) claims enhancement of mucociliary transport rates in dogs after administration of atropine, others have shown impairment of clearance of secretions from the human lung by the anticholinergic agents hyoscine (Pavia and Thomson, 1971) and atropine (Yeates et al, 1975; Annis et al, 1976; Foster et al, 1976). The impairment of the clearance is attributed either to the drying of secretions (Lopez-Vidriero et al, 1975) or impairment of ciliary beat (Corrson and Allen, 1959). It may of course be due to a combination of these two effects. This property of impairing clearance of secretions led to the anticholinergic drugs, the bronchodilating effects of which have been known for many years (Goodman and Gilman, 1940), being considered unsuitable for the relief of airway obstruction. Since secretions may add to airflow obstruction (Cochrane et al, 1977), retention is undesirable.

Ipratropium bromide is a synthetic anticholinergic agent, developed specifically to relieve airways obstruction by bronchodilatation, but to be without the undesirable side effects of other anticholinergic drugs (Engelhardt and Klupp, 1975). Using isolated canine airways preparations, Iravani and Melville (1975) noted that ipratropium bromide exhibited only a mild depressant effect on ciliary beat frequency, which was not dose-related. The bronchodilator action of ipratropium bromide in bronchitic patients, without any change in volume or rheology of secretions, has been reported by several workers (Krieger and Reitberger, 1975; Puchelle and Uffholtz, 1975; Stresemann, 1975). Francis et al (1977) showed significant bronchodilatation using the whole body plethysmograph after the administration of this agent to 12 normal subjects, in single doses up to four times the recommended therapeutic dose (that is, $4 \times 40 \, \mu g$), with no impairment of mucociliary clearance. In an earlier study on patients with mild obstructive bronchitis and healthy volunteers Matthys et al (1975) using a similar technique to that used here also reported no impairment of mucociliary clearance after bronchodilatation with ipratropium bromide. Their results are to some extent questionable since the drug (0-1 mg) was nebulised with sodium chloride solution. Any possible impairment of lung clearance attributable to the drug could have been reversed by the inhalation of the saline aerosol (Pavia et al, 1977c, 1978; Wood et al, 1977).

The purpose of the present study was to ascertain the effect of ipratropium bromide on the

Table 3  Mean ± SD for 12 patients of number of coughs and sputum weight, radioactive content, and specific activity observed during the six-hour clearance measurements

<table>
<thead>
<tr>
<th></th>
<th>No of coughs</th>
<th>Sputum weight (g)</th>
<th>Sputum radioactive content $10^7$ gamma counts</th>
<th>Sputum specific activity $10^5$ gamma counts g$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>49 ± 34</td>
<td>7.5 ± 0.5</td>
<td>404 ± 476</td>
<td>48 ± 30</td>
</tr>
<tr>
<td>Placebo</td>
<td>45 ± 26</td>
<td>8.5 ± 12</td>
<td>378 ± 496</td>
<td>34 ± 33</td>
</tr>
<tr>
<td>Drug</td>
<td>41 ± 30</td>
<td>5.1 ± 9.0*</td>
<td>211 ± 292</td>
<td>47 ± 67</td>
</tr>
</tbody>
</table>

Differences between clearance measurements: *$p < 0.02$, †$p < 0.05$.  

Fig 4  Individual paired differences (12 patients) for amount of radioaerosol retained at six hours as a percentage of that initially deposited in lungs between (a) control and drug runs and (b) placebo and drug runs.

the (a) day-time and (b) night-time between any two of the three weekly periods before the clearance measurements. Further, the quantity of sputum produced during these periods, as judged by the patients, did not differ.

Table 3 gives the mean ± SD number of coughs and the sputum weight, radioactive content and specific activity (radioactive content/unit weight) observed during the six-hour clearance measurement periods. There was no significant difference for any of the variables between any two trial periods, with the exception of the sputum weight, which was significantly less in the drug than the control ($p < 0.05$) or placebo ($p < 0.02$) periods.
clearance of lung secretions, after its administration over a period of one week to a group of patients with reversible airways obstruction.

The bronchodilator action of the drug in these patients was shown by the increase of the lung function indices after its administration in the two-hour pilot study, and by the increase in the PEFRs recorded by the patients in their diary cards during the drug treatment period compared with the control and placebo periods. The increase in the lung function indices noted on the mornings of the drug clearance measurement days probably reflects the action of the last dose administered about one hour previously, as opposed to an improvement attributable to the long-term use of the drug.

The site of deposition of inhaled aerosols in the human lung depends on (1) the physical properties of the aerosol (Lippmann and Albert, 1969; Pavia and Thomson, 1976), (2) the mode of inhalation (Booker et al, 1967; Goldberg and Lourenco, 1973; Pavia et al, 1977a), and (3) lung function (Thomson and Short, 1969; Lippmann et al, 1970; Goldberg and Lourenco, 1973; Thomson and Pavia, 1974; Dolovich et al, 1976). Since in this study (1) and (2) were kept constant, the enhanced penetration of the radioaerosol towards the periphery in the drug runs is due to the improvement in lung function (Pavia et al, 1977b). We believe this is the first time the bronchodilating action of a drug has been shown by a method other than orthodox pulmonary function tests. Possibly the radioaerosol method might prove to be a more sensitive measure of bronchodilatation than such tests; the mean percentage increases in FEV₁, PEFR, and penetration index after the period of administration of the drug compared with the control period were 38%, 30%, and 109% respectively.

The percentage of radioaerosol remaining in the lungs at six hours, measured by whole lung counts, reflects to some extent the alveolar deposition (Thomson and Short, 1969; Foord et al, 1977). The proportions of radioaerosol present in the lungs at this time for the drug, placebo, and control runs is in agreement with the penetration index (Pavia et al, 1977a)—that is, for the measurement after the drug, the higher the penetration index the higher the mean six-hour retention, and vice versa for the control measurements with the placebo being intermediate. It is interesting to note that, despite the increased transfer path for the deposited radioaerosol along the ciliated (conducting airways) in the drug run, because of the increased penetration the mean rate of clearance was no different to that of the placebo or control runs.

In conclusion, the results show that therapeutic doses of ipratropium that cause bronchodilatation have no apparent effect on the clearance of secretions from the human lung.

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References


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