Postgraduate Medical Journal (August 1984) **60**, 526–528

Ipratopium bromide in patients with nocturnal asthma

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Summary

Fourteen patients with nocturnal asthma were recruited to a two period crossover trial which compared a run-in period on nightly salbutamol (200 μg) with a period on nightly ipratropium bromide (160 μg) and a period on nightly salbutamol plus ipratropium at night.

Morning dipping, as assessed by the fall in peak flow overnight, was significantly reduced in the periods when ipratropium bromide was taken. Peak flow in the morning and also at night was improved when taking ipratropium bromide. Ipratropium bromide in adequate dosage appears to be effective in reducing morning dipping in asthma.

KEY WORDS: ipratropium bromide, nocturnal asthma, morning dipping, asthma, anticholinergics.

Introduction

Many asthmatics experience symptoms at night and a large proportion have their lowest peak flow rates (PEFR) in the early hours of the morning (Hetzel, 1981). While further research continues into the aetiology of this increased bronchoconstriction, treatment remains a problem (Editorial, 1983). Inhalation of beta-stimulants or prophylaxis with oral slow-release theophyllines or beta-stimulants has proved disappointing clinically.

It has been suggested that cholinergic mechanisms may be involved in the pathogenesis of asthma (Simonssen, Jacobs and Nadel, 1967). A theoretical advantage of a combination of beta-stimulants and an anticholinergic agent therefore exists (Barnes, Brown and Dollery, 1980).

Ipratropium bromide is a synthetic anticholinergic bronchodilator shown to be of use in acute and chronic asthma. We have studied the effect of this agent on a group of asthmatics who have demonstrated significant morning dipping.

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Methods

Fourteen patients with chronic asthma gave informed consent to the study which was approved by the Hospital Ethics Committee. They comprised 13 females and one male, aged between 25 and 75 years. All had previously demonstrated a drop in their morning peak flow of 25% of the previous days maximum on at least 7 days over a 2-week period, and had been shown to have at least 15% reversibility to an inhaled beta-stimulant. All patients except one had a baseline forced expiratory volume at the first second (FEV_1) of less than 75% of predicted value. All 14 patients were regularly using a salbutamol pressurised aerosol. Twelve were taking oral or inhaled steroids. Patients taking slow-release theophyllines or oral beta-stimulants were excluded.

Study design

The trial was designed as a two period cross-over with an initial run-in period. Each period was of 2-weeks duration. In a small pilot study patients found the taste of ipratropium bromide distinctive and we therefore felt it impossible to make the study blind.

In the run-in period (A) patients took their normal therapy which included two puffs of salbutamol (100 μg/puff) on retiring. Then in the cross-over stage they took either usual therapy plus four puffs ipratropium bromide (40 μg/puff) on retiring (Period B) followed by usual therapy without their night-time dose of inhaled salbutamol but with four puffs of ipratropium bromide (40 μg/puff) on retiring (Period C) or C followed by B according to the randomization schedules.

Patients kept a diary throughout the study. Peak flow readings were recorded twice on three occasions

during each day; immediately on rising, at midday, and on retiring, each time before taking any inhaled medication. In addition patients were required to record symptom scores for wheezing, breathlessness and cough (0 = nil, 1 = mild, 2 = moderate, 3 = severe). Nocturnal waking and use of inhalers at night was also recorded.

Results

Twelve patients completed the study. One withdrew because of an acute exacerbation of her asthma. The other withdrawal was due to the patient feeling nauseous approximately 1·5 hr after inhaling ipratropium bromide.

The percentage fall in peak flow (calculated from the highest of either the midday or the night-time readings to the peak flow the following morning) showed a significant reduction when ipratropium bromide was added to treatment. This morning dipping was reduced in both treatment periods with ipratropium bromide when compared with normal therapy with nightly salbutamol (period B, $P<0·01$; period C, $P<0·05$) (see Fig. 1).

In period B and C (when ipratropium bromide was taken) peak flow rates were higher on waking ($P<0·01$) and on retiring ($P<0·05$) when compared with period A. There was no significant difference between periods B and C with respect to morning dipping or peak flow rates (Table 1).

A significant improvement was also observed for both the symptom scores for breathlessness and cough for both the treatment periods B and C compared with period A ($P<0·01$). There was no significant difference between any of the three periods with respect to the patient's assessment of morning wheezing.

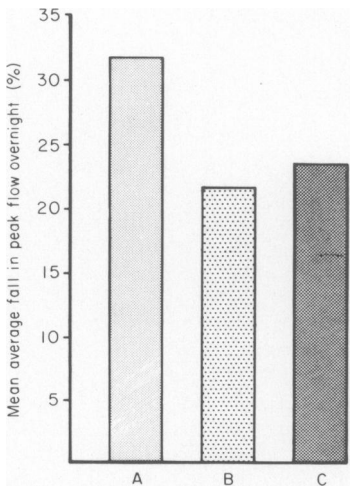

FIG. 1. Mean average fall in peak expiratory flow overnight during the three treatment periods. A = run in; B = ipratropium bromide 160 μg and salbutamol 200 μg; C = ipratropium bromide 160 μg.

TABLE 1. Average peak expiratory flow rates (litres/min) during the three treatment periods (A, B and C as in Fig. 1, mean ± s.e.).

	Mid-day	Night	Following morning
Run-in on usual therapy (A)	270 ± 25	242 ± 27	191 ± 22
Usual therapy—salbutamol & ipratropium bromide (B)	284 ± 27	260 ± 29	229 ± 26
Usual therapy & ipratropium bromide (C)	284 ± 28	257 ± 28	230 ± 24

Five patients commented on the taste of ipratropium bromide while three reported a dry mouth. Two patients who complained of these symptoms failed to complete the study. Other reported symptoms were minor and could not be attributed to the treatment.

Discussion

The parasympathetic nervous system has been implicated in the aetiology of asthma (Simonssen *et al.*, 1967). In nocturnal asthma most attention has been directed towards the discovery that the fall in peak flow coincides with the nadir of the circadian rhythm of circulating catecholamines (Barnes *et al.*, 1980b). It was initially suggested that nocturnal asthma may be caused by this fall in plasma adrenaline, but other circadian rhythms reach their bathysphase in the night or the early morning (Hetzel, 1981).

Increased vagal tone during the night coinciding with the fall in circulating catecholamines would make asthma more likely to occur at night. Barnes *et al.* (1980a) accepted that a combined treatment with β_2 stimulants and an anticholinergic agent might be of value. Our results would support this hypothesis.

The effective treatment of nocturnal asthma remains a problem in clinical practice. Steroids are not helpful while inhaled β_2 stimulants have a duration of action that is too short to last the whole night. Oral slow release β_2 stimulants or theophyllines may reduce bronchoconstriction (Fairfax *et al.*, 1980; Barnes *et al.*, 1982) but do not abolish nocturnal asthma in the clinical setting. We have shown that the long duration of action of 160 μg of inhaled ipratropium bromide also reduces overnight bronchoconstriction.

Ipratropium bromide is a synthetic anticholinergic agent which is of use in both asthma and chronic bronchitis. The duration of action may depend on the dose and a 120 μg inhaled dose has been shown to produce significant bronchodilatation for at least 6 hr (Allen and Campbell, 1980). It is safe in much higher

doses than the usual recommended dose of 40 μg (Ruffin *et al.*, 1978). We have used 160 μg as a night-time dose to see the effect overnight.

We have demonstrated that high-dose inhaled ipratropium bromide 160 μg taken at night has a significant advantage ($P<0.01$) over inhaled standard dose of salbutamol (200 μg) in reducing the morning 'dip' of peak expiratory flow rate and in improving nocturnal symptoms. A combination of ipratropium and salbutamol was no more effective than ipratropium alone in reducing the severity of nocturnal asthma. It may be that the effect we have demonstrated is dependent on the relative doses of the two drugs but have no data on comparison of high dose ipratropium with salbutamol at higher doses, which could well be used with safety. Though the peak flow rates on retiring during treatment periods B and C (whilst the patients received ipratropium) were significantly higher ($P<0.05$) this effect is unlikely to be due to the ipratropium inhaled nearly 24 hr previously. This finding does not invalidate our conclusion about the effectiveness of ipratropium in alleviating nocturnal and morning asthma.

We have carried out a limited trial directed towards the clinical problem of nocturnal asthma. Our results suggest that 160 μg of ipratropium bromide inhaled on retiring produces objective and subjective benefit to patients with nocturnal asthma. It should therefore be considered as part of the therapeutic armamentarium for this distressing and potentially dangerous condition.

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(*Accepted* 15 *February* 1984)