A single dose comparison of a combination of fenoterol and ipratropium aerosols in bronchial asthma

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Summary

Nine patients with reversible obstructive airways disease were studied to compare the bronchodilator response to a combination of fenoterol and ipratropium aerosols with two dose levels of fenoterol alone.

Using a double-blind, cross-over, single dose regime, 200 µg fenoterol hydrobromide and 80 µg ipratropium bromide was compared to 400 µg fenoterol + placebo, and to 200 µg fenoterol + placebo.

There was no significant difference between the combination and either dose of fenoterol in terms of peak or duration of response as determined by absolute or percent change in forced expiratory volume in one second, or forced vital capacity, over baseline.

KEY WORDS: bronchodilator, fenoterol, ipratropium, aerosol.

Introduction

Since its introduction ipratropium bromide has been recommended for the treatment of chronic bronchitis (Crompton, 1980) but its place in the management of reversible airflow obstruction remains uncertain (Cole, 1981) and it is not clear whether the combination with a β_2 agonist has any advantage over individual drugs.

This study sought to determine whether the combination of ipratropium bromide and fenoterol produced greater bronchodilator response than fenoterol alone in patients with chronic asthma.

Patients and methods

Nine patients of mean age 56 (45-66) attending the Asthma Clinic took part in a single-dose, double-blind crossover study which had the approval of the Hospital's Ethical Committee. All gave a history of chronic or episodic wheeze and their forced expiratory volume in one second (FEV₁) improved by 15% or more after two puffs isoprenaline or salbutamol.

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Their initial FEV₁ was less than 80% predicted and all had good timing of aerosol release. They attended on three separate occasions a week apart and omitted bronchodilator therapy for 9 hr before attendance. None was receiving a slow-release oral theophylline preparation. Nine continued to take inhaled steroids, six oral corticosteroids and one sodium cromoglycate. Two patients had positive prick skin tests to common allergens.

After baseline measurements of FEV₁, forced vital capacity (FVC) (Vitalograph—best of three readings) and pulse rate, they received four puffs of aerosol on each occasion at the same time of day from masked inhalers according to a randomized plan.

The dose of ipratropium bromide used in the combination was higher than the manufacturer's recommended dose, as suggested by Allen and Campbell (1979). This was compared with two doses of fenoterol; 400 µg being the recommended dose and 200 µg matching the dose in the combination.

Treatment day A: 2 puffs × 100 µg fenoterol + 2 puffs × 40 µg ipratropium;

B: 2 puffs × 200 µg fenoterol + 2 puffs placebo;

C: 2 puffs × 100 µg fenoterol + 2 puffs placebo.

Patients inhaled at their usual inspiratory flow rate from residual volume to total lung capacity; breath-holding time was 4 sec. Aerosol release was patient-activated. Subsequent measurements of pulse, FEV₁ and FVC were made at $\frac{1}{2}$, 1, 2, 3, 4, 5, 6 and 7 hr after aerosol administration, the latter being expressed as litres (ATPS).

Statistical analysis of absolute change was by analysis of variance (Table 1) and *t*-testing using residual variation.

Mean initial FEV₁ was 1.02 litres (41% predicted) and there was no difference in mean initial FEV₁ on any treatment day.

Results

The mean baseline and maximum increment values of FEV₁ and FVC on the three drug regimens are shown in Table 1.

TABLE 1. Mean ($\pm$ s.e.m.) baseline and maximum increments (l) in FEV₁ and FVC after the three treatments

	FEV ₁		FVC	
	Baseline	Maximum increment	Baseline	Maximum increment
Fenoterol 200 μ g	0.97 $\pm$ 0.10	0.49 $\pm$ 0.09	1.87 $\pm$ 0.15	0.63 $\pm$ 0.10
Fenoterol 400 μ g	1.12 $\pm$ 0.14	0.56 $\pm$ 0.07	1.96 $\pm$ 0.20	0.73 $\pm$ 0.11
Fenoterol 200 μ g Ipratropium 80 μ g	0.97 $\pm$ 0.08	0.49 $\pm$ 0.06	1.83 $\pm$ 0.16	0.72 $\pm$ 0.11

Absolute FEV₁ levels were significantly higher than baseline for all three treatment days up to and including 7 hr post-administration ($P < 0.05$). There were no significant differences between the three treatments with respect to either absolute or percent change for baseline.

Absolute FVC levels were significantly higher than baseline at the 5% level for the combination up to 7 hr post-administration, for fenoterol 200 μ g $\times$ 2 up to 6 hr and up to 5 hr for fenoterol 100 μ g $\times$ 2. There were no significant differences between the three treatments in terms of absolute or percentage change from baseline. The percentage changes in FVC and FEV₁ are shown in Figs 1 and 2 respectively.

FIG. 1. Mean percentage change in FVC up to 7 hr after fenoterol and placebo and a combination of fenoterol and ipratropium.

FIG. 2. Mean percentage change in FEV₁ up to 7 hr after fenoterol and placebo and a combination of fenoterol and ipratropium

There were no significant differences in mean absolute change in pulse rate between any of the three treatment days.

Discussion

Prolonged effect is a desirable property for an aerosol bronchodilator. Fenoterol hydrobromide has been shown to have a significant effect up to 4 hr in recommended dosage (Plit *et al.*, 1972; Lawford, Dowd and Palmer, 1981) although there is some evidence of longer duration (Anderson, Wilkins and Jariwalla, 1979; Benjamin, 1972). Ipratropium bromide has likewise been found to have a significant bronchodilator effect up to 4 hr (Gross, 1975) in a dosage of 20 μ g and a significant prolongation of response with higher dosage (Baigelman and Chodosh, 1977; Allen and Campbell, 1979).

This study has shown that a combination of 200 μ g fenoterol with 80 μ g ipratropium gives comparable duration of response to 400 μ g fenoterol alone, and is slightly superior to 200 μ g fenoterol alone in terms of FVC response over baseline at 6 and 7 hr, although this may not represent a significant clinical improvement.

Although an additive effect on peak bronchodilator response has been shown for a combination of wet nebulized atropine and salbutamol using cumulative dosing (Pierce, Allen and Campbell, 1979), and for ipratropium and salbutamol using a sequential study in bronchitis (Douglas *et al.*, 1979) and over a 3 day period in both an asthmatic and bronchitic group (Lightbody *et al.*, 1978) no significant increase in duration of response has been found in single dose studies combining ipratropium and β_2 agonist compared to either drug alone (Petrie and Palmer, 1975; Ruffin, Fitzgerald and Rebuck, 1977).

Further combination studies are needed in patients with steroid-unresponsive airflow obstruction, particularly as ipratropium may produce a comparable or greater response in chronic bronchitis than β_2 sympathomimetic drugs (Altounyan, 1964; Crompton, 1968; Poppius and Salorinne, 1973).

Acknowledgments

To G. Cox, D. Alston, A. Eyre-Brook and Miss E. Allan of W.B. Pharmaceuticals for supply of inhalers and statistical assistance.

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(Accepted 6 July 1982)