

Dose response of ipratropium bromide assessed by two methods

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ABSTRACT The dose-response relationships of ipratropium bromide were assessed by two different techniques in two groups of 10 male patients with partially reversible airways obstruction. In a randomised double-blind fashion on four days, 10 patients were given 40 μg , 80 μg , or 120 μg of ipratropium bromide or placebo from identical containers. Baseline FEV₁ and vital capacity were measured and the measurements repeated after 40 minutes, one, two, four, and six hours, and any symptoms were elicited. In the second study, each patient received cumulative doses of 40 μg , 80 μg , and 120 μg . Baseline FEV₁ was obtained and repeated 35 minutes after each dose. The peak increase of the FEV₁ was comparable in both studies. The FEV₁ was slightly greater after 120 μg than after 40 μg . Although this reached statistical significance only in the first study, it was concluded that the cumulative dose-response technique was suitable for determining the peak response. However, this technique was unsuitable for assessing duration of effect, which could be examined only in the first study. After 120 μg of ipratropium bromide, the FEV₁ was significantly greater than after 40 μg at each time interval and it was greater than 80 μg at six hours ($p < 0.05$). No significant side effects were noted in either study. When prolonged effective bronchodilation is sought, a dose of 120 μg of ipratropium bromide may be preferable to the recommended dose of 40 μg .

The anticholinergic bronchodilator ipratropium bromide is a quaternary ammonium derivative of atropine. Its quaternary structure prevents it crossing the blood-brain barrier and causing central effects. As an aerosol it is highly specific and virtually free of side effects even in doses well in excess of those recommended.^{1,2}

It has been reported that the recommended dose, 40 μg from a metered dose inhaler, achieves a peak bronchodilator effect.³ Nevertheless, higher doses may prolong the duration of bronchodilation^{4,5}.

To assess both the peak bronchodilation and the duration of the response, we have determined the dose-response relationships of ipratropium bromide with two different techniques. In the first study we administered the test doses on different days. In this way we were able to assess the peak response, duration of action, and unwanted side effects. The second study employed a cumulative dose-response technique.⁶ It is simpler and allows several doses of a drug to be assessed over a short

period of time, and the peak effect and unwanted effects can be determined. Its limitation is that it does not allow the duration of action to be assessed.

Methods

A group of 16 male patients gave informed consent to taking part in the investigation. All had asthma characterised by episodes of wheeze and shortness of breath requiring bronchodilators for relief of symptoms, and 12 were receiving beclomethasone dipropionate by inhalation or oral corticosteroids or both. Only six of the 16 patients had positive skin tests to common allergens and all but one had chronic productive cough. Eleven were current cigarette smokers.

SINGLE DOSE STUDIES

For the first study, 10 male patients were admitted to hospital in a stable condition. Bronchodilators were withheld for at least nine hours before any test. However, steroids were continued unchanged.

In a randomised, double-blind fashion on four

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days (consecutive where possible), the 10 patients studied were given 40 µg, 80 µg, or 120 µg of aerosol ipratropium bromide or placebo from identical containers. Two unlabelled containers were used, containing either placebo or active agent (20 µg per puff), so that the patient each day received six puffs of aerosol over 90 seconds.

Each study started at about 0900 hr. Baseline measurements of forced expiratory volume in one second (FEV₁) and vital capacity (VC) were performed, and the best of three readings taken. The patient then inhaled the aerosol. At 40 minutes, one, two, four, and six hours after the aerosol measurements of FEV₁ and VC were performed. Again the best of three measurements was taken, corrected to BTPS. Symptoms were recorded before each measurement. Baseline measurements each day were within 15% of each other. Tests were postponed when the baseline values were outside this range. The significance of the results obtained was analysed using analysis of variance.

CUMULATIVE DOSE-RESPONSE STUDY

For the cumulative dose-response study, 10 male outpatients were assessed (four common to the first study). Bronchodilators were withheld as before.

The peak effect of ipratropium bromide is not reached until about 30–40 minutes.³ This peak is then maintained for two to three hours. For this reason, after baseline measurements of FEV₁ and VC, and then the inhalation of 40 µg of ipratropium bromide, 35 minutes were allowed to elapse before three measurements of FEV₁ were made. The patient then inhaled another 40 µg and the measurements were repeated beginning 35 minutes after this dose. A third dose of 40 µg was then inhaled and measurements repeated 35 minutes later.

In this way, the patient received cumulative doses of 40 µg, 80 µg, and 120 µg. The best of three FEV₁ readings were taken each time. The readings were uncorrected because of the brief duration of the investigation. Symptoms were elicited after each dose. The significance of the results were analysed using analysis of variance.

Results

SINGLE DOSE STUDIES

The baseline mean FEV₁ values before placebo and to each dose of ipratropium bromide did not differ significantly. The mean and range in litres before placebo, 40 µg, 80 µg, and 120 µg of ipratropium bromide were 1.08 (0.40–1.80), 1.06 (0.40–1.70), 1.09 (0.40–1.90).

Compared with the placebo, each dose of ipratropium bromide produced a significant increase of the mean FEV₁ (p<0.05). This was found up to two hours for the 40 µg dose and up to six hours with the 80 µg and 120 µg doses. Given the baseline value, after 80 µg the FEV₁ was significantly greater than after 40 µg at four hours (p<0.05) whereas for 120 µg the FEV₁ was significantly greater than 40 µg at all times except zero and was greater than 80 µg at six hours (p<0.05) (fig 1). Apart from a dry cough in one patient after 120 µg there were no side effects.

CUMULATIVE DOSE-RESPONSE STUDY

The results for the cumulative dose response study are shown in fig 2. The mean baseline FEV₁ was 1.06 l (range 0.38–2.03 l). After 40 µg there was a significant increase in mean FEV₁ of 0.30

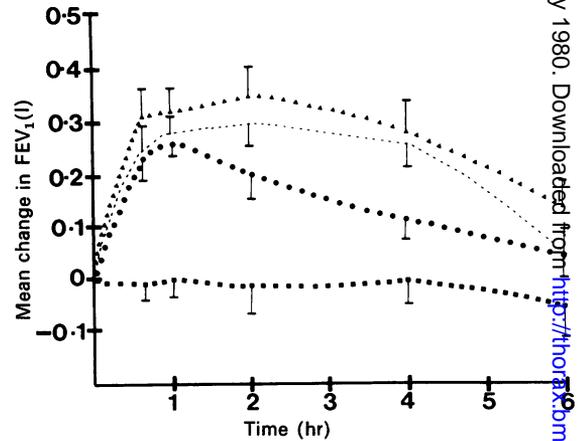


Fig 1 Mean increase ± SEM of FEV₁ after different doses of ipratropium bromide, n=10. ▲=120 mcg, ---=80 mcg, ●●●=40 mcg ■■=placebo.

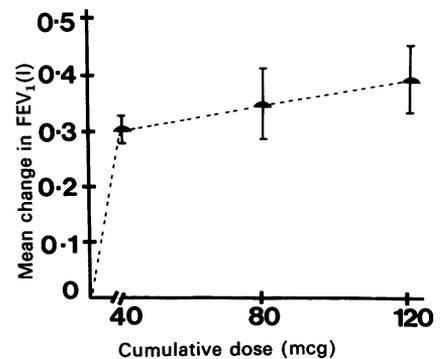


Fig 2 Mean increase ± SEM of FEV₁ after cumulative doses of ipratropium bromide, n=10.

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(28%) compared to the mean baseline FEV₁. After a cumulative dose of 80 µg there was a further rise of 6%, and after a cumulative dose of 120 µg, a further rise of 3% in FEV₁, though neither of these latter changes was statistically significant.

No side effects were recorded.

Discussion

Using two different methods we found a small increase in the peak bronchodilatation when doses of 80 µg and 120 µg of ipratropium bromide were compared with 40 µg. The differences were not statistically significant in the cumulative dose study, but reached significance at the 5% level with the dose of 40 µg versus 120 µg administered on separate days. Ruffin and Newhouse⁵ found that 60 µg of ipratropium bromide gave a significantly greater peak maximum mid-expiratory flow rate than 20 µg and 40 µg, but no difference for peak FEV₁. Most other studies,^{4,7} have failed to show that doses of ipratropium bromide above 40 µg produce a greater response than that achieved by 40 µg. The improvement in the peak response in the present study was small. It can be concluded that a dose of 40 µg of ipratropium bromide produces close to the peak response obtainable. The investigation has shown that the cumulative dose-response technique is suitable for determining the peak response. However, the technique does not allow assessment of duration of effect. For this, the more troublesome procedure of administering doses on different days is necessary. Ruffin and Newhouse⁵ have shown previously that 60 µg of ipratropium bromide gives a significantly longer duration of action than 20 µg or 40 µg, whereas Baigelman and Chodosh⁴ found in a group of chronic bronchitics that 80 µg gave a significantly longer lasting effect than 40 µg. In the present investigation it was found that 120 µg produced significant bronchodilatation for at least six hours. It was superior to 40 µg and marginally better than 80 µg. The patients investigated may have been particularly responsive to anticholinergic drugs. They all had asthma but were investigated when relatively stable and most were receiving steroids. All but one had chronic productive cough consistent with chronic bronchitis.

Only six had positive skin reactions to common allergens. Patients with these characteristics may be more responsive to anticholinergic drugs than other asthmatics.^{8,9}

For the type of patient studied, our results show that 120 µg of ipratropium bromide offers a higher peak and longer duration of bronchodilatation than the usually recommended dose of 40 µg. The dose of 120 µg was well tolerated, and provided this is confirmed, this dose of ipratropium bromide may prove useful to obtain prolonged effective bronchodilatation in clinical practice.

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