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# IPRATROPIUM BROMIDE AND FENOTEROL BY AEROSOLIZED SOLUTION

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Ipratropium bromide (0.5 mg) and fenoterol (2 mg) produced equivalent peak bronchodilatation between 1 and 2 h after administration to eight patients with chronic partially reversible airways obstruction. The duration of action compared with saline was 6 h for ipratropium and 4 h for fenoterol. Both drugs in combination produced greater bronchodilatation than either drug alone. The increase in FVC was disproportionately greater than $FEV_1$ with both drugs and saline, suggesting relief of obstruction of small airways.

## Introduction

The domiciliary use of a bronchodilator aerosolized by a nebulizer has been shown to be beneficial for patients with severe airways obstruction due to chronic bronchitis and emphysema (Wilson & Connellan, 1980). In patients with severe airways obstruction aerosolized bronchodilator with or without intermittent positive pressure breathing will produce greater bronchodilatation than when given by metered pressurized aerosol (Webber *et al.*, 1974; Choo-Kang & Grant, 1975; Berend *et al.*, 1978). However, this improved effect may be related to the greater dose delivered by the nebulizer. Ipratropium bromide, a cholinergic antagonist, has recently become available as a solution for nebulization. Jenkins *et al.* (1981) have shown that doses of ipratropium bromide ranging from 0.125 to 0.5 mg were equipotent with 5 mg salbutamol in patients with chronic, partially reversible airways obstruction. The purpose of this study was to investigate the bronchodilator effect of ipratropium bromide in combination with a $\beta$-adrenoceptor agonist by aerosolized solution compared with either drug singly.

## Methods

Eight male patients, aged from 63 to 73 years, were selected for this study after their informed, written consent was obtained. These patients were being considered for domiciliary therapy with nebulized bronchodilators. All patients had severe chronic obstructive bronchitis with their forced expiratory volume in one second ($FEV_1$) ranging from 20 to 54% of predicted normal. $FEV_1$ improvement after 200 $\mu$g salbutamol ranged from 15 to 40%. Five patients gave a clinical history of spontaneous variability of symptoms of airways obstruction consistent with the diagnosis of asthma. Seven patients were previous smokers.

The study was a double-blind, randomized, factorial design and was conducted in the morning of four days. The four treatments were: (1) ipratropium bromide, saline; (2) fenoterol, saline; (3) ipratropium bromide, fenoterol and (4) saline, saline. The dose of ipratropium bromide was 0.5 mg (2 ml of 0.025% solution), fenoterol 2.0 mg (2 ml of 0.1% solution) and normal saline 2 ml. The solutions were delivered by a Hudson nebulizer with face mask driven by 6 l/min flow rate of air and inhaled by the patient with tidal breathing for 5 min, during which time the solution was completely nebulized. With this method 2 ml of solution is the desirable maximum for nebulization. On each day the two treatments were administered one after the other, each over 5 min.

All patients were in a steady state of moderately severe airways obstruction established on maintenance treatment (prednisone (5), salbutamol and beclomethasone diproprionate aerosols (8) and theophylline (8)). Inhaled salbutamol was withdrawn for 12 h and oral theophylline 72 h before each day, but oral and inhaled corticosteroids were continued at maintenance doses. Pulmonary function was determined by measuring $FEV_1$ and forced vital capacity (FVC) with a Vitalograph. Three resting, basal $FEV_1$ and FVC readings were taken and the highest values used as controls. On each day basal variability was assessed and the study did not proceed if there was greater than 0.15 l variation in $FEV_1$ in patients with $FEV_1$ less than 1.0 l and 0.3 l for patients with $FEV_1$ less than 2.0 l. Two $FEV_1$ and FVC readings were repeated after each treatment at 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0 and 6.0 h, the higher values on each occasion used for comparison. Pulse rate was taken after a 10 min rest immediately before the respiratory recordings. The results were submitted to statistical analysis using the paired Student's *t*-test.

## Results

The mean $FEV_1$ and FVC changes from control after each treatment are shown in Figures 1 and 2 repectively. There were no significant differences between basal $FEV_1$ and FVC values. There were

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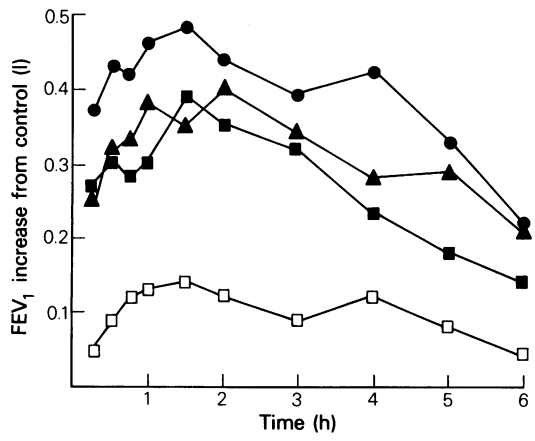


**Figure 1** The mean $FEV_1$ changes from control after 0.5 mg ipratropium bromide ▲, 2.0 mg fenoterol ■, combined treatment ●, and saline □ by aerosolized solution for eight patients with chronic partially reversible airways obstruction. Mean (s.e. mean) basal $FEV_1$ values were 0.92 (0.09) for ipratropium bromide, 0.91 (0.09) for fenoterol, 0.92 (0.10) for combined treatment and 0.90 (0.08) 1 for saline.

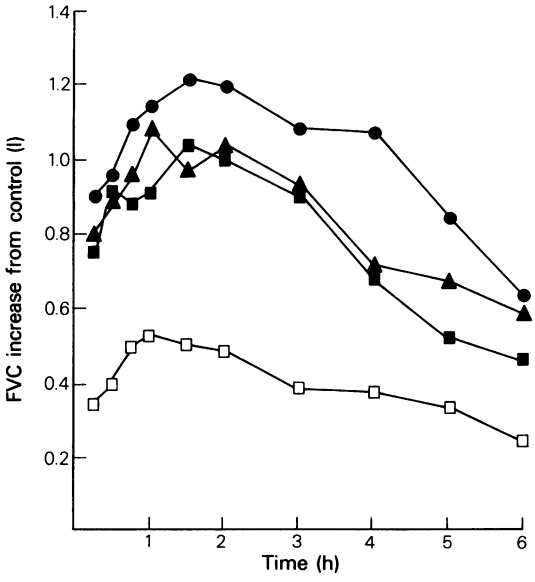


**Figure 2** The mean FVC changes from control after 0.5 mg ipratropium bromide ▲, 2.0 mg fenoterol ■, combined treatment ●, and saline □ by aerosolized solution for eight patients with chronic partially reversible airways obstruction. Mean (s.e. mean) basal FVC values were 2.00 (0.17) for ipratropium bromide, 1.91 (0.20) for fenoterol, 1.88 (0.16) for combined treatment and 1.88 (0.19) 1 for saline.

significant $FEV_1$ increases compared with saline for 3 h with fenoterol, and for 6 h with both ipratropium bromide and combined treatment ($P < 0.05$). The $FEV_1$ response for combined treatment was significantly greater than for fenoterol (0.5, 0.75, 4 and 6 h) and for ipratropium bromide (0.25 to 1.5 and 4 h) at various times ($P < 0.05$). There were significant FVC differences compared with saline for 4 h with fenoterol and for 6 h with ipratropium bromide and combined treatment ($P < 0.05$). The FVC response for combined treatment was significantly greater than for fenoterol (4 to 6 h) and for ipratropium bromide (1.5, 3 and 4 h) at various times ($P < 0.05$). There were no significant differences between the $FEV_1$ and FVC responses for ipratropium bromide and fenoterol. There were no significant pulse rate changes with the treatments.

## Discussion

Ipratropium bromide and fenoterol produced equivalent peak bronchodilatation. Significant improvement in pulmonary function occurred within 15 min for both drugs and all patients claimed relief of symptoms. The duration of action of ipratropium bromide compared with saline (6 h) was significantly greater than fenoterol (4 h). Additional improvement was achieved with both drugs in combination, but there was no evidence of synergistic interaction. Recently, Ward *et al.* (1981) have shown aerosolized ipratropium bromide (0.5 mg) to be as effective as salbutamol (10 mg) in acute asthma and that both drugs in sequence produced greater bronchodilatation than either drug alone. Additive responses with ipratropium bromide and a β-adrenoceptor agonist by pressurized aerosol have also been demonstrated in patients with chronic, partially reversible airways obstruction (Lightbody *et al.*, 1978; Marlin *et al.*, 1979).

A disproportionate increase in FVC compared with $FEV_1$ occurred with all treatments. This suggests dilatation and increased stability of peripheral airways. In chronic bronchitis and asthma, intraluminal mucus in peripheral airways also contributes to airflow obstruction (Mossberg, 1979; Thurlbeck, 1980). Removal of mucus from peripheral airways would result in this physiological response. Sputum expectoration in the morning is common in untreated patients with chronic bronchitis. In this study, all patients expectorated sputum after the treatments, presumably because the inhaled particles also stimulated the cough reflex.

In summary, this single dose study demonstrates that additive bronchodilatation may be achieved with ipratropium bromide and a β-adrenoceptor agonist by aerosolized solution in patients with severe, chronic partially reversible airways obstruction.

Bronchodilator therapy with two drugs possessing different side-effect profiles may be associated with less unwanted effects than when the dose of a single drug is increased to produce a better response. Bronchodilators by aerosolized solution should be considered in patients who are not responding to conventional bronchodilators as maintenance treatment. Studies of ipratropium bromide and β-adrenoceptor agonists by aerosolized solution singly and in combination during domiciliary therapy are warranted.

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