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Oxitropium Bromide: An Acute Dose Response Study of a New Anticholinergic Drug in Combination with Fenoterol in Asthma and Chronic Bronchitis

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SUMMARY. **The aim of this study was to compare the bronchodilator response of patients with either stable asthma or stable chronic bronchitis to the acute administration of oxitropium bromide and a β agonist (fenoterol) when given both separately and together in order to determine the responses of these two groups of patients and the optimal doses of these agents when given in combination. The responses of 23 patients with asthma and 25 patients with chronic bronchitis to 400 micrograms of fenoterol, and 200 micrograms of oxitropium given either alone or together with 100, 200 or 400 micrograms of fenoterol was studied. The peak bronchodilator response to oxitropium bromide of the patients with chronic bronchitis was equivalent to the fenoterol response while, in the patients with asthma, the response to oxitropium bromide was approximately 30% of the response to fenoterol. In both groups of subjects the addition of oxitropium bromide to fenoterol significantly increased both the magnitude and the duration of the bronchodilator response without a significant increase in side effects. In both groups of subjects 200 micrograms of oxitropium bromide and 200 micrograms or more of fenoterol gave the optimal response.**

INTRODUCTION

Oxitropium bromide is a new quarternary anticholinergic compound based on scopolamine instead of atropine.[1] It appears to be slightly more potent and to have a longer duration of action than ipratropium with bronchodilator activity up to at least 8 h after drug administration.[1–3] However there are no published studies to date of the effects of optimal doses of inhaled oxitropium bromide in combination with a β agonist over an 8 h study period in a controlled laboratory environment in patients with either clearly characterised asthma or chronic bronchitis. The aim of this study was to compare the bronchodilator response of patients with either asthma or chronic bronchitis to the acute administration of oxitropium bromide and fenoterol both when given together and separately in order to compare the responses of these 2 groups of patients and to determine the optimal dose of fenoterol when given in combination with oxitropium.

PATIENTS AND METHODS

Patients

23 patients with asthma were studied. All fulfilled the ATS criteria for asthma,[4] had stable symptoms within the preceding 6 weeks, were lifelong non-smokers, were not taking oral corticosteroids and had an FEV_1 (after β agonist drugs had been withheld for 12 h) of between 25% and 75% of the predicted value. Only patients who had reversible airflow obstruction (FEV_1 increased by 20% or more after 400 micrograms of fenoterol by metered dose inhaler) and bronchial hyperresponsiveness to histamine[5] were included in the study. All patients were atopic (positive skin prick test reactions to 2 or more common inhalant allergens).

25 patients with chronic bronchitis were studied. All fulfilled the ATS criteria for chronic bronchitis,[4] had not smoked cigarettes within the preceding 12 months, had had no change in symptom severity or treatment in the preceding 6 weeks, were not taking oral corticosteroids, and had an FEV_1 (after β agonist drugs had been withheld for 12 h) of between 25% and 75% of the predicted value. Only patients whose FEV_1 increased by more than 5% but less than 15% after the inhalation of 400 micrograms of fenoterol from a metered dose inhaler and who had no bronchial hyperresponsiveness to histamine[5] were included.

Methods

No oral agents were permitted for 1 week before and during the study and inhaled bronchodilator was not permitted for 8 h prior to each test. At the beginning of each test day spirometry was measured using a dry spirometer (Vitalograph). The best of three measurements was taken and the test did not proceed unless the readings were within 10% of each other and within 20% of the initial readings on the first day.

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Each patient attended the laboratory from 08.30–17.00 on 6 consecutive days. After a 30 min rest period baseline spirometric data were collected and pulse rate was measured. One of the 6 drug treatments was then administered using identical blank metered dose inhalers in a randomised double-blind manner using a double dummy technique. The treatments given were placebo, fenoterol 400 micrograms alone, and oxitropium bromide 200 micrograms either alone or together with fenoterol 100, 200 or 400 micrograms.

Spirometry was measured 15, 30, 45, 60, 80 and 100 minutes and then hourly for a total of 8 h after each drug treatment. On each occasion 3 measurements were taken and the highest value was used and the bronchodilator response was expressed as percentage change from the initial value obtained on each day. At each observation time the presence of a dry mouth or blurred vision was rated on a scale of 0 to 4 (0 = absent: 4 = marked) according to the patient's symptoms, and tremor was rated similarly. Statistical analysis was carried out using one-way analysis of variance and Newman-Keuls test. The level of statistical differences were adjusted for the number of time intervals at which tests were done.

RESULTS

The clinical features of the patients are listed in Table 1. There was no significant difference ($p > 0.05$) between the mean (± 1 S.E.) basal FEV_1 (expressed as a % of the predicted value) on each of the 6 test days of the patients with asthma ($57.2 \pm 1.6\%$, $58.4 \pm 1.8\%$, $56.7 \pm 1.5\%$, $59.3 \pm 1.2\%$, $58.1 \pm 1.6\%$, $56.1 \pm 1.9\%$) or chronic bronchitis ($46.5 \pm 2.8\%$, $48.4 \pm 2.5\%$, $47.3 \pm 2.9\%$, $47.1 \pm 2.7\%$, $46.6 \pm 3.1\%$, $45.9 \pm 3.0\%$).

Table 1. Baseline patient data (mean $\pm$ 1 S.E.)

	Asthma	Chronic bronchitis
Number of patients	23	25
Mean age (years)	42.0 ± 3.1	60.3 ± 1.4
Duration of symptoms (years)	40.0 ± 3.2	13.5 ± 1.5
FEV_1 (litres)	2.08 ± 0.18	1.37 ± 0.08
FEV_1 (% predicted)	57.9 ± 1.6	47.3 ± 2.9
Vital capacity (litres)	3.42 ± 0.20	2.52 ± 0.16
Vital capacity (% predicted)	81.0 ± 2.9	55.1 ± 2.9
Serum IgE (U/ml)	472 ± 32	82 ± 12
Number of positive skin prick test reactions	5 ± 1	0
Total dose of histamine causing a 20% fall in FEV_1 (micromoles)	0.25 ± 0.03	4.2 ± 0.5
% increase in FEV_1 after fenoterol administration	$23 \pm 1\%$	$7 \pm 1\%$

The mean % increases of FEV_1 from the baseline value of the patients with asthma (FEV_1 being expressed as % of predicted value) on each of the different treatment days are shown in Figure 1. The peak % changes in FEV_1 (expressed as % change from the actual baseline value on each day) are shown in Table 2, the mean peak bronchodilator response to oxitropium alone being 31% of the response to fenoterol alone. There was no significant difference between the peak % increase in FEV_1 after oxitropium plus either 200 or 400 micrograms fenoterol ($p > 0.05$) but the results after the higher dose of fenoterol tended to be greater than those after 200 micrograms. The mean times after drug administration for the peak increase in FEV_1 are also shown in Table 2. There was no significant difference between oxitropium plus fenoterol at any of the doses used ($p > 0.05$) but these

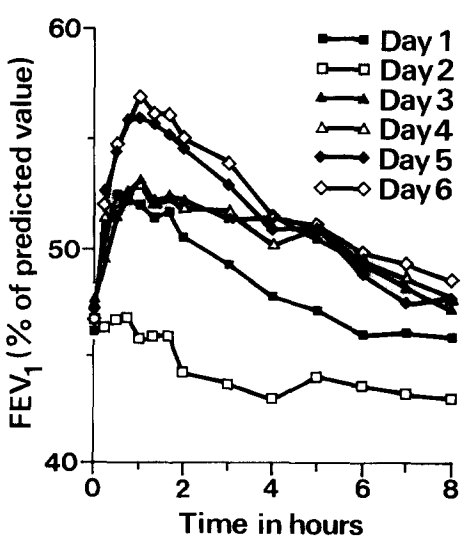

Fig. 1—Mean FEV_1 readings (expressed as percentage of predicted value) in patients with asthma on each treatment day. Day 1 = Fenoterol 400 μg; Day 2 = Placebo; Day 3 = Oxitropium 200 μg; Day 4 = Oxitropium 200 μg & Fenoterol 100 μg; Day 5 = Oxitropium 200 μg & Fenoterol 200 μg; Day 6 = Oxitropium 200 μg & Fenoterol 400 μg.

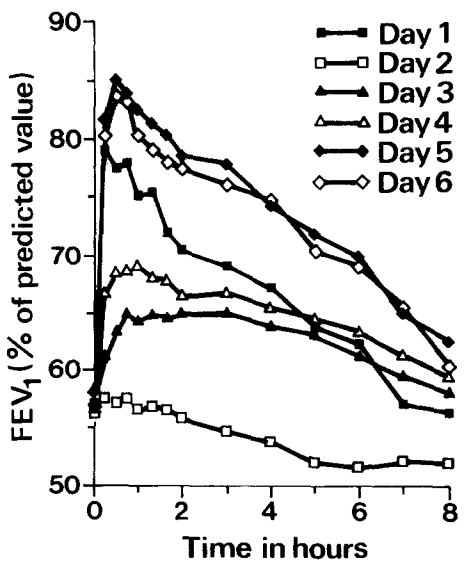

Fig. 2—Mean FEV_1 readings (expressed as percentage of predicted value) on each treatment day in the patients with chronic bronchitis. Day 1 = Fenoterol 400 μg; Day 2 = Placebo; Day 3 = Oxitropium 200 μg; Day 4 = Oxitropium 200 μg & Fenoterol 100 μg; Day 5 = Oxitropium 200 μg & Fenoterol 200 μg; Day 6 = Oxitropium 200 μg & Fenoterol 400 μg.

Table 2. Time (± 1 S.E.) for peak effect and duration of effect in asthmatic patients

	Peak % increase in FEV_1 from basal value	Time to peak FEV_1 (min)	Time for FEV_1 to reach 50% of peak change (h)
Placebo	2.4±0.3% p<0.01	—	—
Oxitropium 200 μg	7.3±0.8% p<0.01	73±4 p<0.01	5.8±0.5 p>0.05
Oxitropium + Fenoterol 100 μg	12.4±1.2% p<0.001	39±4 p>0.05	6.0±1.0 p>0.05
Oxitropium + Fenoterol 200 μg	27.2±0.8% p>0.05	44±5 p>0.05	6.2±0.7 p>0.05
Oxitropium + Fenoterol 400 μg	28.0±1.2% p<0.05	43±4 p<0.01	5.7±0.5 p<0.01
Fenoterol 400 μg	23.4±0.9%	22±3	3.1±0.2

times were all significantly less than that for oxitropium alone ($p<0.01$) and greater than that for fenoterol alone ($p<0.05$). The times taken for the FEV_1 increment of the patients with asthma to fall back to 50% of peak rise are also shown in Table 2. The data obtained with oxitropium or oxitropium plus any of the doses of fenoterol were not significantly different ($p>0.05$) but these data were all significantly greater than the value obtained with fenoterol alone ($p<0.01$). In the asthmatic subjects there was no significant correlation between the magnitude of the response to oxitropium alone and either fenoterol alone ($r_{xy}=0.09$, $p>0.05$) or oxitropium plus any of the doses of fenoterol used ($r_{xy}=0.11$, $p>0.05$). Similarly there was no significant correlation ($p>0.05$) between the magnitude of the oxitropium response and any of the clinical variables listed in Table 1.

The mean % increases from baseline in FEV_1 of the patients with chronic bronchitis (FEV_1 being expressed as a % of the predicted value) are shown in Figure 2 and the peak changes (expressed as % change from the actual baseline value on each day) are shown in Table 3. There was no significant difference between the peak % increase in FEV_1 after oxitropium plus either 200 or 400 micrograms fenoterol ($p>0.05$) but the results after the higher dose of fenoterol tended to be greater than after 200 micrograms. There was no significant correlation between the magnitude of the maximal response to either oxitropium or fenoterol alone and any of the clinical variables in Table 1.

There was no significant change in pulse rate in either of the patient groups on any of the treatment days. The only side effect detected by patients was tremor and this only occurred in 2 of the patients after

Table 3. Time (± 1 S.E.) for peak effect and duration of effect in patients with chronic bronchitis

	Peak % increase in FEV_1 from basal value	Time to peak FEV_1 (min)	Time for FEV_1 to reach 50% of peak change (h)
Placebo	1.7±0.2% p<0.01	—	-
Oxitropium 200 μg	6.8±0.8% p>0.05	50±5 p>0.05	5.9±2.3 p>0.05
Oxitropium + Fenoterol 100 μg	7.1±0.7% p<0.05	52±4 p>0.05	5.4±1.1 p>0.05
Oxitropium + Fenoterol 200μg	9.2±0.8% p>0.05	48±4 p>0.05	5.6±0.7 p>0.05
Oxitropium + Fenoterol 400μg	10.4±0.6% p<0.01	45±4 p<0.05	5.1±0.9 p<0.05
Fenoterol 400μg	6.6±0.5%	35±3	3.8±1.6

fenoterol alone. No side effects were reported with oxitropium.

DISCUSSION

These findings indicate that the combination of oxitropium and fenoterol give a greater peak bronchodilator effect than fenoterol alone and suggest that 200 micrograms of oxitropium plus 200 micrograms or more of fenoterol in the optimal dose combination to achieve maximal peak bronchodilatation in patients with stable asthma or chronic bronchitis. It could be argued that a similar result may have been obtained by using a higher dose of fenoterol alone. This is unlikely as previous data has shown that 400 micrograms of fenoterol is the optimal dose in patients with stable asthma with additional increases in dose enhancing only the duration of response at the expense of greater side effects.[6] Furthermore previous dose-response experiments with fenoterol plus ipratropium have shown that the increased response to the use of fenoterol and ipratropium together could not be obtained merely by increasing the dose of fenoterol and that when these agents were used together there was a real additive effect.[7,8]

It has been suggested that patients with chronic bronchitis and also asthmatic patients who are non-atopic or who have been cigarette smokers have the greatest probability of responding to anticholinergic agents.[9,10] For these reasons a group of patients with well-characterised atopic asthma and another with chronic bronchitis were studied so that the efficacy of oxitropium could be properly determined in both types of subject. The lack of correlation obtained in this study between any of the clinical variables and the magnitude of the oxitropium response in either patient group resembles the findings of others who have also reported that age, atopic status, and duration and severity of symptoms do not separate responders from non-responders.[11] An assessment of the usefulness of oxitropium in an individual patient can therefore only be made after an appropriate clinical trial of the drug.

In this study the response of patients with stable chronic bronchitis to oxitropium was equivalent to the fenoterol response while, in patients with stable asthma, the response to oxitropium was approximately 30% of the fenoterol response. In both groups of subjects the addition of oxitropium significantly increased both the magnitude and duration of the response to fenoterol without a significant increase in side effects and this response was sustained for at least 8 h.

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