Effect of short-term treatment with fluticasone propionate nasal spray on the response to nasal allergen challenge

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- 1 The aim of the study was to investigate the effect of short-term treatment with fluticasone propionate on the response to nasal allergen challenge in patients with allergic rhinitis.
- 2 Responses to nasal allergen challenge were assessed subjectively by recording symptom scores on visual analogue scales, and objectively by measuring histamine, PGD₂ and LTC₄ in nasal lavage and by measuring nasal inspiratory peak flow following challenge.
- 3 Nasal allergen challenge resulted in an increase in all symptom scores ($P < 0.05$); an increase in histamine and PGD₂ ($P < 0.05$), and a decrease in nasal inspiratory peak flow at 1 h, 5 h and 7 h following challenge ($P < 0.05$).
- 4 The allergen-induced changes in symptom scores, mediator levels and nasal inspiratory peak flow were attenuated by treatment with fluticasone propionate ($P < 0.05$ for all parameters measured). Post-challenge nasal obstruction was decreased by 45%; sneezing, itching and rhinorrhoea by 73, 78 and 80% respectively in the group as a whole comparing scores whilst on fluticasone propionate with those on no therapy.
- 5 Fluticasone propionate, 200 µg twice daily for 2 weeks is effective in reducing significantly the early and late response to nasal allergen challenge.

Keywords fluticasone propionate nasal allergen challenge histamine LTC₄ PGD₂

Introduction

Intranasal corticosteroid therapy is widely used in the management of allergic rhinitis. Corticosteroids have been shown to reduce both the inflammatory changes which occur in the nasal airway in allergic rhinitis [1, 2], as well as reducing nasal airway hyperresponsiveness [3], a cardinal sign of allergic rhinitis.

Corticosteroids have been used topically in the nose for over 30 years [4, 5]. Initial trials with dexamethasone by Boxer [6] showed the occurrence of both local and systemic effect; the development in the 1970s of a second generation of agents, such as beclomethasone dipropionate and budesonide largely removed the unwanted systemic effects [7, 8], alterations in circulating steroid levels being noted only with betamethasone nasal drops when used in excess of the routine 4 twice daily dosage [9]. However there is evidence for dose-related decreased short-term bone growth in children receiving inhaled

budesonide 10, and in those on beclomethasone dipropionate [11].

Fluticasone propionate is the first of a third generation of inhaled steroid. It has less potential for systemic adverse effects because it is very poorly absorbed in the gastrointestinal tract and is subject to extensive first-pass metabolism in the liver [12]. The results of toxicology studies indicate that the swallowed portion of an inhaled dose of fluticasone propionate would have no systemic effects at doses well above the suggested clinical range [13]. It is potent, possessing a potency ratio of 2:1 with beclomethasone dipropionate in animal models *in vivo*, and has minimal activity with other steroid receptors [14].

In patients with seasonal allergy, it is advisable to start corticosteroid therapy before the season begins, immediately prior to the time when 'priming' and cellular infiltration into the nasal mucosa occurs. This

phenomenon probably leads to increased responsiveness to allergen during the season. Therefore, we decided to examine the effect of short-term intranasal treatment with fluticasone propionate, for 2 weeks prior to the pollen season, on the response to nasal challenge with grass pollen antigen in patients with seasonal allergic rhinitis.

Methods

Patients

Twelve patients aged between 19 and 55 years, with a history of seasonal allergic rhinitis took part in the study. They were taking no medication at the time of, or in the 4 weeks prior to the study. All had positive skin prick tests and nasal provocation tests to grass pollen antigen. All patients gave informed consent and the study was approved by the Ethics Committee at the Royal National Throat, Nose and Ear Hospital, London.

Symptom scores

At the start of each experiment after the equilibration period and 10 min after each challenge (saline, then antigen) patients were asked to indicate the degree of nasal blockage they were experiencing by making a mark on a 10 cm scale, the left hand end of which was labelled 'no symptoms' and the right hand end of which was labelled 'the worse possible'. In a similar fashion they were asked to score nasal itching, running and sneezing at each time point as above.

Nasal challenge

All nasal allergen challenges took place during May 1992. Challenges were performed with a nasal spray which delivered 100 µl per activation. Saline (control) and antigen solution (Grasses, Allergopharma, 2057 Reinbeck, Hamburg, Germany) was warmed to 37°C and the dose of antigen was controlled by the concentration of the solution. Antigen solutions varied 100 to 500 PNU ml⁻¹, diluted from a stock concentration of 5000 PNU ml⁻¹. Patients received doses ranging from 20 to 100 PNU to each nostril, based on their previous response to challenge with the same antigen.

Nasal lavage

The patient was seated with his or her head tipped back 30° and 5 ml of warmed saline was put in each nasal cavity using a pipette. This was held for 10 s and then the patient was asked to expel the lavage fluid into a small beaker. This was repeated twice and the fluid discarded in order to reduce the pre-existing mediator levels within the nasal cavity and achieve a baseline. The patient then underwent nasal lavage with 2.5 ml saline in each nasal cavity. These samples were retained for analysis.

Study protocol

On day 1 of the study (first visit) patients were initially given vehicle and a nasal lavage was performed. They were then challenged with grass pollen antigen at a dose which was adjusted according to the individual, and determined on the basis of preliminary nasal challenge experiments. A nasal lavage was performed and nasal inspiratory peak flow was recorded every hour over the following 24 h.

On day 2 of the study patients started intranasal administration of fluticasone propionate, two sprays of 50 µg per spray, in each nostril twice daily, amounting to a total daily dose of 400 µg. The patients were unaware of the nature of the spray having consented to receive either active or placebo medication.

On day 15, the patients returned and underwent a repeat nasal challenge with vehicle and grass pollen antigen, identical to that performed at the first visit. Again nasal inspiratory peak flow was monitored over the following 24 h.

Biochemical analyses

The concentration of histamine, LTC₄ and PGD₂ in nasal lavage was determined by radioimmunoassay.

Materials

Grass pollen antigen was obtained from Allergopharma, Hamburg, Germany. Radioimmunoassay kits for LTC₄ and PGD₂ were obtained from Amersham, UK and a radioimmunoassay for histamine was obtained from IDF Ltd, Bolton, UK. Fluticasone propionate aqueous nasal spray, 50 µg per spray, was supplied by Allen and Hanburys, Greenford, Middlesex, UK.

Data analysis

All data are presented as mean ± s.e. mean. Student's *t*-test for paired data was used to evaluate the statistical difference between responses. A probability value, *P*, of less than 0.05 was considered significant.

Results

Nasal challenge with vehicle did not produce any significant changes in symptom scores, nor in mediators assayed in nasal washings.

Nasal challenge with grass pollen antigen caused increases in symptom scores above vehicle control for all symptoms recorded; sneezing, *P* = 0.0001; itching, *P* = 0.0004; nasal blockage, *P* = 0.008; running, *P* = 0.01 (*n* = 12 for each symptom; Figure 1). Nasal challenge with grass pollen antigen also produced an increase in concentrations, above vehicle challenge values, in histamine, LTC₄ and PGD₂ in nasal lavage (Figures 2, 3 and 4). The only statistically significant increases above control values were

Figure 1 The effect of 2 week treatment with fluticasone propionate on symptom scores recorded before, and 10 min after an intranasal challenge. The data are the mean of 12 measurements and vertical bars represent the s.e. mean. *Significant difference ($P < 0.05$; $n = 12$) compared with immediate pre-challenge score. ■ sneeze, □ itch, Obs ▨ = nasal obstruction. Run ▩ = rhinorrhoea.

Figure 3 The effect of 2 week treatment of fluticasone propionate on leukotriene C₄ concentration of nasal lavage, taken before, and 10 min after an intranasal allergen challenge. □ Before allergen challenge; ▨ after allergen challenge. The data are presented as the mean of the group and vertical bars represent the s.e. mean.

Figure 2 The effect of 2 week treatment with fluticasone propionate on histamine concentration of nasal lavage, taken before, and 10 min after an intranasal allergen challenge. □ Before allergen challenge; ▨ after allergen challenge. The data are presented as the mean with vertical bars to represent the s.e. mean. * Significant difference ($P = 0.05$, $n = 12$).

Figure 4 The effect of 2 week treatment with fluticasone propionate on prostaglandin D₂ concentration of nasal lavage, taken before, and 10 min after an intranasal allergen challenge. □ Before allergen challenge; ▨ after allergen challenge. The data are the mean of 12 measurements and vertical bars represent the s.e. mean. *Significant difference ($P = 0.013$, $n = 12$).

for histamine (Figure 2; $P = 0.05$; $n = 12$) and PGD₂ (Figure 4; $P = 0.01$; $n = 12$).

Two weeks treatment with fluticasone, 200 µg twice daily, resulted in an inhibition of challenge-induced symptom scores for itching, nasal blockage and running (Figure 1) and an inhibition of the antigen-induced increases in histamine (Figure 2) and PGD₂ (Figure 4).

Nasal blockage was objectively monitored by nasal inspiratory peak flow over 24 h following nasal antigen challenge, both during the no treatment period and during the fluticasone treatment period. This showed that fluticasone reduced the antigen-induced nasal blockage over the 24 h following challenge (Figure 5), reaching statistical significance at 1 h ($P = 0.0002$), 5 h ($P = 0.005$) and 7 h ($P = 0.002$) after challenge.

Figure 5 The effect of 2 week treatment with fluticasone propionate, 200 µg twice daily for 2 weeks on nasal inspiratory peak flow (NIPF) recorded over 24 h after an intranasal allergen challenge. Symbols represent the mean of 12 measurements and vertical bars represent the s.e. mean. *Significant differences ($P < 0.05$; $n = 12$). ● fluticasone propionate, ○ no treatment.

Discussion

We have shown that fluticasone propionate at 200 µg twice daily for 2 weeks is effective in attenuating both the acute response and the later blockage following nasal challenge with grass pollen antigen in patients with seasonal allergic rhinitis.

A control group undergoing nasal challenge pre and post 2 weeks of placebo nasal spray was not included in this study. However, all the participants were known grass pollen responders, and rechallenge, immediately prior to the grass pollen season, would be expected to show a rise in symptoms due to the priming effect of small quantities of allergen in the atmosphere and to the previous challenge itself. Thus any decrease in symptoms experienced on rechallenge after drug therapy are almost certainly due to the drug itself.

Nasal lavage taken after allergen challenge demonstrated increases in the local release of histamine and PGD₂ but no significant increases were observed for the LTC₄ content of nasal lavage. The increase in histamine and PGD₂ levels occurred in association with nasal symptoms, including sneezing, itching, nasal blockage and running. This is consistent with previous findings [14]. The fact that intranasal treatment with fluticasone propionate reduced the allergen-induced increase in local histamine and PGD₂ release agrees with the action of locally administered more established corticosteroids [1]. There are many reports on the inhibitory effects of corticosteroids in both the upper [1, 2, 3] and lower airways [15, 16]. Such

effects are particularly well-documented for the late response to allergen, although some studies have indicated beneficial effects of this class of drugs in the early response. Studies with corticosteroids have shown that only topical treatment is effective in blocking early antigen-induced mediator release [1, 2, 3]. Oral steroids failed to block the acute phase of experimental antigen challenge in the nasal [17] and bronchial airways [18, 19].

Our results demonstrate effective inhibition of the acute response and our measurements of nasal inspiratory peak flow indicate that fluticasone propionate inhibits the rise in nasal blockage occurring 1, 5 and 7 h after antigen challenge. This probably represents an effect on the late phase of the response. Corticosteroids are known *in vivo* to prevent the influx of basophils in the nasal airway during the late response to antigen challenge [20]. This presumably is associated with a reduction in basophil mediator release and symptom relief.

Fluticasone propionate has been shown to reduce the number of activated eosinophils in biopsies taken during the immediate allergic response. It also abolished antigen-induced eosinophil cationic protein measured in nasal lavage [21]. Such an action on eosinophils is indicative of a possible mechanism by which fluticasone may act to inhibit inflammatory cell recruitment and mediator production.

The production of histamine and LTC₄ following antigen challenge is not specific for mast cells, but the parallel identification of PGD₂ is indicative of a mast cell source and is consistent with mast cell degranulation. The inhibition of histamine and PGD₂ by fluticasone propionate probably accounts for the reduction in allergen-induced nasal blockage. Histamine has nasal vascular effects which facilitate nasal blockage via an increase in nasal vascular permeability and nasal venous engorgement. These effects have been shown many times to produce nasal blockage, although they are relatively short-lived in comparison with the effects of equimolar concentrations of PGD₂ [22] and LTC₄ [23].

We were unable to demonstrate any significant increase in LTC₄ production following allergen challenge, possibly because the initial values in three patients were rather high. Interestingly all three patients had mild seasonal asthma. In a further series of house-dust mite sensitive patients the five who had asthma and rhinitis, had baseline values of LTC₄ significantly higher than the nine patients with rhinitis alone (Scadding, unpublished observations). None of these asthma patients in either study was significantly symptomatic at the time of the study and all had peak expiratory flow rates in the normal range.

Fluticasone propionate has been shown to reduce significantly the early and late response to nasal antigen after 2 weeks of therapy.

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(Received 2 March 1984,
accepted 24 June 1994)