Effects of ipratropium bromide and fenoterol aerosols in pulmonary emphysema

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ABSTRACT In patients with radiological evidence of pulmonary emphysema the bronchodilator drugs fenoterol and ipratropium bromide produced a considerable increase in vital capacity and reduction in residual volume. The response to fenoterol was virtually complete 15 minutes after administration, but after ipratropium bromide vital capacity was still increasing at 60 minutes. The change in vital capacity was slightly greater with a combination of the two drugs than with either used alone. Changes in FEV₁ and peak flow rate were small.

The anticholinergic ipratropium bromide and sympathomimetic agents such as fenoterol have been widely used for their bronchodilator properties in patients with bronchial asthma and other forms of airflow obstruction.¹⁻³ It has been conventional to assess bronchodilator responsiveness by measurement of changes in peak expiratory flow rate or similar lung function indices, but in patients with emphysema any beneficial effects of bronchodilator treatment are largely associated with increase in the vital capacity.⁴ In patients with chronic airflow obstruction the combination of sympathomimetic and anticholinergic agents may confer an additional benefit.^{3,5} In this study we set out to assess the effects of fenoterol and ipratropium bromide, administered singly and in combination, on lung function in patients with definite evidence of pulmonary emphysema.

Patients and methods

Male patients with radiological evidence of pulmonary emphysema⁶ were selected for this study. No patient was taking oral or inhaled corticosteroids and all bronchodilator treatment was stopped 12 hours before the start of each day of study.

The trial was of double-blind crossover design, the treatments being given according to a randomisation schedule. The four treatments were as follows: (1) ipratropium bromide (40 µg) and placebo; (2) fenoterol (400 µg) and placebo; (3) ipratropium

bromide (40 µg) and fenoterol (400 µg); (4) placebo. Each treatment was administered by two puffs from each of two identical metered-dose inhalers, delivered successively and without delay. Treatments were not given on successive days.

Forced expiratory volume in 1 second (FEV₁), relaxed vital capacity, and inspiratory capacity were measured with a Bernstein spirometer, and peak expiratory flow rate with a Wright's peak flow meter. Functional residual capacity was measured with a Collins 09001 body plethysmograph.

The patients rested for 15 minutes after arrival at the laboratory. Three baseline measurements of FEV₁, vital capacity, and peak expiratory flow rate were made at 15-minute intervals, the largest being accepted as the baseline value. Baseline measurements of FRC (mean of six) were then obtained. FEV₁, vital capacity, and peak expiratory flow rate were measured again 15, 30, 60, and 90 minutes after inhalation of the test aerosols; functional residual capacity was again measured 45 minutes after inhalation, immediately preceded by measurement of vital capacity and inspiratory capacity for calculating residual volume and total lung capacity.

The changes in FEV₁, vital capacity, and peak flow rate have been expressed as the difference between the observed value after treatment and the maximum pretreatment baseline value. All changes in lung function after the three "active" treatments, ipratropium bromide, fenoterol, and the combination of the two, were compared with the change after placebo alone and assessed statistically by analysis of variance; Duncan's multiple-range test was used to compare any two treatments.

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Results

Twelve patients completed all four study days. Their mean age was 58 years (range 54–67) and their lung function data are given in the table. All had normal serum α_1 -antitrypsin concentrations and all were or had been cigarette smokers.

There was no significant difference between any of the four treatment days in the baseline values for any of the lung function tests.

CHANGES IN LUNG FUNCTION AFTER TREATMENT

Vital capacity

Vital capacity (fig 1) was greater after ipratropium, fenoterol, and the combined treatment than after placebo ($p < 0.01$) at all time points. At 15 minutes it was greater after fenoterol than after ipratropium ($p < 0.05$) and at 60 minutes it was greater after the combined treatment than after ipratropium ($p < 0.05$).

Time course of vital capacity **Fenoterol:** vital capacity reached a plateau at 15 minutes and there was no significant change thereafter. **Ipratropium:** vital capacity was greater at 90 minutes than at 15 minutes ($p < 0.01$). **Ipratropium plus fenoterol:** vital capacity was greater at 90 minutes than at 15 and 30 minutes ($p < 0.05$).

Lung function values for the 12 patients studied (as % of predicted normal values)*

	Mean	SD
FEV ₁	38	19
Vital capacity	80	14
Total lung capacity	132	12
Residual volume	245	36
Transfer factor	61	33

*From tables prepared by Cotes.⁷

Fig 1 Changes in vital capacity after aerosol administration (vertical bars indicate 1 SE).

Fig 2 Changes in FEV₁ after aerosol administration (symbols as in fig 1).

FEV₁

FEV₁ (fig 2) was greater after ipratropium, fenoterol, and the combination of the two than after placebo ($p < 0.01$) at all time points. FEV₁ was greater after the combined treatment ($p < 0.01$) and after ipratropium ($p < 0.05$) than after fenoterol at 60 and 90 minutes.

Time course of FEV₁ **Fenoterol:** FEV₁ reached its highest value at 15 minutes and there was no significant change thereafter. **Ipratropium:** FEV₁ values at 60 and 90 minutes were greater than at 15 minutes ($p < 0.01$). **Ipratropium plus fenoterol:** FEV₁ was significantly greater at 60 and 90 minutes than at 15 and 30 minutes ($p < 0.05$).

Peak flow rate

PEFR (fig 3) was greater after ipratropium, fenoterol, and the combined treatment than after placebo at all time points ($p < 0.01$). It was greater after fenoterol than after ipratropium at 15, 30, and 60 minutes ($p < 0.01$) and greater after the combination than after ipratropium at 30, 60, and 90 minutes ($p < 0.01$).

Time course of peak expiratory flow rate **Fenoterol:** Peak flow rate reached its highest value at 30 minutes; this was a significantly greater value than at 15 minutes ($p < 0.01$). **Ipratropium:** Peak flow rate was greater at 90 minutes than at 15 and 30 minutes ($p < 0.01$). **Ipratropium plus fenoterol:** Peak flow rate was greater at 30 minutes than at 15 minutes ($p < 0.05$). There was a further small but not significant increase from 30 to 90 minutes.

Fig 3 Changes in peak expiratory flow rate after aerosol administration (symbols as in fig 1).

Lung volumes

Data on lung volumes are shown in figure 4. Functional residual capacity values showed a significantly greater fall after ipratropium and fenoterol ($p < 0.05$) than after placebo. The fall after the combined treatment was not significant ($p < 0.01$). Residual volume fell significantly more after ipratropium, fenoterol, and the combination of the two ($p < 0.05$) than after placebo, which was followed by no significant change. There was no significant change in total lung capacity on any of the four treatment days.

SIDE EFFECTS

There were fourteen reports of a bad or bitter taste after the test aerosol, four after ipratropium, three after fenoterol, five after the combined treatment, and two after placebo.

Discussion

In this study we have shown that in patients with radiological evidence of pulmonary emphysema the bronchodilator drugs fenoterol and ipratropium bromide (given by aerosol either singly or in combination) can produce significant changes in lung function indices. The greatest changes were seen in vital capacity, which increased on average by over 0.5 litre with all the active treatments; in some patients an increase of over a litre was achieved. The changes in FEV₁ and peak expiratory flow rate, though significant, were small. The dose of ipratropium (40 µg) used in this study would appear to be enough to produce a near-maximal response since Douglas *et*

Fig 4 Changes in total lung capacity, functional residual capacity, and residual volume after aerosol administration (vertical bars indicate 1 SE).

*al*³ obtained similar results using double this dose; they did, however, observe a further increase in FEV₁ and vital capacity when salbutamol was administered three hours after ipratropium.

There were clear-cut differences between the two drugs in the rates of change in the lung function indices that occurred after administration. With fenoterol alone, FEV₁ and vital capacity underwent no significant change after 15 minutes, nor did peak expiratory flow rate after 30 minutes; with ipratropium, on the other hand, all three indices appeared to be still increasing at 60 or 90 minutes. The combination, like ipratropium alone, produced a further rise after the 15-minute or 30-minute time-point; in general, for a given drug treatment (or combination) the time courses of these three lung function indices showed an obvious resemblance to each other (figs 1–3). The greatest overall change in vital capacity was obtained with the combination treatment, though the results were seldom significantly different from the values for the two drugs given alone. For FEV₁ fenoterol gave lower values than the other two treatments, but for peak expiratory flow rate the position was for some reason reversed, ipratropium giving the lowest values; again the three treatments differed little in absolute terms.

A review of previous studies with these two bronchodilator drugs found none in which patients with definite radiological evidence of emphysema had been specifically selected for study. In patients with a diagnosis of chronic obstructive bronchitis⁵ (among whom there may well be patients with

emphysema) both FEV₁ and vital capacity increased after administration of fenoterol or ipratropium, the response to the latter being somewhat delayed as in our patients. In similar groups of patients^{1,2} the same time delay with ipratropium occurred compared with another sympathomimetic agent, salbutamol. The combination of ipratropium with salbutamol was found to yield a slightly greater increase in FEV₁ than either drug used alone, though in a study in which the test drugs were given over three days (much longer than in any of the foregoing studies) the combination of ipratropium with salbutamol was shown to produce more than double the change in FEV₁ observed with either drug alone.⁸ In bronchial asthma comparisons of ipratropium with sympathomimetic agents show similar time relationships, and again the response to ipratropium is rather slower than to fenoterol⁹ or salbutamol.²

In this study the increase in vital capacity was almost entirely at the expense of the residual volume, the total lung capacity undergoing little change, and a fall in functional residual capacity after ipratropium has also been shown in patients with chronic obstructive bronchitis.¹³ Subjective improvement after bronchodilator aerosol has been shown to be related to increase in vital capacity rather than FEV₁ or peak expiratory flow rate.⁴ This beneficial effect is presumably due to the reduction in functional residual capacity that follows release of bronchomotor tone; thus tidal respiration can take place over a lower section of the pressure-volume curve of the respiratory system, where a given change in volume can be achieved for a smaller change in transpulmonary pressure.

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