

Pharmacological modulation of the allergic response: different modes of action

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Introduction

The ideal treatment for allergy is of course avoidance of the relevant allergen. In practice this is rarely completely achievable and some form of additional therapy, usually with pharmaceuticals, is needed.

In previous years these medications have been considered to be of 2 types: those giving symptomatic relief (decongestants, beta-2 agonists antihistamines), and those with anti-inflammatory activity (chromones, corticosteroids). This distinction has now become blurred as antihistamines, long acting beta-2 agonists and more recently anti-leukotrienes are being found to have some anti-inflammatory properties, albeit weaker than those of the corticosteroids.

This review concentrates on the airways and on rhinitis in particular, not only because this is my area of expertise, but also because rhinitis has profound effects not only on quality of life but also on the lower respiratory tract.

Antihistamines

These are antagonists of a single mediator histamine, competing with it for binding to the H₁ receptor which is a G-protein coupled receptor with 7 transmembrane loops. It is linked to multiple signalling events, including the phospholipase-C dependent inositol phosphate pathway, a rise in intracellular calcium and cyclic AMP production. Histamine is present in nasal secretions in seasonal allergic rhinitis, perennial allergic rhinitis and following allergen challenge. Its major effects are sneezing, nasal itching and rhinorrhoea. Although histamine can contribute to nasal blockage it is less potent than prostaglandin D₂ or leukotrienes in this regard. Antihistamines therefore have

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major effects against itching, running and sneezing, but have relatively little effect on nasal obstruction, although when applied topically they appear to be slightly more potent in this regard. Antihistamines have only a minimal effect on asthma, potentiation of beta-2 agonists has been described.

The first generation of antihistamines were closely related to tranquillisers and anti-depressants and caused sedation and dry mouth. This effect is largely absent from the second generation molecules which are to be preferred in the treatment of rhinitis. Most second generation antihistamines are well tolerated, however major side effects of cardiac potassium channel blockage have been noted with terfenadine and astemizole.

Their place in therapy will depend upon a number of factors, including patient preference. However they are mainly used alone in the treatment of mild intermittent rhinitis, or in combination with topical corticosteroids in patients who are not controlled by the corticosteroid alone.

In recent years many second generation antihistamines have been shown to have various in-vitro anti-inflammatory effects including inhibition of eosinophil chemotaxis (cetirizine), and decrease in ICAM-1 expression. Until recently the *in-vivo* relevance of these had not been explored but there are now some data to suggest that ICAM-1 reduction may be relevant in decreasing childhood upper respiratory tract infections and that chronic administration of antihistamines to highly allergic children with atopic dermatitis may decrease the subsequent development of asthma.

H₂ receptor antagonists

Although there is little evidence for H₂ receptors in the nasal mucosa some patients who do not respond completely to H₁ antagonists do derive benefit from the addition of a H₂ receptor antagonist such as ranitidine. The major use of these drugs however is the reduction of gastric acid secretion.

Anti-leukotrienes

Leukotrienes are released following the breakdown of arachidonic acid from the membranes of inflammatory cells such as mast cells and eosinophils. Leukotriene B₄ appears to have chemotactic properties, mainly attracting neutrophils. The cysteinyl leukotrienes C₄, D₄ and E₄ are potent inflammatory mediators and have been demonstrated

in nasal and bronchial lavage following allergen exposure or allergen challenge. Their major effects appear to be induction of airways blockage (leukotriene C₄ is approximately 100 times more potent than histamine in this regard), and mucus production.

There are 2 categories of anti-leukotrienes: synthesis inhibitors either of 5LO or FLAP, and the leukotriene receptor antagonists which are effective against the cysteinyl leukotrienes only. Leukotrienes appear to play a prominent role in aspirin sensitive nasal polyposis and asthma where their production is increased and there is also exquisite leukotriene sensitivity. Abnormalities of the promoter region of leukotriene C₄ synthase have been found in some patients with this condition.

Leukocyte receptor polymorphisms have also been described and this may account for the fact that some patients do not show any evidence of response to the LTRAs.

As yet their use in rhinitis has been largely experimental. The 5LO inhibitor zileuton has been shown to decrease nasal polyp size and to restore olfaction in some patients with aspirin sensitive nasal polyposis. The leukotriene receptor antagonists appear to have some weak anti-rhinitic properties, largely against congestion and rhinorrhoea. Their actions complementary to those of antihistamines and the use of a combination is superior to either drug used alone. However this is obviously expensive.

Studies in asthma suggest that benefit from regular oral leukotriene use may take several weeks to reach their maximum and this, coupled with the demonstration of a decrease in eosinophilia in sputum, suggests a possible anti-inflammatory effect. Further work in this area is needed.

Chromones (sodium cromoglycate, nedocromil sodium)

These have been described as mast cell stabilisers, but their mode of action probably involves chloride channel inhibition and they have wide-spread effects upon inflammatory cells including T-cells. They are highly ionised and hence poorly absorbed. Application is topical to bronchi, nose or eyes and needs to be repeated several times daily, thus reducing compliance.

They have weak anti-inflammatory effects and reduce all symptoms of rhinitis including nasal congestion. They have no effect upon nasal polyposis nor upon the sense of smell. Nedocromil sodium can relieve airways hyper-reactivity to non-specific stimuli.

Clinically their efficacy in rhinitis is similar to that of second generation antihistamines. Their major place in treatment is in individuals who are unsuitable for topical

corticosteroids either because of age, occupation (eg singers), concurrent steroid administration elsewhere, or volition. Chromones are extremely useful in allergic conjunctivitis since topical corticosteroids can be associated with severe side effects such as hepatic keratitis and should not be used except under ophthalmological supervision.

As with topical corticosteroids prophylactic use of chromones is recommended and is more effective than "as needed use".

Corticosteroids

Topical corticosteroids are the mainstay of treatment in asthma, atopic dermatitis and in moderate and severe allergic rhinitis. They have anti-inflammatory effects on many cells of the immune system and also affect structural cells of the nasal mucosa.

Inhaled corticosteroids are very lipophilic and rapidly enter cells, subsequently binding to glucocorticoid receptors (GCRs), in the cytoplasm. Airway epithelium cells contain high levels of GCRs. The complex is transferred to the nucleus where it combines with the DNA at specific sites termed glucocorticoid response elements (GREs), on the upstream promoter sequence of steroid responsive genes and can then alter gene transcription. Possibly the most important alteration is inhibition of gene transcription for pro-inflammatory proteins such as cytokines, enzymes and receptors.

In addition GCRs may interact directly to inhibit certain transcription factors which have been activated by inflammatory cytokines, (eg) nuclear factor-kappa B (NF kappa B), and activator protein 1 (AP1). These when activated in the nucleus would bind to DNA response elements and increase the transcription of pro-inflammatory genes. This is prevented by their prior interaction with GCRs.

Whereas the GCR – DNA interaction is responsible for steroid side effects as well as desired effects, this second protein/protein interaction appears entirely anti-inflammatory.

The inducible form of nitric oxide synthase (iNOS), is inhibited by inhaled corticosteroids via the NF kappa B inhibition. Nitric oxide (NO) levels are raised in asthma and in uncomplicated allergic rhinitis and are decreased in both conditions following inhalation of corticosteroid.

Recent studies on cytokines have demonstrated that inhaled corticosteroids increase the anti-inflammatory cytokine IL10, but decrease macrophage inflammatory protein 1 α , granulocyte macrophage colony stimulation factor (GM-CSF), and interferon gamma (IFN γ), released from alveoli macrophages. IL-8 expression and release from human airway smooth muscle cells has also been shown to be inhibited by dexamethasone and mRNA for IL-4 is decreased *in-situ* hybridisation studies on nasal biopsies.

Immunohistochemical studies have shown that inhaled corticosteroids have effects on many of the cells involved in asthma and allergic rhinitis. Langerhan's cells are almost completely obliterated in the nose, T-lymphocytes are exquisitely steroid sensitive and numbers of eosinophils and mast cells are also reduced, especially in the epithelium. Epithelial cell shedding is reduced in asthma as is goblet cell hyperplasia. Reduction of basement membrane thickening has also been demonstrated in one study. Less leakage from blood vessels occurs in patients on inhaled corticosteroids. Airways hyper-reactivity both to allergens and to non-specific stimuli such as cold air, exercise and irritants is gradually reduced over weeks and even months by corticosteroids.

It was previously thought that one action of corticosteroids was to decrease the breakdown of arachidonic acid by inhibiting phospholipase A₂. This now appears unlikely since no decrease in leukotriene production occurs in patients on inhaled or oral corticosteroids. Thus inflammatory effects remaining in patients on inhaled corticosteroids may respond to therapy with anti-leukotrienes.

All symptoms of rhinitis are reduced by corticosteroids, which are again best used prophylactically on a regular basis. Severe rhinitis may respond better if a few days of oral corticosteroid are given in addition to topical therapy. Corticosteroids can reduce polyp size and can restore olfaction.

A recent meta-analysis suggests that corticosteroids are superior to antihistamines in terms of clinical effectiveness on nasal and ocular symptoms. They are also cheaper than other forms of treatment. Provided total inhaled levels are below a 1000 μ g (adults), and 400 μ g (children) daily there is no significant effect on bones and growth in the majority of patients. Total steroid load however should always be considered.

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