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A comparison of the anti-inflammatory properties of intranasal corticosteroids and antihistamines in allergic rhinitis

Allergic rhinitis manifests itself clinically due to the local release of mediators from activated cells within the nasal mucosa. Treatment strategies aim either to reduce the effects of these mediators on the sensory neural and vascular end organs, or to reduce the tissue accumulation of the activated cells that generate them. Corticosteroids intervene at a number of steps in the inflammatory pathway, and, by reducing the release of cytokines and chemokines, inhibit cell recruitment and activation. These effects are evident both *in vivo* and *in vitro*. While antihistamines also have some anti-inflammatory effects *in vitro*, these require higher concentrations than with corticosteroids and are not consistently reproduced *in vivo*. In addition, although antihistamines and corticosteroids might appear to have complementary mechanisms of action, clinical trials suggest that their co-administration does not confer any additional long-term benefits compared with that achieved with corticosteroids alone. Topical corticosteroids are therefore the preferred anti-inflammatory therapy for persistent allergic rhinitis.

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Introduction

Allergic rhinitis is the clinical manifestation of the local release, within the nasal mucosa, of mediators from activated inflammatory cells (1). Immunohistochemical studies of nasal biopsies taken from patients with allergic rhinitis show an accumulation within the epithelium of eosinophils, basophils, and mast cells (2–4), which are believed to be the primary effector cells in this condition, while nasal lavage reveals elevated levels of eosinophil cationic protein and tryptase in seasonal and perennial allergic rhinitis, indicative of cell activation (5).

Treatment for allergic rhinitis is directed toward reducing either the tissue accumulation of these activated cells or the end-organ effects of the released mediators. The two most important classes of pharmacologic agents used to achieve these aims are, respectively, topical corticosteroids and H_1-antihistamines. While H_1-antihistamines are clearly effective in relieving symptoms, particularly those associated with sensory neural stimulation, it has been proposed that many drugs within this class have more extensive actions, modifying the inflammatory process in addition to inhibiting the H_1-receptor-mediated end-organ effects of histamine. As such, H_1-antihistamines might be potentially considered an alternative prophylactic therapy to topical corticosteroids in rhinitis. To address this consideration, this paper briefly reviews the mechanisms involved in airways inflammation in allergic rhinitis and examines the *in vitro* and *in vivo* evidence for the relevant anti-inflammatory potential and effects of these two classes of pharmacologic agents.

Allergic airways inflammation

The major pathways involved in allergic airways inflammation are shown in Fig. 1. In addition to IgE-dependent activation of mast cells inducing mediator release, activated mast cells and T cells produce TH_2 cytokines, which, in turn, activate both endothelial and epithelial cells (1). Endothelial activation results in the expression of endothelial adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and, more importantly, vascular cell adhesion molecule-1 (VCAM-1). While both these adhesion molecules are potentially involved in tissue-cell recruitment (6), the interaction between VCAM-1 and the ligand VLA-4 is more specific for allergic inflammation, being involved not only in eosinophil adherence but also in basophil and lymphocyte endothelial interactions. The directed movement of cells through the tissue toward the nasal lumen, once transendothelial migration has taken place, is dependent upon cell–cell contact and the local release of chemokines. Epithelial activation is associated with the generation and release of a number of chemokines – such as regulated on activation, normal T-cell expressed and secreted (RANTES), macrophage inflammatory protein (MIP)-1α, monocyte chemotactic protein

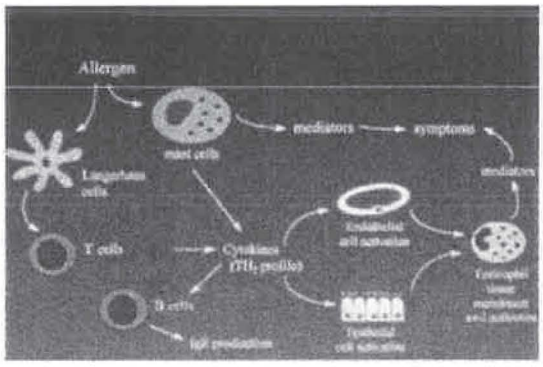

Figure 1. Allergic airways inflammation.

(MCP)-1, interleukin-8 (IL-8), and eotaxin – which are chemoattractants for eosinophils, mast cells, lymphocytes, neutrophils, and basophils, and direct the migration of these cells toward the epithelium and nasal airway lumen (7). Epithelial activation can thus account for the specific accumulation of mast cells, eosinophils, basophils, and T cells within the epithelium in allergic rhinitis.

It follows that therapy which reduces either the expression of these chemokines or the cytokines associated with endothelial and epithelial activation will diminish the recruitment of these effector cells and thus decrease the availability of mediators to induce symptom expression.

Cytokine and chemokine expression is regulated by transcription factors such as nuclear factor kappa B (NFκB), AP-1, and NF-AT (8). In the unactivated cell, transcription factors exist in an inactive form, and cell stimulation results in their activation with a resultant upregulated expression of cytokine and chemokine messenger RNA (mRNA). For example, NFκB exists as a dimer bound to an inhibitory protein, I kappaB (IκB), within the cytoplasm (9). When exposed to an activation stimulus, phosphorylation of the inhibitory protein leads to loss of binding, and the dimer dissociates from the inhibitory protein and translocates to the nucleus. Once there, it interacts with the DNA, resulting in a directed increase in gene expression and upregulation of specific cytokine (e.g., IL-1 and TNF-α) and chemokine (e.g., RANTES and eotaxin) synthesis. The transcription factor NFκB also controls the synthesis of adhesion molecules (such as VCAM-1) and enzymes (such as inducible nitric oxide synthase [iNOS]) of relevance to allergic nasal inflammation.

Corticosteroids

Corticosteroids act by modifying the ability of transcription factors to up-regulate gene expression (10). Thus, by acting very early in the inflammatory pathway, corticosteroids can prevent the cascade of events associated with cell recruitment and activation, and, ultimately, clinical disease expression.

The glucocorticoid molecule enters the cell and binds to the cytoplasmic glucocorticoid receptor, displacing the associated heat-shock proteins. The glucocorticoid/glucocorticord receptor complex can either bind to the transcription factors themselves within the cytoplasm, thereby preventing their interaction with DNA and thus indirectly blocking their effects on gene expression, or translocate to the nucleus and bind as a dimer to the DNA. This direct interaction with DNA modifies gene transcription, down-regulating the production of pro-inflammatory proteins or up-regulating the generation of anti-inflammatory ones. This latter action may require higher concentrations than the down-regulatory activity. Corticosteroids thus have both direct and indirect effects in inhibiting transcription factor-induced gene expression.

In vitro studies

Studies with corticosteroids *in vitro* have shown that this class of drug has potent effects on T cells, inhibiting their stimulated proliferation and synthesis of TH_2 cytokines at low concentrations (11–13). In this respect, fluticasone propionate is the most potent of the currently available topical corticosteroids, having an IC_{50} (inhibitory concentration producing a 50% reduction in the stimulated response) in the range of 10^{-10} M (13, 14). In addition to this inhibitory effect on T cells, fluticasone propionate inhibits the release of IL-4, IL-6, IL-8, and TNF-α from stimulated mast cells with an IC_{50} of <1 nM (15). The IC_{50} for inhibiting the release of TNF-α and GM-CSF from the stimulated epithelium are 0.1 and 1.0 nM, respectively (16). Epithelium-generated IL-6 and IL-8 are less sensitive to the effects of fluticasone, with IC_{50} of 5 and 10 nM, respectively (16).

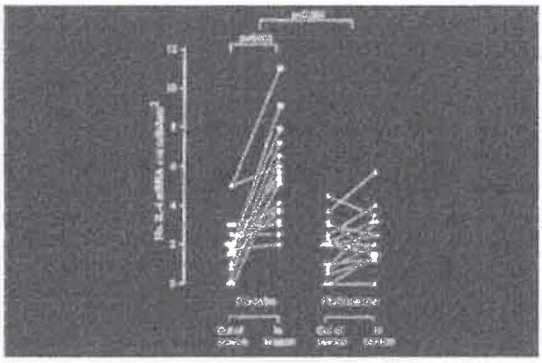

Figure 2. Influence of fluticasone propionate on mucosal IL-4 mRNA in nasal biopsies in seasonal allergic rhinitis (Cameron et al. [17]).

In vivo studies

Topical corticosteroid therapy influences many aspects of the allergic mucosal response. Much of the published literature concerns fluticasone propionate, and, to a lesser extent, budesonide. Fluticasone propionate significantly blunts the seasonal increases in the expression of mRNA for both IL-4 (Fig. 2) (17) and IL-5 (18), in nasal mucosal biopsies in seasonal allergic rhinitis. In addition, prophylactic treatment with fluticasone propionate, as compared to placebo, prevents the pericellular expression of the activated and secreted form of IL-4 (as demonstrated by the number of immunoreactive 3H4 + cells) on nasal mucosal mast cells in seasonal rhinitis (Fig. 3) (19). Thus, fluticasone propionate downregulates both IL-4 and IL-5 gene expression as well as the active secretion of IL-4 within the nasal mucosa. These are key cytokines in regulating endothelial VCAM-1 expression and, consistent with this, fluticasone propionate has also been shown to inhibit the seasonal increase in endothelial VCAM-1 expression (20). This action, along with a reduction in IL-5, a cytokine known to stimulate the proliferation and differentiation of eosinophil progenitor cells within the bone marrow, can account for the decrease in eosinophils within the nasal mucosa and lumen with topical corticosteroid therapy in rhinitis (20, 21).

This inhibitory effect on inflammatory cell accumulation in allergic rhinitis will also be promoted by the downregulation, by corticosteroids, of chemokine synthesis by the epithelium. Fluticasone propionate has been shown to reduce significantly the levels of IL-1β, MIP1α, RANTES, and GM-CSF recovered from nasal lavage after allergen challenge (Fig. 4) (22), indicating inhibition of epithelial activation. This action may underlie the inhibitory effect of fluticasone propionate in preventing the seasonal accumulation of mast cells within the epithelium in grass pollenosis (Fig. 5).

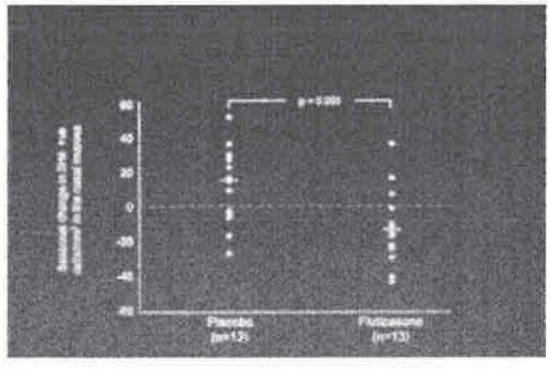

Figure 3. Influence of prophylactic fluticasone propionate on IL-4 secretion by mast cells in seasonal allergic rhinitis (Bradding et al. [19]).

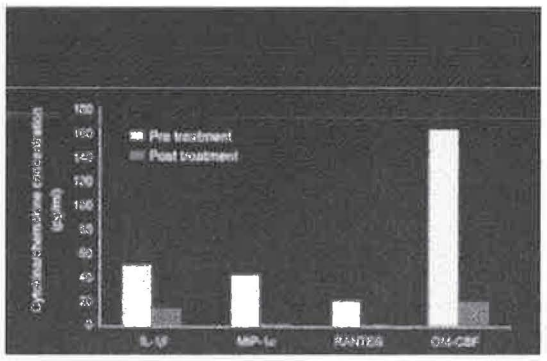

Figure 4. Nasal lavage chemokine levels: influence of fluticasone propionate (Weido et al. [22]).

Thus, fluticasone propionate modifies a number of steps in the inflammatory pathway: it blocks cytokine and chemokine generation, endothelial and epithelial cell activation, and the tissue recruitment and activation of mast cells and eosinophils. It follows that the fewer the number of these primary effector cells, the lower the amount of inflammatory mediators produced and, as a consequence, the fewer the nasal symptoms.

Antihistamines

Since many rhinitis symptoms are mediated by histamine, antihistamines offer a therapeutic alternative to corticosteroids. With short-term therapy, H_1-antihistamines are most effective at reducing the neurally mediated symptoms of itch, sneeze, and rhinorrhoea (23). This can be attributed to end-organ receptor blockade. There is, however, an indication that a number of these agents also have the potential for antiallergic activity that, theoretically, may increase their spectrum of clinical effectiveness.

In vitro studies

Studies undertaken *in vitro* show that H_1-antihistamines modify mediator release from mast cells and basophils (24, 25). These investigations reveal that, for most traditional antihistamines, the antiallergic activity requires higher concentrations than the H_1-antihistaminic activity. For example, the pA_2 value to inhibit anti-IgE induced mast cell degranulation is about 2 logs lower; i.e., the dose required to abolish the allergic response is approximately 100-fold higher than for the H_1-antihistaminic activity (24). The exception is oxatomide, which has similar antiallergic and antihistamines pA_2 values (26). Thus, for these effects to be fully evident *in vivo*, most H_1-antihistamines would have to be administered at doses higher than generally tolerated, due to their sedative effects.

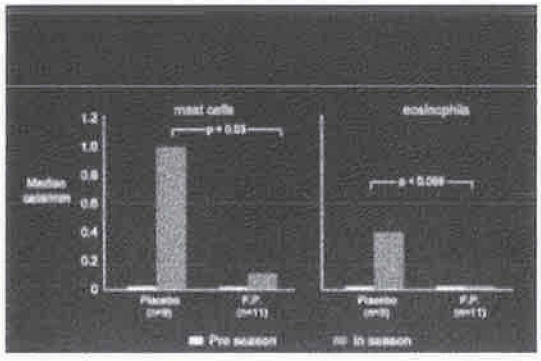

Figure 5. Epithelial eosinophil and mast-cell accumulation in seasonal allergic rhinitis: influence of prophylactic fluticasone propionate, 200 μg once daily (Bradding et al. [19]).

For some more recently introduced non-sedating antihistamines, including terfenadine, cetirizine, and loratadine, IC_{50} values for inhibition of anti-IgE- or allergen-induced histamine release are in the 10 μM range (27, 28). In other words, the inhibition of histamine release by these agents requires a concentration at least 1000 times higher than that those of fluticasone propionate required to inhibit cytokine or chemokine release. The "antiallergic" effects are considered to be independent of the H_1-receptor antagonistic activity and to be related to nonspecific cell membrane stabilization due to ionic association with cell membranes. This leads to modification of ion transport and membrane-associated enzyme activity (29–31).

In addition, several H_1-antihistamines have been shown to modify *in vitro* the epithelial expression of the adhesion molecule ICAM-1. Both terfenadine and cetirizine have been found to reduce the expression of ICAM-1 on epithelial cell lines *in vitro* (32).

In vivo studies

Antihistamines may exert their effects either directly, by inhibiting end-organ effects, or indirectly by inhibiting mast cell degranulation. This has been investigated in allergen-challenge models *in vivo*, with nasal lavage to measure postchallenge mediator levels. Pretreatment with standard doses of antihistamines, as compared to placebo, has been shown to decrease the recovery of mediators following allergen challenge (33). Overall, however, the effects of the various agents appear to be somewhat variable. Thus, azelastine, cetirizine, and ketotifen (34–36) have no effect on histamine release, although a decreased recovery of leukotrienes has been reported with both azelastine and cetirizine (34, 35). Conversely, several studies show decreased histamine release with loratadine and terfenadine (37–39), but no change in the recovery of leukotrienes. None of these drugs appear to have a consistent effect on the subsequent eosinophil accumulation in the allergen challenge model (40). The interpretation of these findings is also complicated by the report that factors, including histamine, which increase plasma protein exudation, increase mediator recovery in nasal lavage (41). Thus, inhibition of a histamine-related increase in vascular permeability after allergen challenge, due to the H_1-receptor blockade on the endothelial surface, could reduce mediator recovery in nasal lavage and be interpreted as reflecting an "anti-allergic" effect.

An antihistamine that decreased leukotriene production might be expected to have a broader clinical profile than one with antihistamine activity alone. In clinical studies, however, agents that inhibit leukotriene production in the allergen challenge test have similar clinical benefits to those that do not (42, 43), raising some doubt about the interpretation of the allergen-challenge findings. Also unknown is whether or not the inhibition of mast-cell mediator release occurs in parallel to an inhibition of cytokine release and thus cell recruitment. There is conflicting evidence for cetirizine. For example, cetirizine appears not to affect eosinophil recruitment in the nasal allergen challenge model (40) but does have such an effect in some other challenge models, such as skin blister (44). Lavage studies also have produced contradictory findings (45, 46). In our own studies in naturally occurring seasonal rhinitis, cetirizine failed to show a clear anti-inflammatory effect, at least as indicated by tissue eosinophil accumulation (47). Cetirizine, however, has been found to reduce nasal epithelial ICAM-1 expression in naturally occurring disease (48).

Moreover, if cetirizine does prevent eosinophil accumulation, greater clinical benefit would be expected with prophylactic than with short-term use, but this does not appear to be the case. The effect of active prophylactic therapy of H_1-antihistamines on nasal congestion is also not significantly superior to that of placebo (49), in contrast to that with corticosteroids. A study of prophylactic flunisolide and beclomethasone in patients with ragweed-sensitive rhinitis found that both prevented the development of seasonal rhinitis (50).

Comparative and combination clinical studies

In clinical comparisons, corticosteroids are significantly more effective than H_1-antihistamines (51). The *in vitro* findings with the two classes of compounds suggest a complementary mechanism of action; i.e., that there is a potential for inhibition both of mast-cell and basophil degranulation and of cell activation and eosinophil recruitment. If corticosteroids and antihistamines were used concomitantly, this might be translated into additional clinical benefit. The limited studies available, however, do not support a superior effect with long-term regular therapy with the

combination compared with topical corticosteroid alone (52, 53).

Conclusions

The broad effect of topical corticosteroid therapy in reducing the mucosal accumulation of the major effector cells of the disease, mast cells and eosinophils, accounts for their substantial clinical benefit. The lack of additional clinical benefit when antihistamines are used in combination with corticosteroids indicates that, *in vivo*, the anti-inflammatory effects on the airway of corticosteroids overlap those of the H_1-antihistamines, making the action of the latter redundant. An alternative explanation is that the *in vitro* effects of antihistamines are not evident *in vivo*, possibly due to inadequate potency at the dose used.

Thus, first-line therapy for rhinitis based on anti-inflammatory activity is a topical corticosteroid such as fluticasone propionate. A better understanding of those properties of H_1-antihistamine molecules that are relevant to cell activation and accumulation may allow the development of other molecules with appropriate potency at standard oral doses. This would extend the profile of antihistamines beyond their inhibition of the end-organ effects of histamine.

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