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 µg) 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 µg) 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 µg). We report a controlled, double-blind cross-over study to ascertain the effect of (a) regular use (40 µg four times daily for seven days) and (b) a single dose (40 µg) of ipratropium bromide (and of the propellants) on lung mucociliary clearance and on bronchodilatation in 12 patients with reversible airways obstruction.

Methods

PATIENTS

Twelve patients (10 men, 2 women) 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 1 *Physical characteristics, tobacco consumption, and ventilatory capacity indices in 12 patients*

Characteristics	Results (mean ± SD)
Age (yr)	63 ± 8
Height (m)	1.68 ± 0.09
Tobacco consumption (pack years)	64 ± 30
FEV ₁ observed (l)	1.14 ± 0.50
FEV ₁ % predicted*	42 ± 15
FVC observed (l)	2.70 ± 0.62
FVC % predicted*	76 ± 22
FEV ₁ /FVC observed (%)	41 ± 11
PEFR observed (l/min ⁻¹)	163 ± 70
PEFR % predicted*	34 ± 16

*Cotes (1975).

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 ($\pm$ SD) PEFRs in the mornings were 152 ($\pm$ 49), 148 ($\pm$ 49), and 161 ($\pm$ 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 ($\pm$ SD) late evening PEFRs were 162 ($\pm$ 60), 156 ($\pm$ 47), and 186 ($\pm$ 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

Fig 1 Mean changes of (a) PEFR, (b) FVC, and (c) FEV₁ for 12 patients after inhalation of two puffs of ipratropium bromide, 40 mg (●), or placebo (▲) at 0 min and two puffs of isoprenaline, 1 mg (○, △), at 123 min.

Table 2 Mean $\pm$ SD, FEV₁ and PEFR for 12 patients on the control, placebo, and drug mucociliary clearance measurements days

	FEV ₁ (l)	FVC (l)	PEFR (l/min)
Control	1.14 $\pm$ 0.50*	2.70 $\pm$ 0.62†	163 $\pm$ 70‡
Placebo	1.16 $\pm$ 0.64‡	2.77 $\pm$ 0.82†	176 $\pm$ 74
Drug	1.40 $\pm$ 0.70*‡	3.32 $\pm$ 1.00†‡	197 $\pm$ 91‡

Paired differences statistically significant at the 5%*, 2%†, and 1%‡ levels.

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.

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 $\pm$ 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.

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

	No of coughs	Sputum weight (g)	Sputum radioactive content 10^3 gamma counts	Sputum specific activity 10^3 gamma counts g^{-1}
Control	49 $\pm$ 34	7.5 $\pm$ 8.5†	404 $\pm$ 476	48 $\pm$ 30
Placebo	45 $\pm$ 26	8.5 $\pm$ 12.1*	378 $\pm$ 496	34 $\pm$ 33
Drug	41 $\pm$ 30	5.1 $\pm$ 9.0†*	211 $\pm$ 292	47 $\pm$ 67

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

Discussion

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 (Corrsen 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

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 PEFs 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, PEF, 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 penetrance 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.

We thank Miss R Brownbill for technical help, Dr G A Cox for advice, and Boehringer Ingelheim Ltd for supplying the drugs and financial support.

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