Effect of formoterol, a long-lasting β_2 -adrenoceptor agonist, against methacholine-induced bronchoconstriction

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1 The effects of a new long-acting inhaled β_2 -adrenoceptor agonist aerosol formoterol (12 μg), on FEV_1 , and on methacholine-induced bronchoconstriction, were compared with those of terbutaline (250 μg) and placebo in 12 mildly asthmatic subjects.

2 PC_{20} , the concentration of methacholine needed to cause a 20% fall in baseline FEV_1 , was determined 2 and 5 h after formoterol, terbutaline and placebo on separate days. Baseline PC_{20} was determined on a different day.

3 Compared with terbutaline and placebo, formoterol hastened recovery from methacholine-induced bronchoconstriction, and significantly increased mean PC_{20} (by 2.2- and 2.9-fold at 2 and 5 h respectively).

4 Thus, formoterol has a protective effect against methacholine-induced bronchoconstriction which lasts for at least 5 h.

Keywords β_2 -adrenoceptor agonist formoterol terbutaline methacholine

Introduction

Inhaled β_2 -adrenoceptor agonists are the most effective bronchodilator therapy used to treat asthma. The inhaled route enables the dose to be delivered directly to the airways. A rapid onset of action and high efficacy can be obtained with a low dose, thereby minimising unwanted systemic effects. One of the disadvantages of currently-available β_2 -adrenoceptor agonists is their relatively short duration of action, which peaks within 0.5 h and lasts approximately 3–5 h (Paterson *et al.*, 1979). Studies with formoterol, a new β_2 -adrenoceptor agonist, have shown that this bronchodilator had a markedly more prolonged effect than other currently available β_2 -adrenoceptor agonists.

In the present investigation, we examined whether formoterol, when administered by aerosol, could protect against methacholine-induced bronchoconstriction for up to 5 h in asthmatic patients. Fenoterol aerosol has been shown to possess a duration of effect of approximately 2–3 h in protecting against histamine-

induced bronchoconstriction (Salome *et al.*, 1983). We compared the effect of formoterol against that of terbutaline, another commonly-used β_2 -adrenoceptor agonist in asthma.

Methods

Twelve asthmatic patients (six males, six females, mean age 25.4 ± 4.27 years, FEV_1 $88.4 \pm 14.6\%$ predicted), with mild to moderate symptoms as defined by a history of recurrent episodes of wheezing, chest tightness, and reversible airway obstruction, were studied. Their mean height and weight were 170.3 cm and 69.8 kg respectively. This study was approved by the Ethics Committee of the National Heart and Chest Hospital and informed consent was obtained from all participants. All patients denied having any upper respiratory tract infection within 4 weeks, and stated that they had been clinically stable for at least 5 days, prior to the

study. Seven patients were taking regular inhaled corticosteroids and all were on regular inhaled β_2 -adrenoceptor agonist therapy using either salbutamol or terbutaline metered-dose inhalers. Patients abstained from using sympathomimetic medication for at least 12 h prior to each day's methacholine challenge. None was taking xanthine preparations, and xanthine-containing beverages were withheld for 2 h prior and during the 5 h observation periods.

The study was double-blind and designed to test the effect of formoterol (12 μg), terbutaline (250 μg) and placebo against methacholine-induced bronchoconstriction at 2 and 5 h. Patients were randomly allocated to one of six sequences in the form of a 3×3 Latin squares of the three treatments. Each patient attended on 4 different days over a period of 1 to 4 weeks with the first visit being a familiarisation procedure. During this first visit, the patients' personal data, case history, and the results of a medical examination were recorded. In addition, the airway responsiveness to methacholine was measured in order to obtain a baseline value. Measurements of pulse rate and blood pressure were taken using an automated recorder (Dinamap). Pulmonary function was measured using a dry wedge spirometer (Vitalograph, Buckinghamshire, UK). Methacholine solutions (Sigma Chemical Company, Dorset, UK) were prepared by diluting with normal saline in doubling concentrations (0.125–32 mg ml^{-1}).

Methacholine aerosols were delivered from a nebuliser attached to a dosimeter (Mefar, Brescia, Italy) with a mean delivery of 6.7 μl with each inhalation. The nebuliser was triggered at functional residual capacity while the subject inhaled to total lung capacity, followed by a breath hold of 10 s. FEV_1 and FVC were measured 1 min after four nebulisations at each concentration. Consecutive nebulisations, starting at the lowest and increasing by doubling concentrations every minute, were given until the FEV_1 had decreased by more than 20% compared with a control post saline value. The $\text{PC}_{20}\text{-FEV}_1$, i.e. the provocative concentration of methacholine in mg ml^{-1} causing a 20% reduction in FEV_1 , was calculated by linear interpolation of the log dose-response curve.

One puff of the coded medications was administered from a metered-dose inhaler on each trial day. Measurements of FEV_1 , FVC, pulse rate and blood pressure were taken immediately prior to the inhalation of the medication, and 30 min, 1, 2, 3, 4, and 5 h post medication. PC_{20} methacholine was determined at 2 and 5 h. Following the methacholine challenge at 2 h, FEV_1 was allowed to recover spontaneously.

Data analysis

A two-way analysis of variance (ANOVA) with repeated measures on both factors (Cohen & Halliday, 1982) was used to evaluate the effects of treatment and time on FEV_1 and PC_{20} . Multiple paired *t*-tests with Bonferroni correction were then used to compare PC_{20} after formoterol and terbutaline with placebo at 2 and 5 h, and PC_{20} after formoterol and terbutaline at 2 h with baseline values.

Results

Control FEV_1 , on each of the 3 treatment days did not differ by more than 12.5% from the baseline FEV_1 obtained on the familiarisation day; only three subjects showed variation $> 10\%$ at one of their three subsequent visits. Formoterol, but not terbutaline or placebo, produced significant bronchodilation at 0.5, 1 and 2 h after inhalation. FEV_1 increased from 3.34 ± 0.261 at baseline to 3.68 ± 0.201 2 h after formoterol. One hour after methacholine challenge, bronchoconstriction persisted irrespective of treatment. The decrease in FEV_1 , compared with the 2 h value was formoterol $9.9 \pm 3\%$, terbutaline $9.9 \pm 2.3\%$, placebo $9.7 \pm 3.9\%$. FEV_1 gradually increased so that by the time the second methacholine challenge was performed at 5 h, FEV_1 was not significantly

Figure 1 Time-course of formoterol (12 μg , ○), terbutaline (250 μg , ●) and placebo (□) on FEV_1 in 12 asthmatic subjects. Methacholine challenges were performed at 2 and 5 h. Data shown as mean $\pm$ s.e. mean.

Figure 2 Effect of formoterol (12 μ g, ○), terbutaline (250 μ g, ●) and placebo (□) on PC₂₀ methacholine in 12 asthmatic subjects at 2 and 5 h after inhalation. These results are compared with mean PC₂₀ obtained during the familiarisation day (B). Data shown as geometric mean $\pm$ geometric s.e. mean.

different from the value obtained at 2 h for formoterol and placebo; mean FEV₁ at 5 h was significantly higher for formoterol compared with placebo ($P < 0.01$). In contrast, values obtained for terbutaline remained significantly lower at 3, 4, and 5 h compared with FEV₁ at 2 h (Figure 1).

ANOVA revealed a significant treatment effect ($F = 14.4$, $P < 0.01$); multiple comparisons showed that formoterol caused a significant increase in PC₂₀ when compared with placebo and terbutaline at 2 h ($P < 0.01$), 5 h ($P < 0.01$), and baseline ($P < 0.01$) (Figure 2). The effect of terbutaline was not significantly different from that of placebo. Compared with placebo, formoterol caused a mean 2.23- and 2.92-fold decrease in methacholine responsiveness at 2 and 5 h respectively. There was no significant difference in pulse rate, blood pressure or baseline FEV₁ on the 3 study days. The major side-effect experienced by the subjects was headache reported on five occasions in three subjects: two after placebo, two after formoterol and one after terbutaline. One subject complained of tremor after formoterol.

Discussion

We have shown that formoterol at an inhaled dose of 12 μ g causes significant bronchodilation for up to 2 h and rapidly reverses methacholine-induced bronchoconstriction, such that by 5 h FEV₁ is back to the previous bronchodilated level. In addition, formoterol causes a significant decrease in airway responsiveness to methacholine which is substained for up to 5 h after inhalation. Neither placebo nor terbutaline at an inhaled dose of 250 μ g caused significant bronchodilation or decreased methacholine responsiveness.

Our results, which showed bronchodilation lasting at least 5 h despite an intervening bronchoconstrictor challenge, confirm the prolonged bronchodilator effect of formoterol observed by others. For example, Lofdahl & Svedmyr (1989) reported a more prolonged effect of formoterol aerosol (6 μ g) when compared with salbutamol (100 μ g), with an effect lasting up to 8 h. Similar results were found by Nolte & Rolke (1988) using formoterol aerosol (24 μ g) compared with fenoterol (400 μ g).

When this study was initiated, the inhaled dose of formoterol to cause maximal bronchodilator effect had not been determined. However, 12 μ g of formoterol aerosol seems to be an adequate therapeutic dose because similar profiles of actions are shown with 6, 12 and 24 μ g of formoterol in terms of degree and duration of bronchodilation (Lofdahl & Svedmyr, 1989; Nolte & Rolke, 1988). Terbutaline had a small bronchodilator effect but this did not achieve statistical significance perhaps due to the sub-optimal dose of terbutaline used (half of the recommended therapeutic dose) and the mild asthmatic status of our subjects.

Previous investigators have demonstrated dose-dependent protection against histamine-induced bronchoconstriction by the β -adrenoceptor agonist, fenoterol, but this only lasted 2 to 3 h with a return of bronchial responsiveness to baseline values by 5 h even at the high dose of 400 μ g (Salome *et al.*, 1983). Our results suggest that formoterol is effective for a longer period of up to 5 h in protecting against methacholine-induced bronchoconstriction. The degree of protection (approximately 8-fold) afforded by fenoterol (400 μ g) against histamine-induced bronchoconstriction was larger than that found in our study (approximately 3-fold). This is probably due to the fact that 400 μ g fenoterol has more β -adrenoceptor agonist activity than 12 μ g formoterol (Nolte & Rolke, 1988). Again, it is surprising that terbutaline had little protective effect against methacholine-induced broncho-

constriction. Although the 5 h pre-challenge FEV₁ during placebo and terbutaline days had not returned exactly towards baseline values, this did not alter methacholine responsiveness. Thus, the small changes in starting airway calibre did not affect subsequent airway responsiveness and would have been unlikely to do so (Chung & Snashall, 1984).

The mechanisms underlying the prolonged protection afforded by formoterol against methacholine-induced bronchoconstriction can only be speculative at present. Although its bronchodilator effect at 5 h coincided with this continued protection, it seems unlikely that bronchodilation *per se* had any direct effect on airway responsiveness. Thus, when equipotent bronchodilator doses of salbutamol and ipra-

tropium were compared, salbutamol caused a much greater decrease in responsiveness than ipratropium (Britton *et al.*, 1988). The protection afforded by β -adrenoceptor agonists against methacholine-induced bronchoconstriction is likely to be the result of functional antagonism, as has been demonstrated in *in vitro* studies of airway smooth muscle (Ariens, 1987). Whether the prolonged bronchodilator and protective effect of formoterol is due to increased β -adrenoceptor binding is not known. Whatever the mechanism(s) involved, this longer duration of action over currently available β -adrenoceptor agonists may prove to be clinically useful.

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