

The effect of fluticasone propionate aqueous nasal spray on nasal mucosal inflammation in perennial allergic rhinitis

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Mast cell degranulation, and the subsequent recruitment of infiltrating inflammatory cells, such as eosinophils, into the nasal mucosa has long been considered the most important model to explain allergic rhinitis. Several studies show a decrease in the number of eosinophils and possibly also mast cells during local corticosteroid treatment. Over the last decade, a new model to explain allergic inflammation has evolved. In this model, Langerhans' cells and T-cells play an important role. Langerhans' cells possess a high affinity receptor for IgE. In patients with allergic rhinitis, allergen provocation results in stimulation of T-cells by the IgE-positive Langerhans' cells. The T-cells produce a number of cytokines which stimulate IgE production as well as the inflammatory reaction. The number of T-cells is not usually influenced by corticosteroid treatment; however, the function of the T-cells, shown by the spectrum of cytokines produced, is clearly influenced. The cells that are most dramatically affected by local corticosteroid treatment are the Langerhans' cells, which completely disappear during treatment. This decrease suggests that there is a reduction in antigen presentation. The subsequent decrease in T-cell stimulation may result in a reduction of the reactions that are dependent on T-cell-derived mediators.

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Introduction

Topical corticosteroids have proven efficacy in the treatment of allergic rhinitis and have been shown, with regular administration, to inhibit both the immediate and late response to allergen provocation. New insights into the pathogenesis of allergic rhinitis and the importance of inflammation have led to a number of studies on the effects of topical corticosteroids on cellular infiltrates in the nasal mucosa, with a particular focus on mast cells, antigen presenting cells, T-cells and eosinophils.

Mast cells

There is no consensus regarding the effect of corticosteroids on the number of metachromatic cells in the nasal mucosa. However, most authors have found a decrease in metachromatic cells on the epithelial surface and in nasal secretions after corticosteroid therapy (1, 11, 12). It is beyond the scope

of this paper to discuss whether basophilic or mast cells are present in the different layers of the nasal mucosa, and to discuss the effects of corticosteroid therapy on different types of mast cells. The metachromatic cells are therefore referred to as described by the authors of the original published work.

Otsuka studied the effect of corticosteroids on metachromatic cell populations in the nasal mucosa during natural exposure to allergen in seasonal allergic rhinitis (11). He found that formalin-sensitive mast cells and basophils were reduced by corticosteroids to a greater extent than formalin-resistant mast cells. Formalin-sensitive mast cells and basophils also re-appeared more quickly than formalin-resistant cells after the end of the treatment period.

In a double-blind, placebo-controlled study, Juliusson found no difference in mast cell numbers and tissue and lavage fluid histamine levels during allergen challenge after 4 weeks of treatment with fluticasone propionate in hay fever sufferers (9). Similar findings were reported by Lozewicz who, using the

same method, found no changes in the early and late phase reaction after allergen provocation (10). Juliusson, however, did observe a decrease in tryptase release in nasal lavage fluid (8).

A further double-blind, placebo-controlled study was undertaken in the Department of Otorhinolaryngology at Erasmus University Hospital, comparing fluticasone propionate aqueous nasal spray with placebo. In this study, 22 patients who were allergic to grass pollen received trial treatment for 3 weeks before allergen provocation. After the run-in period, patients were subjected to daily provocation with grass pollen spray. Biopsies of the nasal mucosa of the inferior turbinate were taken before the start of the first provocation, and after 1 h, 1 day and 14 days of allergen provocation. The mast cells in the biopsy samples were stained with tryptase and chymase. During corticosteroid treatment, there was a reduction in the percentage of epithelial sections showing tryptase-positive mast cells at 14 days. However, there was no reduction in epithelial chymase-positive cells during corticosteroid therapy. In the lamina propria, no relevant differences were found between the corticosteroid-treated group and the placebo group.

Thus, the topical effects of corticosteroids on metachromatic cell numbers are not conclusive, although most authors seem to find a decrease in cell numbers on the surface of the nasal mucosa. Further double-staining studies using IgE, tryptase and chymase on the surface as well as in deeper layers of the nasal mucosa are in progress.

Antigen presenting cells

Antigen presenting cells, such as Langerhans' cells (CD1-positive dendritic cells) and other HLA-DR-positive cells, are necessary for the presentation of allergen to T-lymphocytes. Langerhans' cells possess a high affinity receptor for IgE (2). It is only over the last decade that the role of Langerhans' cells in allergic rhinitis has been elucidated. Langerhans' cells and HLA-DR-positive cells have been found to increase in number in the nasal epithelium and the lamina propria during symptomatic allergic rhinitis (4, 5).

A long-term, double-blind, placebo-controlled study was undertaken in our hospitals to evaluate the effect of fluticasone propionate aqueous nasal spray on CD1- and HLA-DR-positive cells in 30 patients with perennial allergic rhinitis. Biopsies of nasal mucosa were taken after a run-in period, after 3 months and after 1 year of treatment with placebo or fluticasone propionate at a dose of 100 µg twice daily. After 3 months of treatment, a significant reduction in the number of CD1-positive cells and HLA-DR-positive cells was found in the fluticasone

propionate aqueous nasal spray group compared with placebo in both the epithelium and the lamina propria of the nasal mucosa (7). Similar findings were observed after 1 year. During the 2-week study of continued allergen provocation described earlier, again the influx of Langerhans' cells was found to be almost totally inhibited during treatment with fluticasone propionate.

It can be concluded from these studies that the accumulation of antigen presenting cells during allergen provocation is almost totally abolished by nasal corticosteroid therapy.

T-cells

After presentation by IgE-positive Langerhans' cells, recognition of allergen by sensitised T-lymphocytes leads to a cascade of regulatory lymphokine-mediated events, resulting in IgE production and allergic inflammation. Activated T-helper type 2 cells (TH₂) produce lymphokines, including interleukin-4 (IL-4) and interleukin-5 (IL-5), which play a significant role in the IgE-mediated inflammatory reaction.

In a short-term study involving 37 patients with house dust mite perennial allergic rhinitis, nasal biopsies were taken before and after 6 weeks of treatment with fluticasone propionate. The results showed no change in CD3, a general T-cell marker; CD4, a marker for T-helper cells; CD8, a marker for T-suppressor cells; and CD25, a marker for activated T-cells (13).

In our 1-year double-blind, placebo-controlled study of 30 patients with perennial allergic rhinitis, no significant differences in CD3-, CD4-, CD8- and CD25-positive cells were found in the epithelium and lamina propria after 3 months of therapy with fluticasone propionate (7). However, after 1 year of therapy, there was a significant decrease in CD3-, CD4- and CD8-positive cells in the epithelium, though no significant changes were observed in the number of CD25-positive cells. Furthermore, no significant changes in these cell types were found in the lamina propria, which from a functional point of view is probably more important. In their *in situ* hybridisation studies, however, Durham et al. found a decrease in the expression of RNA of cytokines potentially produced by TH₂ cells after treatment with fluticasone propionate aqueous nasal spray (3). These results were confirmed by our group using the polymerase chain reaction technique, where a reduction in IL-4, an important cytokine in allergic rhinitis, was found in nasal biopsy specimens.

In conclusion, corticosteroid treatment does not appear to affect the number of T-cells or their subpopulations during short-term treatment, although a reduction in T-cell numbers is observed in the epi-

thelium during long-term treatment. Corticosteroids do, however, have a substantial effect on T-cell function, as evidenced by a reduction in the spectrum of T-cell-derived cytokines.

Eosinophils

Eosinophils, particularly activated eosinophils, increase in the epithelium and lamina propria during allergen provocation. In our 2-week continued daily threshold allergen provocation study described earlier, eosinophils were totally eradicated from the epithelium and a significant reduction in eosinophil accumulation was observed in the lamina propria. A significant reduction in accumulation of EG2-positive activated eosinophils was also observed with fluticasone propionate treatment when compared with placebo after 2 weeks of continued provocation (6). Tendencies for activated eosinophil reduction have also been observed by other authors (3, 14).

These results, and the results of other studies not described here, indicate that the accumulation of

activated eosinophils is decreased by topical corticosteroids and that the total number of eosinophils tends to decrease more clearly in the epithelium than in the lamina propria. The magnitude of this response seems to be related to the intensity of the allergen challenge.

Conclusion

The effects of corticosteroid treatment on infiltrating cells in the nasal mucosa are summarised in Fig. 1. Intranasal corticosteroids have an effect on a number of different cells involved in the nasal allergic inflammatory reaction, which may explain their potent effect in clinical nasal allergy studies.

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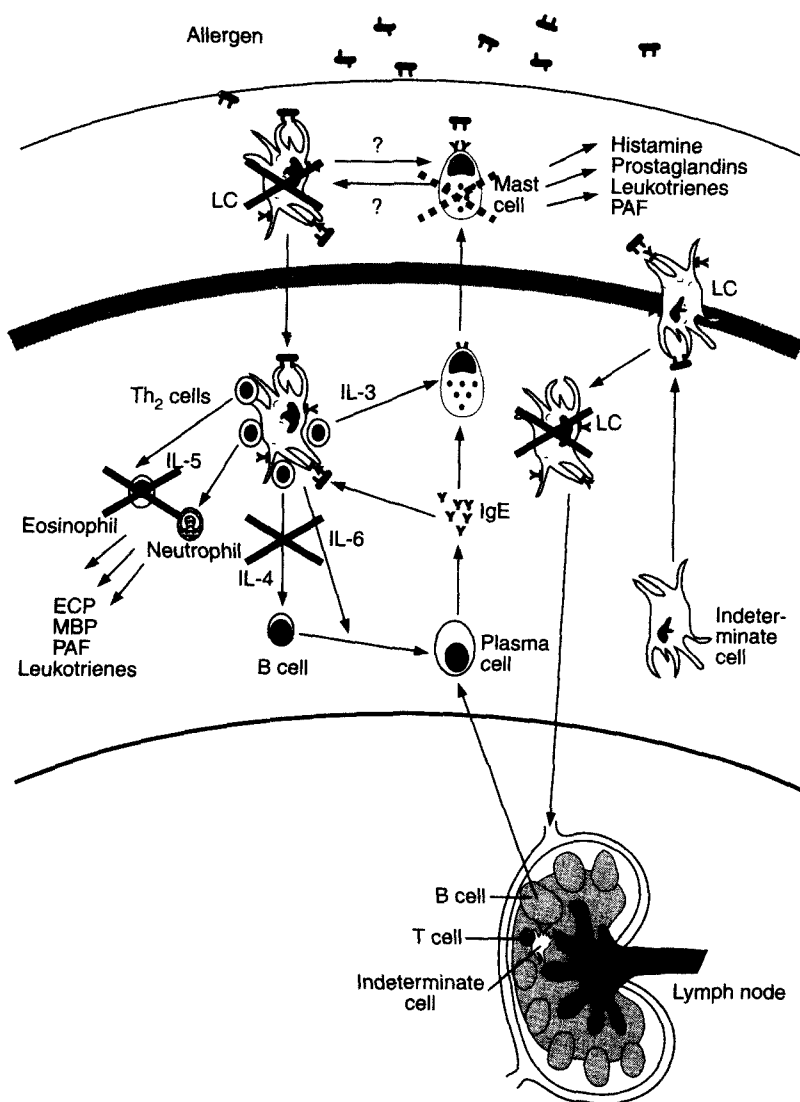


Fig. 1. The effect of nasal corticosteroid treatment on infiltrating inflammatory cells in the epithelium and lamina propria of the nasal mucosa. LC = Langerhans' cell; PAF = platelet activating factor; IL = interleukin; ECP = eosinophil cationic protein; MBP = major basic protein; solid cross = decrease in accumulation of inflammatory cells; broken cross = possible decrease in accumulation of inflammatory cells.

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