Thorax 1984;**39**:453–456

A dose response study of oxitropium bromide in chronic bronchitis

ET PEEL, G ANDERSON

From the Newport Chest Clinic, Newport

ABSTRACT In a dose response study 12 patients with chronic bronchitis and airflow obstruction received inhaled placebo and incremental doses of oxitropium bromide. Significant improvements in peak expiratory flow rate, forced expiratory volume in one second, and forced vital capacity were recorded at all times up to 10 hours after all doses of oxitropium bromide. Oxitropium bromide is an effective bronchodilator in chronic bronchitis with an optimal dose of 400–600 μg.

Oxitropium bromide is a quaternary ammonium compound derived from scopolamine that has anticholinergic properties. It is an effective bronchodilator in bronchial asthma[1] and we report a dose response study in chronic bronchitis.

Methods

Twelve patients were studied. Their mean age was 62 years (range 54–69 years) and nine were men. All were ex-cigarette smokers and had chronic bronchitis according to the Medical Research Council criteria[2] with peak expiratory flow rates (PEFR) of less than 70% of predicted.[3] All patients had a relatively fixed degree of airways obstruction during a preceding period of observation as outpatients and had no blood eosinophilia and negative responses to routine skin prick testing with house dust mite, feathers, and mixed grass and tree pollen extracts. The mean PEFR was 248 l min^{-1} before salbutamol 200 μg and 273 l min^{-1} afterwards (the post-bronchodilator PEFR was recorded 15 and 30 minutes after salbutamol and the higher reading taken). The range of salbutamol reversibility was from −2·4% to +18·8%, with a mean of 10·7%. The study was carried out over five consecutive days. All bronchodilator drugs were withheld for at least 12 hours before the start of the trial and until its completion. Drugs were given by pressurised aerosol; on the first day patients received a single dose of placebo and on subsequent days increasing doses (100, 200, 400, and 600 μg) of oxitropium bromide. Patients were not aware of the dose received. Measurements were made of PEFR, one second forced expiratory volume (FEV_1), forced vital capacity (FVC), and pulse rate immediately before the inhalation and at intervals after inhalation of the trial drugs—namely, at 0·5, 1, 1·5, 2, 2·5, and 3 hours. Blood pressure was measured immediately before and two hours after inhalation. Subsequently patients recorded their PEFR on diary cards at home 4, 6, 8 and 10 hours after the inhalations. The lung function tests in the laboratory and at home were performed on three occasions and the best value was selected for analysis. Patients recorded any side effects on the diary cards and at the end of the study they were specifically questioned about palpitations, dry mouth, visual disturbance, and problems with micturition.

Lung function, pulse rate, and blood pressure were analysed by the analysis of variance technique coupled with Duncan's multiple range test.[4]

Results

PULMONARY FUNCTION

The baseline readings of PEFR showed no significant variability between study days. For both FEV_1 and FVC, however, the baseline values on day 3 (200 μg oxitropium) were significantly lower than those on day 5 (600 μg oxitropium) and they have therefore been excluded from the statistical analysis. Analysis of variance showed significant dose response relationships for each of the three indices and the mean data are plotted in figures 1–3.

Address for reprint requests: Dr G Anderson, Newport Chest Clinic, 129 Stow Hill, Newport, Gwent NPT 4GA.

Accepted 13 January 1984

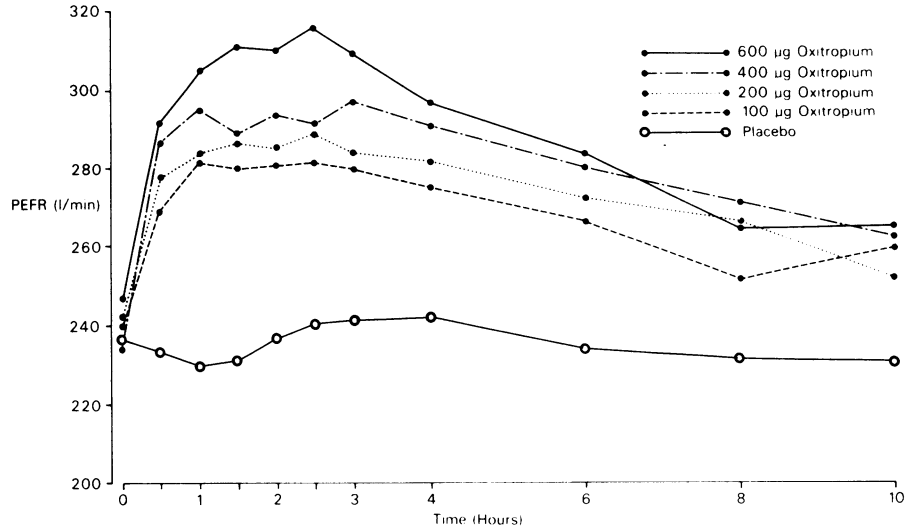

Fig 1 *Relationship of peak expiratory flow rate (PEFR) to time with four doses of oxitropium and placebo. Analysis of variance shows a significant overall dose response relationship. All doses of oxitropium produced PEFR values that were higher ($p < 0{\cdot}01$) than the corresponding values for placebo. Compared with placebo, 100 µg was more effective at all time intervals up to and including 10 hours ($p < 0{\cdot}01$). Compared with 100 µg, 200 µg produced a significant increase at 8 hours only ($p < 0{\cdot}05$); 400 µg produced higher values at all times except 1·5, 2·5, and 10 hours; and 600 µg produced higher values at all times except 10 hours. The mean maximum improvement in PEFR after 600 µg oxitropium, seen after 2·5 hours, was +58 l/min (+33%). The standard errors of the PEFR values at different times ranged from 20 to 27 l/min.*

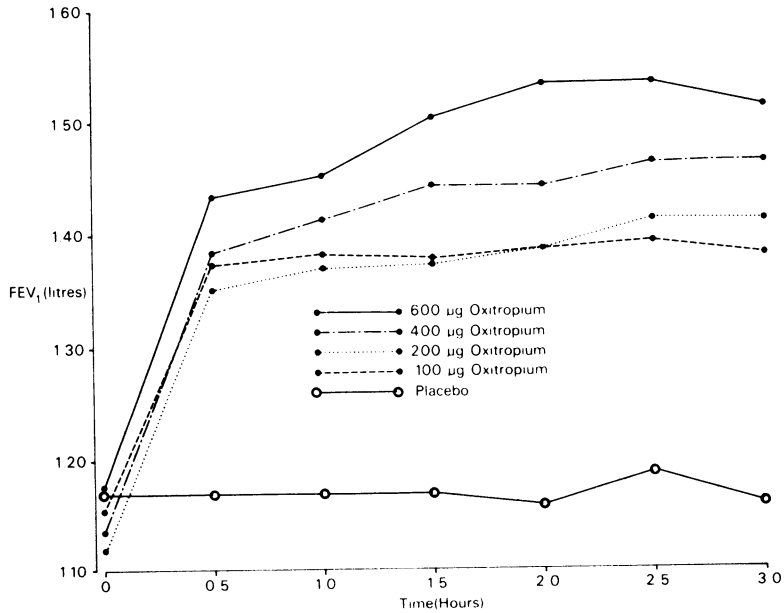

Fig 2 *Relationship of mean FEV_1 to time for three doses of oxitropium and placebo. The results for day 3 (200 µg oxitropium) have been excluded from statistical analysis as the baseline was significantly lower than that for placebo and on day 5 (600 µg oxitropium). All doses of oxitropium produced values of FEV_1 that were higher ($p < 0{\cdot}01$) than were the corresponding values for placebo. There was a significant dose response relationship. The 400 µg dose produced higher values than 100 µg at 1·5, 2, and 3 hours ($p < 0{\cdot}01$) and at 2·5 hours ($p < 0{\cdot}05$); 600 µg produced higher values than 400 µg at 1·5, 2, 2·5 ($p < 0{\cdot}01$), and 3 hours ($p < 0{\cdot}05$). The standard errors of FEV_1 values at different times ranged from 0·14 to 0·17 l.*

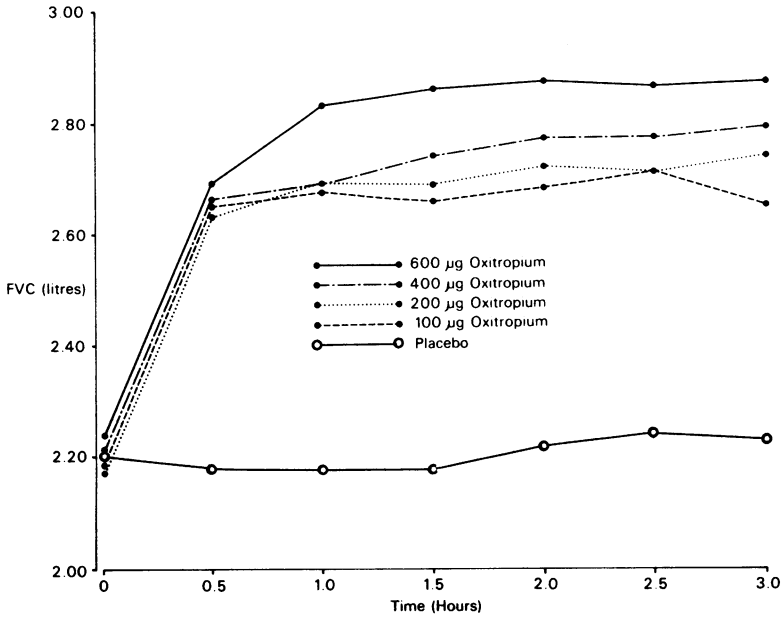

Fig 3 *Relationship of mean forced vital capacity (FVC) to time after three doses of oxitropium and placebo. Results of day 3 (200 μg oxitropium) were excluded from the statistical analysis as the baseline value was significantly lower than for 600 μg. All doses of oxitropium produced values of FVC that were higher ($p < 0.01$) than were the corresponding values for placebo. The 400 μg dose produced higher values than 100 μg at 1·5 and 2 hours ($p < 0.05$) and 3 hours ($p < 0.01$); 600 μg produced higher values than 400 μg at 1, 1·5, 2, and 3 hours ($p < 0.01$) and at 2·5 hours ($p < 0.05$). The standard errors of FVC values at different times ranged from 0·18 to 0·23 l.*

Significant differences between individual doses are indicated in the legends to the figures. The maximum improvements were seen between 2 and 3 hours following the largest dose used. The PEFR results showed that significant improvements were sustained for as long as 10 hours.

PULSE RATE AND BLOOD PRESSURE

There were no clinically significant changes in pulse rate or blood pressure during the study.

SIDE EFFECTS

Six patients mentioned side effects. Unpleasant taste was experienced by four, mainly at the higher doses of the drug. Dry mouth was reported by three, all at the 600 μg dose. Two patients had a headache, (each at only one dose, 200 μg and 400 μg).

There were no problems with vision or micturition.

Discussion

The anticholinergic agent ipratropium bromide is widely used in both bronchitis and asthma and oxitropium bromide, a new anticholinergic drug, is a potent bronchodilator in asthma. In this study it is shown to have a powerful bronchodilating effect in patients with chronic airways obstruction, with bronchodilator effects lasting up to 10 hours. The maximum improvement in PEFR, FEV_1, and FVC, after 400 μg and 600 μg, was about 30% and this represents a clinically useful effect in a group of bronchitic patients with a poor response to 200 μg of inhaled salbutamol. The degree of reversibility achieved with oxitropium bromide might suggest that some patients had asthmatic features in addition to chronic bronchitis. In the selection of patients care was taken to exclude anyone with features suggesting asthma but we accept that no diagnostic test is totally reliable in excluding asthma, which may coexist in patients with chronic airways obstruction.

Side effects were minor. The dry mouth is likely to be an anticholinergic effect, limiting the maximal dose to 400–600 μg. The prolonged duration of action suggests that twice or thrice daily administration is adequate.

We wish to thank Boehringer Ingelheim Limited for the supply of drugs and Dr A Eyre-Brook for advice and help, and Mr Nicholas Pready for carrying out the statistical analysis.

References

[1] Peel ET, Anderson G, Cheong B, Broderick N. A comparison of oxitropium bromide and ipratropium bromide in asthma. *Eur J Respir Dis* (in press).

[2] Medical Research Council. Definition and classificaton of chronic bronchitis for clinical and epidemiological purposes. *Lancet* 1965;i:775–9.

[3] Gregg I, Nunn AJ. Peak expiratory flow in normal subjects. *Br Med J* 1973;iii:282–4.

[4] Duncan DB. Multiple range, multiple F-test. *Biometric* 1952;**11**:1–42.