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Effect of four weeks' high dose ipratropium bromide treatment on lung mucociliary clearance

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ABSTRACT In a randomised, double blind crossover study the effect of high dose ipratropium bromide (200 μg three times daily given by metered dose inhaler for four weeks) on lung mucociliary clearance and on the wet weight and mean apparent viscosity of sputum was compared with that of placebo. Six smokers, six ex-smokers, and three non-smokers (12 men and three women, median age 60 years) were studied. Eight subjects had chronic obstructive lung disease (median FEV_1 46% predicted) and seven had asthma (FEV_1 70% predicted). Seven subjects produced sputum regularly, two of whom had asthma. Clearance of secretions was measured by an inhaled radioaerosol technique. The number of coughs and the wet weight, radioactive content, and mean apparent viscosity of sputum produced during the six hour observation period were recorded, as was the mean wet weight of sputum produced during the last two 24 hour periods ending each treatment. Comparison with placebo showed that treatment with high dose ipratropium bromide was associated with a significant increase in the penetration index of inhaled particles, but there was no significant change in alveolar deposition of particles or in tracheobronchial clearance, uncorrected or corrected for sputum expectorated. The wet weight of sputum produced, its radioactive content, and mean apparent viscosity were similar after treatment with ipratropium bromide and placebo. These results show that high dose inhaled treatment with the synthetic anticholinergic bronchodilator ipratropium bromide for four weeks is not associated with detectable modification of the clearance of secretions from the lungs, or of sputum volume or viscosity.

The synthetic anticholinergic drug ipratropium bromide is an effective bronchodilator when given by metered dose inhaler 40 μg (that is, two puffs) four times daily, and this dosage for a week does not alter the clearance of secretions from the lungs.[1 2] Reports of the effects of higher doses of ipratropium bromide come from studies in which only single doses were given. Doses of up to 400 μg caused greater and longer lasting bronchodilatation,[3–8] while doses of up to 200 μg did not affect lung mucociliary clearance.[5 9]

Bearing in mind the effect of atropine on secretions and lung clearance,[10] we have looked more closely for any deleterious effect of treatment with ipratropium bromide inhaled in high doses. We report here the effects on sputum production and apparent viscosity and on lung mucociliary clearance of four weeks' treatment with ipratropium bromide 200 μg three times daily given by metered dose inhaler to patients with airflow obstruction.

Table 1 *Details of the patients and their usual medication*

Male:female	12:3
Age: median (range) (y)	60 (27–71)
Smoking habit (n)	
Smoker	6
Ex-smoker	6
Non-smoker	3
Diagnosis	
Chronic obstructive lung disease (n)	8
Median (range) (% predicted FEV_1)	46 (24–70)
Asthma (n)	7
Median (range) (% predicted FEV_1)	70 (29–91)
Medication: number normally taking:	
Inhaled β_2 adrenoceptor agonist	13
Oral and inhaled β_2 adrenoceptor agonist	4
Inhaled corticosteroid	9
Oral and inhaled corticosteroid	3
Inhaled ipratropium bromide (standard dose)	2
Inhaled sodium cromoglycate	1
Oral aminophylline	7

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Methods

SUBJECTS

Twenty three patients were recruited to the study, but eight of them failed to complete it. The physical characteristics and usual medication of the 15 patients who completed the study are given in table 1. An ex-smoker was defined as one who had not smoked for at least a year, and a non-smoker as one who had never smoked. All the subjects had airflow obstruction. Those who had reversibility of their obstruction amounting to 20% or more with conventional bronchodilator treatment were diagnosed as having asthma; smokers or ex-smokers with less reversibility were diagnosed as having chronic obstructive lung disease.

The study was approved by the hospital's ethical committee, and all the subjects gave their written consent to be studied.

LUNG FUNCTION

Peak expiratory flow (PEF) was measured with a Wright meter, and FEV_1, forced vital capacity (FVC), and forced mid expiratory flow (FEF_{25-75}) with a Vitalograph spirometer. Maximal expiratory flow at 50% ($\dot{V}max_{50}$) and 25% ($\dot{V}max_{25}$) of vital capacity were measured with an Ohio 840 spirometer and Bryans 26000 x–y recorder. The largest of three recordings of PEF, FEV_1, FVC, and FEF_{25-75} and the value of $\dot{V}max_{50}$ and $\dot{V}max_{25}$ from the largest of three vital capacity tracings were each expressed as a percentage of the predicted value.[11 12]

LUNG MUCOCILIARY CLEARANCE

The method of measurement of lung mucociliary clearance has been fully described.[1 2] Five micron polystyrene particles were tagged firmly with technetium 99m (^{99m}Tc)[13] and inhaled under strictly controlled conditions. The clearance of the particles from the lungs was monitored by collimated scintillation counters placed anteriorly and posteriorly to the chest. Thirty second counts were taken immediately after and at half hour intervals for six hours after inhalation of the radioaerosol. Alveolar deposition was determined as the percentage of the initial lung burden remaining in the lungs at 24 hours.[14] The results were expressed as whole lung clearance, and as tracheobronchial clearance (whole lung clearance minus alveolar deposition) uncorrected and corrected for cough productive of sputum containing radioactivity.[15]

The initial topographical distribution of the radioaerosol deposited in the lungs was monitored with a gamma camera (International General Electric) with a large field of view interfaced with a computer (Nodecrest). Posterior views were obtained to derive a penetration index for the ^{99m}Tc labelled particles (ratio of counts recorded over peripheral lung to those recorded over central lung).[16] This index estimates the degree of penetration into the lungs of this radioaerosol relative to that of labelled krypton gas, ^{81m}Kr, that was subsequently inhaled.

STUDY PROTOCOL

The study was conducted in a double blind, crossover fashion. After baseline measurement of lung mucociliary clearance, the patients were allocated randomly to receive either ipratropium bromide—two puffs three times daily (100 μg per puff)—or a placebo that was identical in composition except for active drug—two puffs three times daily—for four weeks from identical metered dose inhalers. They were instructed to inhale in the recommended manner.[17] Randomisation was arranged so that half the patients should receive ipratropium bromide first; in fact, six received the active drug and nine placebo. The subjects continued to use the test inhalers for four weeks and while their mucociliary clearance was being measured after inhaling radioaerosol, but they stopped taking aminophylline and oral and inhaled β_2 adrenoceptor agonist drugs during these six hours and for at least 12 hours beforehand, to avoid any influence on mucociliary function.[18] Otherwise, since this study was not designed to assess the bronchodilator effect of high dose ipratropium bromide, the patients continued to take their regular treatment throughout the study, recording the number of puffs taken daily from their usual β_2 agonist inhaler during each four week treatment period. While having each treatment, the subjects also recorded on diary cards their daily assessment of breathlessness, cough, wheeze, and satisfactory sleep according to a four point scale. Smoking was not permitted for at least one hour before or during the six hour observation period. During this period the number of coughs was counted and any expectorated sputum collected, its wet weight and radioactive content were recorded, and its mean apparent viscosity was measured with a modified capillary viscometer (Moleculex). We also recorded the wet weight of sputum produced at the end of each treatment period and during the 24 hours immediately before and the 24 hours after inhalation of radioaerosol. The 24 hour sputum wet weight was taken as the mean of these two observations.

The subjects performed lung function tests at the end of each four week treatment period, immediately before they inhaled the radioaerosol for measurement of lung mucociliary clearance, and about two hours after inhaling the last dose of test medication.

All adverse effects occurring during the course of the study were noted.

Table 2 *Results of lung function tests (as percentage of predicted, means with standard errors in parentheses) at the beginning of the study, and after four weeks' treatment with placebo and ipratropium bromide*

	FEV_1	FVC	PEF	$\dot{V}max_{50}$	$\dot{V}max_{25}$
Baseline	53.1 (5.4)	77.4 (5.3)	54.3 (6.0)	12.0 (2.5)	18.3 (4.5)
Placebo	55.6 (5.1)	80.7 (4.9)	57.7 (7.0)	12.9 (2.8)	19.1 (4.7)
Ipratropium bromide	60.6 (6.3)	84.9 (5.0)	60.3 (6.7)	12.1 (1.7)	19.9 (4.2)

FVC—forced vital capacity; PEF—peak expiratory flow; $\dot{V}max_{50}$ and $\dot{V}max_{25}$—maximal expiratory flow at 50% and 25% of vital capacity.

The data were initially analysed by means of Friedman's two way analysis of variance.[19] Where this showed significant differences between groups, the results were analysed further with Wilcoxon's signed rank test for matched pairs.[19] Analysis of the results of the lung function tests (apart from PEF) was based on the results from 14 patients, because one patient was breathless at one visit and did not complete the tests. The penetration index was not determined in two subjects because of technical failure.

Results

The results of lung function tests are shown in table 2. Treatment with ipratropium bromide was associated with a significant ($p < 0.01$) increase in forced vital capacity, but there was no significant change in measures of expiratory flow.

Table 3 shows the values for mean inspiratory flow, penetration index, and alveolar deposition of radioaerosol. The penetration index was higher after treatment with ipratropium bromide than with placebo ($p = 0.01$) and higher after placebo treatment than at baseline ($p < 0.01$), although alveolar deposition and mean inspiratory flow did not change significantly.

Comparison of the results obtained after treatment with placebo and with ipratropium bromide showed no significant difference in the amount of radioaerosol remaining in the lungs at any half hour interval up to six hours. No significant difference was detected whether the results were expressed as whole lung clearance or as tracheobronchial clearance uncorrected (figure) or corrected for productive cough, and no significant difference was evident when analysis was confined to the seven subjects who regularly produced sputum. In these seven subjects, two of whom were asthmatic, the number of coughs and the wet weight and mean apparent viscosity of sputum produced during the six hour observation period were all the same after ipratropium bromide as after placebo, as was the wet weight of sputum collected during 24 hours at the end of each treatment period (table 4).

There was no significant difference between the baseline results and those obtained after use of the placebo inhaler for four weeks in respect of uncorrected (figure) or corrected tracheobronchial clearance, sputum wet weight, or mean apparent viscosity (table 4).

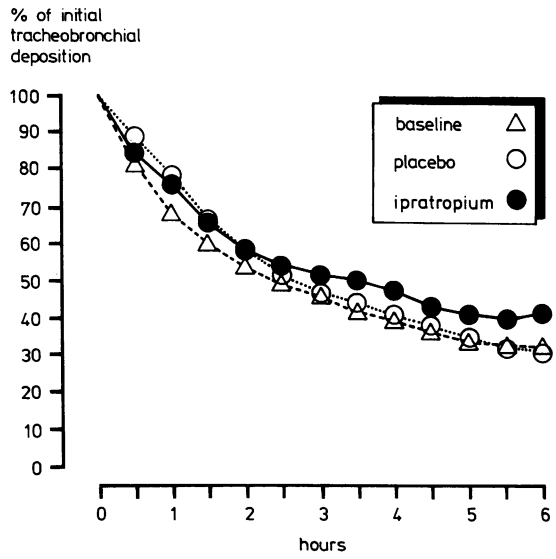
There were no significant differences between the periods of treatment with placebo and with ipratropium bromide in the number of puffs subjects took daily from their β_2 agonist inhalers or in the diary card scores for breathlessness, cough, wheeze, or satisfactory sleep.

There were isolated reports in both treatment periods of cough, sore throat, wheeze, less sputum, rhinitis, breathlessness, and tightness in the chest. Most patients guessed which was the active treatment from its taste, and two described this as unpleasant. One man who had mild difficulty passing urine reported that this became worse after using ipratropium bromide for three and a half weeks, but did not report this after he changed to placebo.

Eight patients were withdrawn from the study. Three patients did not comply with the instructions for taking the trial medication, two had exacerbations of asthma while taking placebo, and three were with-

Table 3 *Mean inspiratory flow, penetration index, and alveolar deposition of radioaerosol (as percentage of initial lung burden remaining at 24 hours) for baseline, placebo, and ipratropium bromide runs*

	Inspiratory flow ($l\ min^{-1}$)		*Penetration index*		*Alveolar deposition (%)*	
	Mean	*SE*	*Median*	*Range*	*Mean*	*SE*
Baseline	43.5	2.9	0.28	0.17–0.63	20.4	2.0
Placebo	42.8	3.1	0.35	0.20–0.66	28.7	3.4
Ipratropium bromide	46.9	3.3	0.47	0.26–0.91	28.7	2.8



Mean tracheobronchial retention (uncorrected for sputum production) at half hourly intervals for 15 patients for baseline run and after four weeks' treatment with placebo and ipratropium bromide.

drawn while taking ipratropium bromide but for unconnected reasons.

Discussion

Ipratropium bromide is an effective bronchodilator in chronic obstructive lung disease and asthma, and its bronchodilator effect is increased and prolonged with doses up to 10 times greater than the standard dose of 40 μg.[3-8 20 21] The drug appears to be free of systemic side effects even when given in doses of up to 500 μg to treat acute severe asthma.[22] Indeed, it came into use as a bronchodilator because it lacked the systemic anticholinergic effects of atropine.[23]

Nevertheless, concern has been expressed about the use of ipratropium bromide, on the grounds that it might increase sputum viscosity and so exacerbate mucus plugging, particularly in asthma.[24] The clearance of secretions from the airways is determined by the physical characteristics of the airways, by ciliary action, and by cough.[25] The clearance of lung secretions may be impaired if any of these determinants is altered.

Previous studies showed that smaller doses of ipratropium bromide caused little or no alteration in the volume or viscoelastic properties of sputum produced by patients diagnosed as having chronic bronchitis, though some probably had asthma.[26-29] The results of the present study are consistent with these observations, but firm conclusions about the effect of high dose ipratropium bromide on sputum cannot be drawn because the number of subjects who produced sputum was small. In studies of isolated animal airways the drug showed only a mild depressant activity on ciliary beat frequency, which was not dose related.[30] Ipratropium bromide did not significantly reduce the frequency of spontaneous coughing in the present study, but in another study nebulised drug reduced the cough response to inhaled citric acid in patients with asthma, though this could have been due to an improvement in airways impedance.[31] In clinical practice, however, the overall effectiveness of lung mucus clearance is more important than each of its components, which may in any case be difficult to evaluate. We found that ipratropium bromide inhaled in the high dose of 200 μg three times daily for four weeks did not alter overall tracheobronchial clearance. This is the most important conclusion from our study, and it extends the observations from previous studies that ipratropium bromide does not alter lung mucociliary clearance when inhaled in single doses of up to 200 μg,[1 5 9 32] or in regular doses of up to 40 μg four times daily for a week.[1 2] While it is difficult to assess the power of the study to detect small alterations in mucociliary clearance, previous studies of as few as 10 or 12 subjects have demonstrated both significant acceleration[33] and retardation[34] of clearance after drug treatment; and the within subject coefficient of variation of the six hour tracheobronchial clearance measurement in patients with chronic bronchitis was 17%.[35]

Table 4 *Number of coughs and wet weight and mean apparent viscosity of sputum produced during the six hour observation period, and mean 24 hour wet weight of sputum produced at the end of each four week treatment period*

	During six hour observation period						*24 hour sputum wet weight (g)*	
	No of coughs		*Sputum wet weight (g)*		*Mean apparent sputum viscosity (mPa)*			
	Median	*Range*	*Median*	*Range*	*Median*	*Range*	*Median*	*Range*
Baseline	28	2–69	4.3	0.1–25.5	2859	1464–8730	11.6	3.8–34.1
Placebo	14	1–36	2.0	0.5–9.2	2284	618–8043	8.4	3.7–35.2
Ipratropium bromide	8	3–81	1.9	0.6–16.6	4286	1011–7425	11.6	0.2–32.1

There have been reports of temporary worsening of lung function after inhalation of nebulised ipratropium bromide, but this appears to be caused by bronchoconstriction rather than retention of secretions. Paradoxical impairment of lung function has occurred after administration of ipratropium bromide by wet nebulisation to patients with asthma.[36 37] It appears to have been caused by the hypotonicity of the solution[38] then in use, and was probably due to exaggerated non-specific bronchial reactivity[39] rather than retention of secretions; subjects who developed bronchoconstriction with nebulised ipratropium bromide showed bronchodilatation after inhaling the drug from a metered dose inhaler (PH Howarth, *et al*, personal communication). Nebulised ipratropium bromide diluted with physiological saline did not impair lung mucociliary clearance in healthy non-smokers or in patients with mild chronic obstructive bronchitis,[40] even though the solution was hypotonic.

Connolly has published the only reports of bronchoconstriction developing after inhalation of ipratropium bromide from a metered dose inhaler.[36] In one case wheezing increased immediately and lasted 15 minutes; it was thus unlikely to have resulted from retention of secretions. Another patient, however, experienced a progressive reduction in peak expiratory flow for four days after he started to use metered dose ipratropium bromide; progressive recovery occurred over the next two days after treatment was withdrawn. Retention of secretions might have been to blame, although this seems unlikely.

We conclude that treatment with the synthetic anticholinergic bronchodilator ipratropium bromide given in the dose of 200 μg three times daily from a metered dose inhaler for four weeks is not associated with any modification of the volume or apparent viscosity of secretions, or of their clearance from the lungs.

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