

Bronchodilatation and the site of airway resistance in severe chronic bronchitis

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ABSTRACT Twenty-one patients with severe chronic bronchitis and emphysema ($FEV_1 < 1$ l) inhaled 80 μ g of the atropine-like agent ipratropium or placebo in a double-blind study and three hours later inhaled 200 μ g salbutamol. After 80 μ g ipratropium, mean FEV_1 was significantly greater than after 200 μ g salbutamol ($P < 0.025$), but the difference was only 40 ml and the clinical significance of this difference is unproved. There was no correlation between the patient's response to ipratropium and the response to salbutamol. When salbutamol was administered three hours after ipratropium, the FEV_1 rose to higher levels than after either agent alone ($P < 0.01$). Studies breathing 80% helium/20% oxygen suggest that ipratropium dilates both large and small airways. There was no correlation between the response to helium/oxygen and the response to either bronchodilator.

The results suggest that in severe chronic bronchitis and emphysema ipratropium is at least as effective as salbutamol, and that such patients should have reversibility studies with salbutamol alone, ipratropium alone, and after both agents together. The combination of ipratropium and salbutamol may be clinically useful.

Atropine inhalation has been used to treat obstructive airways disease in the West since the early nineteenth century, when the smoking of various *Datura* species was introduced from India (Christie, 1811). With the advent of sympathomimetic drugs, atropine fell into disuse for the treatment of asthma and bronchitis, but recently interest in its role as a bronchodilator has been revived (Herxheimer, 1959; Altounyan, 1964; Yu *et al*, 1972). Atropine is thought to act by inhibiting the bronchomotor tone, which depends on efferent fibres in the vagus (Cabezas *et al*, 1971).

Ipratropium bromide (Atrovent, SCH 1000, Boehringer Ingelheim) is an atropine-like drug available in a metered dose inhaler. In the past few years it has been evaluated both in asthma and chronic bronchitis (Poppius and Salorinne, 1973; Petrie and Palmer, 1975; *Postgraduate Medical Journal*, 1975; Storms *et al*, 1975). In chronic bronchitis it is as effective as salbutamol in increasing FEV_1 (Petrie and Palmer, 1975) and peak expiratory flow rate (Poppius and Salorinne, 1973), and possibly even more effective than salbutamol in increasing specific airways conductance (sGaw) (Poppius and Salorinne, 1973). High doses of ipratropium can be given by aerosol, thus pro-

ducing inhibition of vagally mediated bronchomotor tone without the systemic side effects of atropine, for ipratropium by aerosol yields very low plasma concentrations of the drug (*Postgraduate Medical Journal*, 1975).

We have used ipratropium to assess the importance of vagally mediated bronchomotor tone in patients with severe chronic bronchitis and emphysema. Despite the hypertrophied bronchial muscle found in such patients (Hossain and Heard, 1970), we thought that reduction of tone in this muscle would have little effect on the resistance to airflow in their bronchial tree, which we presumed to be extensively deranged, with loss and permanent obstruction of many airways, as a result of their long-standing disease (Thurlbeck *et al*, 1970).

Methods

We studied 17 men and four women, aged 49-71 (mean 65) who suffered from chronic obstructive bronchitis (Medical Research Council, 1965). All had an FEV_1 of less than 1 l, none had a history of asthma, none had a blood eosinophilia greater than $0.2 \times 10^9/l$, and no patient was taking oral

steroids. Eleven were cigarette smokers and 10 ex-smokers. All were severely dyspnoeic on minimal exertion, and none was at work. No patient had had a chest infection within six weeks of the study, each patient's FEV₁ had been stable within 0.15 l over the past six months, and in each the initial FEV₁ on the days of the tests was within 0.15 l of their usual outpatient value. Their arterial PO₂, when breathing air, varied from 5.1–11.1 kPa (38–83 mmHg), mean 8.4 kPa (63 mmHg), arterial PCO₂ 5.1–8.3 kPa (38–62 mmHg), mean 6.7 kPa (50 mmHg), and arterial H⁺ concentration 36–46 nmol/l (pH 7.34–7.44), mean 39 nmol/l (pH 7.41), indicating compensated respiratory acidosis. All bronchodilator treatment was stopped for 12 hours before the studies. The study was approved by the hospital ethical committee, and each patient gave informed consent to the studies.

In a preliminary study FEV₁ and FVC were measured in four of the patients before and 15, 30, 45, 60, 75, 90, 120, 180, and 240 minutes after inhaling 400 µg salbutamol. A cumulative salbutamol dose-response study was performed on the same four patients in which each patient inhaled salbutamol 100 µg at time 0, 100 µg at 30 min, 200 µg at 60 min, 400 µg at 90 min, and finally 80 µg ipratropium at 120 min, FEV₁ and FVC being measured at 0, 30, 60, 90, 120, and 180 minutes.

In a double-blind crossover study each patient received either 80 µg (four puffs) of ipratropium bromide, or four puffs of a placebo, from a metered dose inhaler at the same time of day on two consecutive days. Immediately before the inhalation, and at 90 and 180 minutes thereafter, we recorded expiratory volume and flow rate (Ohio 840 spirometer) during the FVC manoeuvre. We measured FEV₁, FVC, and the flow rate at 50% vital capacity (V max₅₀) on three occasions when breathing air, and also after three vital capacity breaths of an 80% helium and 20% oxygen mixture (He/O₂), recording the highest values observed when breathing each gas.

One hundred and eighty minutes after inhaling either ipratropium or the placebo each patient inhaled 200 µg of salbutamol from a metered dose inhaler (two puffs), FEV₁ and FVC being measured again 15 and 30 minutes later. We also noted pulse rate and side effects before and after each inhalation. This experimental design allows comparison of measurements after ipratropium alone, after salbutamol alone, after placebo alone, and after the sequential administration of ipratropium and salbutamol.

In six patients (two men and four women) lung volumes and sGaw were measured before and 90

minutes after inhaling 80 µg ipratropium bromide, and also after four puffs of placebo, using a pressure compensated flow body plethysmograph (Stanescu *et al*, 1972).

We assessed the significance of changes by paired *t* test.

Results

Studies in four of the patients have suggested that the maximal effect both on FEV₁ and FVC occurred within 15 minutes (fig 1) and lasted for about two hours after inhalation of 400 µg salbutamol alone. Thus the change in FEV₁ and FVC measured in the cumulative dose-response study can be taken to reflect total inhaled dosages of salbutamol of 100, 200, 400, and 800 µg (fig 2), and there would have been no appreciable reduction of response to the inhaled salbutamol by 180 minutes when measurements were made after ipratropium. There was no change in FEV₁ be-

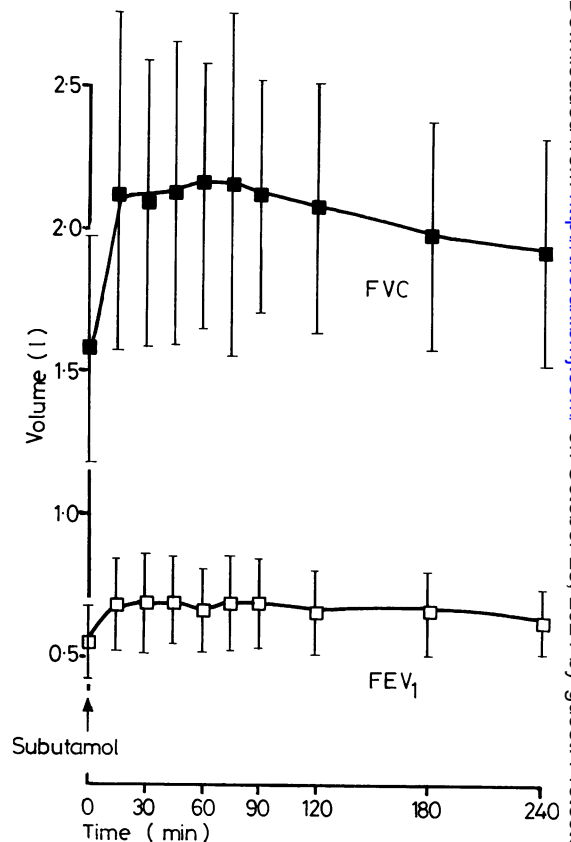


Fig 1 Time course of FEV₁ and FVC after inhaling 200 µg salbutamol—mean ± SD for four patients.

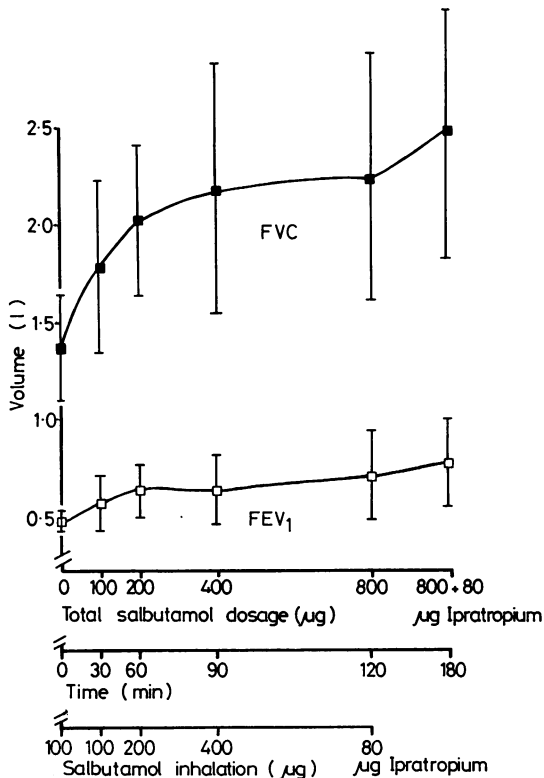


Fig 2 Cumulative dose response studies in four patients with mean \pm SD for FEV₁ and FVC.

tween the 200 and 400 μ g dose, but there was a slight rise at 800 μ g. FVC rose gradually up to the 800 μ g dosage level. In all four patients the addition of 80 μ g of ipratropium resulted in a higher FEV₁ and FVC than after 800 μ g salbutamol alone.

In the main study (fig 3) 180 minutes after the inhalation of ipratropium the FEV₁ had risen on average from 0.58 to 0.73 l ($P < 0.001$) and FVC had risen from 1.45 to 1.93 l ($P < 0.001$). Salbutamol also produced a significant rise in mean FEV₁ from 0.58 to 0.69 l ($P < 0.001$) and in FVC from 1.50 to 1.84 l ($P < 0.001$), the maximal rise being seen 30 minutes after inhalation. After ipratropium the FEV₁ was significantly greater than after salbutamol ($P < 0.025$), but there was no significant difference in FVC ($0.20 > P > 0.10$). When salbutamol was inhaled 180 minutes after ipratropium both the FEV₁ and FVC rose to significantly higher levels than after either agent alone ($P < 0.01$) (fig 3).

Nineteen of the 21 subjects reproduced their FVC breathing air and breathing He/O₂ to within

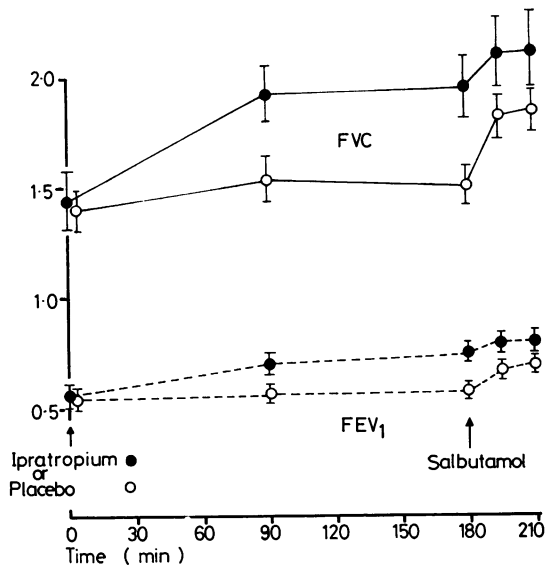


Fig 3 Effects of inhaling ipratropium or placebo aerosol followed by salbutamol on FEV₁ and FVC. Mean values \pm SE for the 21 patients are shown.

100 ml both in the control period and two hours after inhaling ipratropium. In the control period there was no difference between the mean flow rate at 50% VC achieved breathing air (0.33 SD 0.18 lps) or breathing He/O₂ (0.33 SD 0.19 lps) in these 19 patients. In 10 patients V max₅₀ was greater, and in five smaller, when breathing He/O₂ as compared with breathing air, and in four there was no change (fig 4). Two hours after the inhalation of ipratropium V max₅₀ was significantly greater ($P < 0.01$), both breathing air (0.35 SD 0.15 lps) and breathing He/O₂ (0.38 SD 0.24 lps), but the difference between the flow rates breathing air and breathing He/O₂ was not significant ($P > 0.3$).

In the six patients studied in the body plethysmograph sGaw rose from 0.35 to 0.50 sec⁻¹kPa⁻¹ (0.035 to 0.050 sec⁻¹cmH₂O⁻¹) after ipratropium. A paired *t* test carried out on the logarithm of sGaw values showed this rise in sGaw to be significant ($P < 0.02$). Ipratropium did not change the total lung capacity, but the residual volume fell from 3.76 (SD 0.82) l to 3.47 (SD 0.87) l ($P < 0.02$).

There was no significant change in pulse rate either after ipratropium (88 SD 3) as compared to placebo (91 SD 3) or after salbutamol (94 SD 3) as compared to placebo (91 SD 3) or after the combination of both agents (91 SD 4). No side effects were reported, although the dose of ipratropium given was twice that normally recom-

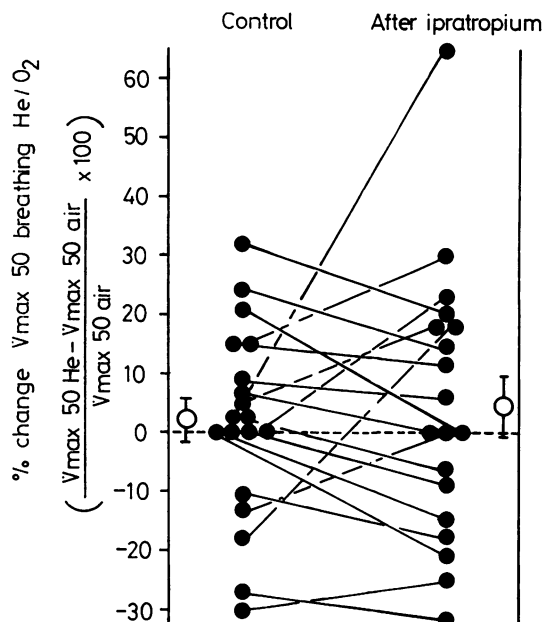


Fig 4 Effects of breathing He/O₂ on forced expiration before (control) and two hours after ipratropium inhalation. Individual values (●) for percentage change in maximum flow at 50% vital capacity (calculated as shown) and mean \pm SE are given.

mended by the manufacturers. Several patients disliked the bitter taste of ipratropium.

Discussion

The inhalation of ipratropium bromide produced a small but significant increase in both FEV₁ (26%) and FVC (33%) in our patients with severe chronic obstructive airways disease, with a maximal effect at 180 minutes after the inhalation, extending previous observations on smaller numbers of less severely affected patients (Petrie and Palmer, 1975). Herxheimer (1959) found a small increase in FVC in a mixed group of both asthmatics and bronchitics after smoking a cigarette impregnated with atropine. Although the FVC rose after ipratropium inhalation in our severely bronchitic patients, their total lung capacity did not change, but their residual volume fell, indicating that the rise in FVC resulted from this fall in residual volume. In patients with chronic bronchitis and emphysema the residual volume is probably determined by closure of small airways. The fall in residual volume after ipratropium may result from an increase in the stability of

these small airways, so that they then close at a higher pleural pressure. This notion is consistent with the observation that methacholine (which has the opposite effect to atropine, increasing airway tone) increases residual volume in normal subjects, probably by reducing airway stability (Engel *et al.*, 1976).

The ratio of FEV₁ to FVC (FEV₁/FVC) is usually over 70% in health, and a fall in this ratio is widely accepted as indicating airway obstruction. In asthmatics bronchodilatation with salbutamol increases the FEV₁/FVC ratio (Palmer and Diament, 1969). In our bronchitics ipratropium produced a proportionately greater rise in FVC than in FEV₁, so that the FEV₁/FVC ratio fell from 42% (SD 13%) to 39% (SD 11%) ($p < 0.05$). This might have been taken to imply an increase in airway obstruction, whereas our direct measurements of sGaw show that the drug caused significant bronchodilatation. Salbutamol did not alter the FEV₁/FVC ratio.

We found a greater rise in FEV₁ after ipratropium in these patients with severe chronic bronchitis than after salbutamol. Petrie and Palmer (1975) did not find such a difference between these drugs, and Poppius and Salorinne (1973) found both drugs to have a similar effect on the peak expiratory flow rate. Our results may arise from studying patients with more severe disease, and also from our use of twice the dose of ipratropium, but others (*Postgraduate Medical Journal*, 1975) have found that the response to ipratropium in mild bronchitis or in asthma was maximal with 40 μ g dose of ipratropium—half the dosage used in this trial.

This difference does not seem to be due to achieving poor β_2 -sympathetic stimulation with 200 μ g salbutamol, as the cumulative dose response study (fig 2) suggests that the increase in FEV₁ after 200 μ g was the greatest that could be achieved without the unpleasant effects and potential hazards experienced at 800 μ g. It must be emphasised that although FEV₁ after ipratropium was significantly higher than after salbutamol, the difference was only 40 ml, and the clinical significance of this difference is dubious and remains to be proved. It can be said, however, that ipratropium is at least as effective as salbutamol in these patients.

So far as we are aware this is the first study to show that the combination of ipratropium and salbutamol produced a significantly greater bronchodilatation in patients with bronchitis than either agent alone. Other workers have noted that such combination therapy has produced a slightly greater effect on FEV₁ than either agent alone,

but these differences were not significant (Petrie and Palmer, 1975; Baronti and Grieco, 1976). After both agents given in combination there was a 35% increase in FEV₁ and a 45% increase in FVC. In the dose-response study (fig 2) the addition of 80 µg ipratropium to 800 µg salbutamol resulted in further bronchodilatation in all four subjects. The combined use of a beta-sympathetic stimulant and an atropinic agent by inhalation may prove valuable in clinical practice.

The change in FEV₁ after salbutamol was not correlated with that in the same patient after ipratropium ($r=0.16$), whereas Petrie and Palmer (1975) did find the two responses to be correlated significantly in a mixed group of patients with asthma and bronchitis. In patients with bronchitis the response of the individual patient should be assessed to both a beta-sympathomimetic bronchodilator and an atropinic agent, both separately and together.

A mixture of 80% helium and 20% oxygen (He/O₂) has a density that is only 30% that of air but is 11% more viscous. The cross-sectional area of the bronchial tree greatly increases as the airways divide (Weibel, 1963), so that flow in the small airways may be slow and laminar, contrasting with the more rapid and disturbed flow in the trachea and major bronchi. As laminar flow depends on viscosity, if expiratory flow rates are determined by the resistance of small airways, breathing He/O₂ would cause a fall in $\dot{V}_{max_{50}}$, as seen in five of our patients (fig 4). Conversely, rapid and disturbed flow depends on the density of the gas in the bronchial tree, and therefore, if flow was limited by the resistance of large airways, flow rates would rise when breathing the He/O₂ mixture (Pedley *et al.*, 1970). In normal subjects $\dot{V}_{max_{50}}$ breathing He/O₂ is 40–60% greater than breathing air (Despas *et al.*, 1972; Benatar *et al.*, 1975). In our patients $\dot{V}_{max_{50}}$ rose on average only 2% when breathing He/O₂ (fig 4) compared with 11–13% increases previously found in groups of less severely disabled bronchitics (Despas *et al.*, 1972; Wellman *et al.*, 1976). We have studied (Kanbour *et al.*, 1977) the washout of nitrogen by three vital capacity breaths of He/O₂ in seven patients whose chronic bronchitis and emphysema were of similar severity to that of the patients in this study. We found that the mean nitrogen concentration in the ultimate forced expiration was 31% (range 28–41%) and thus even in the case of the worst washout of nitrogen there was a 35% reduction in the density of the exhaled gas. Therefore the small increase in expiratory flow rates we observed in the present study cannot be explained by inadequate replacement of air by He/

O₂ implying that most of the resistance to airflow on forced expiration in our patients with severe chronic bronchitis lay in their small airways, where gas viscosity determines the pressure/flow relationships.

The change in flow on breathing He/O₂ before ipratropium was significantly correlated to that breathing He/O₂ after ipratropium ($r=0.48$, $P<0.05$) but there was a wide degree of variation in some individuals (fig 4). Ipratropium had no significant effect on the change in $\dot{V}_{max_{50}}$ breathing He/O₂. As $\dot{V}_{max_{50}}$ is the flow rate when 50% of the VC has been exhaled into the spirometer, however, because of the increase in FVC (mean 0.5 l) after ipratropium, $\dot{V}_{max_{50}}$ after ipratropium was measured at a different lung volume and thus a different lung recoil pressure than in the control period. It is therefore difficult to draw physiological conclusions by comparing $\dot{V}_{max_{50}}$ and the response to He/O₂ before and after ipratropium. In the six subjects studied in the plethysmograph, however, lung volumes were measured before performing forced expiratory manoeuvres and so flow rates can be compared at the same absolute lung volume (50% VC_{VTG}) and at the same lung recoil pressure. In these subjects $\dot{V}_{max_{50}}$ VC_{VTG} rose by 79% ($P<0.001$) after ipratropium, but there was no change in the percentage response to He/O₂ before (10% SD 12%) as compared with after ipratropium (15% SD 14%; $P>0.5$). In fact there was no difference between the percentage response to He/O₂ measured at 50% VC_{VTG} after ipratropium (15% SD 14%) and the percentage response to He/O₂ measured at 50% VC_{exhaled} (18% SD 32%; $P>0.7$). Extrapolating this to the unaltered response to He/O₂ in $\dot{V}_{max_{50,exhaled}}$ after ipratropium in all 21 patients we suggest that the distribution of resistance to expiratory flow was not altered by ipratropium and that expiratory flow was still limited by the small airways in these severe chronic bronchitics. This is in agreement with results in normal subjects, in whom ipratropium appears to dilate both large and small airways (Douglas *et al.*, 1976).

There was no correlation between the change in flow rates on breathing He/O₂ and the increase in FEV₁ produced either by ipratropium ($r=0.06$) or by salbutamol ($r=0.37$, $P>0.1$). This contrasts with suggestions based on a small group of patients that in asthma, patients with severe airways obstruction who have a poor response to He/O₂ do not subsequently improve whereas those who increase their $\dot{V}_{max_{50}}$ by greater than 20% on breathing He/O₂ will respond to treatment (Benatar *et al.*, 1975). Indeed, there was no cor-

relation between the percentage response to He/O₂ in the control period on two days of the studies ($r=0.12$), even in our very stable group of patients. We therefore feel that measuring the response of an individual bronchitic to He/O₂ is of no predictive value.

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