REVIEW ARTICLE

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Intranasal Corticosteroids for Allergic Rhinitis

Superior Relief?

Lars Peter Nielsen,[1,2] *Niels Mygind*[2] and *Ronald Dahl*[2]

1 Department of Clinical Pharmacology, University of Aarhus, Aarhus, Denmark
2 Department of Respiratory Diseases, Aarhus University Hospital, Aarhus, Denmark

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Abstract

Whether first-line pharmacological treatment of allergic rhinitis should be antihistamines or intranasal corticosteroids has been discussed for several years.

First-generation antihistamines are rarely used in the treatment of allergic rhinitis, mainly because of sedative and anticholinergic adverse effects. On the basis of clinical evidence of efficacy, no second-generation antihistamine seems preferable to another. Similarly, comparisons of topical and oral antihistamines

have been unable to demonstrate superior efficacy for one method of administration over the other.

Current data documents no striking differences in efficacy and safety parameters between intranasal corticosteroids.

When the efficacy of antihistamines and intranasal corticosteroids are compared in patients with allergic rhinitis, present data favours intranasal corticosteroids. Interestingly, data do not show antihistamines as superior for the treatment of conjunctivitis. Safety data from comparative studies in patients with allergic rhinitis do not indicate differences between antihistamines and intranasal corticosteroids. Combining antihistamines and intranasal corticosteroids in the treatment of allergic rhinitis does not provide any additional effect to intranasal corticosteroids alone. On the basis of current data, intranasal corticosteroids seem to offer superior relief in allergic rhinitis than antihistamines.

Allergic rhinitis is a common condition elicited by an immunoglobulin (Ig)E-mediated allergic inflammation of the nasal mucosa and characterised by nasal obstruction, rhinorrhoea, sneezing and nasal itch, and often accompanied by conjunctivitis. It is present in 10 to 20% of the population in industrialised countries.[1] Moreover, this prevalence seems to be increasing.[2,3] Although allergic rhinitis is not a life-threatening disease, it can severely impact on quality of life[4-6] and be associated with comorbidity from other diseases, for example, asthma and conjunctivitis.[7]

Treatment of allergic rhinitis consists of allergen avoidance, allergen-specific immunotherapy and pharmacological intervention, of which the former two lie beyond the scope of the present review. Two mainstream options have evolved for pharmacological treatment, antihistamines and topical corticosteroids. The choice between these options has been extensively discussed since the introduction of intranasal corticosteroid treatment.[8]

This review considers first-line pharmacological treatment of allergic rhinitis and will deal only with antihistamines and intranasal corticosteroids (INCS), as we consider cromones, anticholinergics, leukotriene modifiers, decongestants and systemic corticosteroids as secondary treatment options in allergic rhinitis.

Only data obtained in patients with allergic rhinitis have been considered for the comparative evidence presented in this review.

1. Antihistamines

1.1 General Considerations

Histamine is the major pathophysiological mediator of allergic rhinitis. Its role is almost exclusively mediated through the histamine H_1-receptor, whereas the role of other histamine receptors in allergic rhinitis remains to be clarified. Thus, in the context of allergic rhinitis, antihistamines are H_1-receptor antagonists.[9,10] In addition to H_1-receptor blockade, an anti-inflammatory effect of antihistamines has been proposed, as some of the newer compounds have been shown to influence cytokine production, mediator release and inflammatory cell flux.[11-19] However, other studies have been unable to confirm these findings.[20-23] Whether antihistamines offer a clinically beneficial anti-inflammatory effect in addition to inhibition of histamine remains a question to be answered.

1.2 Oral Antihistamines

Numerous H_1-receptor antagonists have been developed. For oral use, these can be divided into older first-generation [e.g. chlorphenamine (chlorpheniramine), diphenhydramine, promethazine and triprolidine] and newer second-generation antihistamines (acrivastine, astemizole, cetirizine, ebastine, fexofenadine, loratadine, mizolastine and terfenadine). This review deals with the newer antihistamines as the use of the older drugs in allergic

rhinitis is limited by their adverse effects, mainly sedation and anticholinergic activity.

All of the newer antihistamines are effective in the treatment of allergic rhinitis by decreasing nasal itching, sneezing and rhinorrhoea, but they are less effective for nasal congestion.[24-31] They are also effective for conjunctivitis and recent results seem to indicate some influence on lower airway symptoms.[32,33]

Moreover, the pharmacokinetic profile of second-generation antihistamines are advantageous when compared with the first-generation agents.[34] They have an onset of action of 1 to 2 hours which lasts for 12 to 24 hours, except for acrivastine, which has to be administered at 8-hourly intervals. With the exception of cetirizine and fexofenadine, which are excreted almost unchanged, the remaining drugs in this group are metabolised via the hepatic cytochrome P450 (CYP) system by CYP3A. As a number of other compounds, that is, antimycotic azoles, macrolide antibiotics and grapefruit juice, are also substrates for this enzyme, this obviously provides a risk for interactions.[35] This is probably a contributive factor to the occurrence of severe cardiac arrhythmias, for example, 'torsade de pointes', and fatalities, which have been described following treatment with terfenadine and astemizole.[36-38] These effects seem to be enabled through a quinidine-like action, causing a prolongation of the QT interval.[39,40] At present, no clinical evidence has demonstrated cardiac adverse effects with other second-generation antihistamines when they are used at therapeutically appropriate levels. However, it is recommended to avoid antihistamines which are CYP450 metabolised or which possess quinidine-like actions in risk groups, that is, patients with impaired hepatic function or cardiac arrhythmia.[41]

Astemizole can also act as an appetite stimulant and result in increased bodyweight.[42,43] The cause for this action remains obscure, although a central nervous system (CNS)-mediated mechanism, for example, serotonin (5-hydroxytryptamine)-antagonism, is a theoretical possibility. However, whether this adverse effect is seen exclusively with astemizole remains unknown as there is a lack of data on the other second-generation antihistamines for this measure.

Whereas CNS-related adverse effects were a major characteristic of the first-generation antihistamines, the piperazine/piperidine-derived structures of the newer generation agents reduce CNS penetration, although sedative effects have been described for some of the compounds, for example, acrivastine[44] and cetirizine.[45] The binding affinity to muscarinic receptors is also decreased with the second-generation agents. With the exception of the cardiac adverse effects, this provides a more acceptable therapeutic index for the second-generation antihistamines.

1.3 Topical Antihistamines

Two newer H_1-receptor antagonists are available for topical use, azelastine and levocabastine. When applied intranasally, they have both proven effective in the treatment of allergic rhinitis, mainly relieving nasal itching and sneezing.[46,47] They have a faster onset of action than oral antihistamines and act within 15 to 30 minutes. They only need to be applied twice daily.

No sedative effects have been seen with either drug,[46,48] whereas the occurrence of a short lasting perversion of taste has been described for azelastine.[49]

1.4 Comparative Effect of Antihistamines

1.4.1 Single Dose Studies

Many studies have been performed to compare the effects of oral second-generation antihistamines in the treatment of allergic rhinitis. Single dose studies in patients with allergic rhinitis have demonstrated that cetirizine and terfenadine have a faster onset of action than loratadine and astemizole.[50,51] All 4 drugs were equally effective against nasal symptoms and histamine-induced increases in nasal airway resistance. This contrasts somewhat with the results of 2 studies in which cetirizine was superior to loratadine after administration of a single dose in both symptom relief[52] and response to histamine challenge.[53] One study

was able to demonstrate a significantly faster onset of action for fexofenadine compared with terfenadine in relief of rhinorrhoea and sneezing immediately after nasal allergen challenge.[54] This may be explained on the basis of fexofenadine being the active metabolite of terfenadine.

1.4.2 Perennial Allergic Rhinitis

Relatively few studies investigating continuous administration of antihistamines are in patients with perennial allergic rhinitis (PAR). Six studies ranging from 1 to 8 weeks, included comparisons of astemizole[55,56] cetirizine,[56-58] ebastine,[57] loratadine,[55,59,60] mizolastine[59] and terfenadine.[58,60] No differences between agents were seen except that astemizole was more effective than loratadine for rhinorrhoea in 1 short-term study,[55] and cetirizine was better than ebastine according to the investigators opinion in another study.[57] Interestingly, in 1 of the studies, nonresponders were crossed to the opposite drug at the end of a 2 week treatment period, resulting in an effect in 11 of the 16 patients.[60]

1.4.3 Seasonal Allergic Rhinitis

The lack of difference in effectiveness between second-generation drugs is also found in patients with seasonal allergic rhinitis (SAR). One placebo-controlled study in 202 patients with SAR seems to designate cetirizine as superior to loratadine,[61] as seen in the single-dose study,[51] when all symptoms following allergen challenge were considered. However, this effectiveness in symptom relief after a quite short treatment period of 2 days could not be confirmed in another placebo-controlled, cross-over study of identical treatments given for 1 week.[62]

Several seasonal studies involving acrivastine,[63] astemizole[42,64] cetirizine,[64-69] ebastine,[67] fexofenadine,[68] loratadine,[42,70] mizolastine[69] and terfenadine[65,66,70] have been unable to demonstrate any difference in efficacy for symptom relief. Some studies demonstrate small differences, that is, 'subjective rating' of cetirizine over astemizole[71] or investigator preference of ebastine over cetirizine[72] without any support for this in other endpoints, for example, symptom relief. One study shows cetirizine to have a faster onset of action than terfenadine,[73] while another claims ebastine to achieve maximum effect faster than cetirizine.[72] The use of other objective endpoints such as nasal peak flow[70] and inflammatory mediators in nasal lavage fluid[74] has not shown differences between agents.

1.4.4 Studies in Children

Data on the efficacy in children with allergic rhinitis are sparse. One single-blind study in children with SAR for 2 weeks showed equal effect of loratadine and astemizole.[75] In another 4-week study in children with PAR, cetirizine was superior to loratadine according to parental assessment.[76]

1.4.5 Topical vs Oral Antihistamines

In comparisons between oral and topical antihistamines, most topical regimens have included intranasal as well as ocular medications or reports have only addressed nasal symptoms. In 1 study, intranasal azelastine was more effective than cetirizine at relieving nasal congestion,[77] whereas other studies have demonstrated azelastine to be equally effective as cetirizine,[78] ebastine,[79] loratadine[80] and terfenadine.[81] In 2 studies, intranasal levocabastine has been marginally more effective than terfenadine in relieving single symptoms, ie. sneezing[82] and nasal itching,[83] whereas a third study did not show any difference.[84] In 1 study,[83] levocabastine given as eye drops were also judged superior to terfenadine for relieving ocular symptoms. A comparison of levocabastine and loratadine showed identical efficacy.[85]

1.4.6 Safety

When considering adverse effects, only 2 of the previously mentioned studies indicate differences. A large, placebo-controlled, 2-week study in 821 patients with SAR showed a significantly higher degree of sedation after cetirizine than fexofenadine.[68]

In another smaller 8-week study in 27 patients with SAR, terfenadine revealed more adverse effects, that is, headache and dizziness, than a combination of intranasal and ocular levocabastine.[82]

2. Corticosteroids

2.1 General Considerations

Allergic rhinitis is an inflammatory disease of the nasal mucosa and corticosteroids are, at present, the most potent anti-inflammatory medications commercially available for the treatment of allergic rhinitis.[86] Corticosteroids exert their effect by combining with a glucocorticoid receptor localised in target cell cytoplasm. The resulting activated glucocorticoid receptor complex is able to interact with cellular DNA, thereby enabling regulation of cellular functions.[87,88]

Corticosteroids act upon many of the cell types and inflammatory mediators participating in allergic inflammation. Antigen-presenting Langerhans' cells are reduced in number by INCS.[89,90] Moreover, such treatment seems to impair their processing of antigen.[91] Similarly, the migration of basophils and mast cells to the nasal epithelium is inhibited by INCS.[91-94] Evidence suggesting an impact on the release of mast cell mediators, that is, histamine, has also been presented.[95] Corticosteroid therapy interferes with several pivotal aspects of eosinophil function. Cell survival is decreased and the ability to release preformed cytotoxic proteins, that is, eosinophil cationic protein and eosinophil peroxidase, is inhibited.[96,97] Moreover, formation of a number of cytokines and chemokines vital to eosinophil lifespan are inhibited, for example, interleukin (IL)-5 (formation),[98] IL-4 (adhesion)[99] and RANTES [Regulated on Activation, Normal T cell Expressed and Secreted] (chemotaxis).[100] Results demonstrating an inhibitory effect of intranasal corticosteroid on activated T cells in nasal epithelium have been presented.[101] In 2 studies, the allergen-induced increase of specific IgE in patients with PAR during season was abolished.[102,103] In all, this indicates profound effects of corticosteroids on the inflammatory process seen in allergic rhinitis.

2.2 Intranasal Corticosteroids

Since the introduction of beclomethasone,[8] several corticosteroids have been developed for intranasal application, all characterised by a high receptor affinity and an extensive first-pass metabolism in the liver. Effectiveness in relieving the symptoms of allergic rhinitis, including nasal congestion, have been demonstrated for beclomethasone,[104] budesonide,[105] flunisolide,[106] fluticasone propionate,[107] mometasone[108] and triamcinolone.[109] In addition, some reports have indicated that INCS may have a beneficial effect towards bronchial hyperresponsiveness and asthma symptoms.[110-115]

It has been generally considered that INCS have a slow onset of action. However, they usually act within 12 to 24 hours.[116-118] Recent results have even indicated that budesonide acts after 3 hours.[119] However, maximum treatment efficacy occurs after days or a few weeks.[120] Once-daily application has proven sufficient to treat most patients with allergic rhinitis,[121-125] although those with severe symptoms may benefit from twice daily administration.[126]

The different potencies of INCS are important when considering comparative data. It is well established that fluticasone propionate is twice as potent as beclomethasone.[107] There is controversy regarding relative potencies between other INCS. However, it appears that the newer drugs, that is, fluticasone propionate and mometasone, are more potent than the others.[117]

Currently available INCS are generally well tolerated. Sneezing caused by nasal hyperactivity can occur at the start of therapy but this usually disappears with time.[127]

Occasionally, mild and transient dryness, crusting and blood-stained secretions occur, and these are often responsive to a reduction of INCS dose.[120,128,129] Septal perforation has been described as a rare complication.[130,131] Atrophy of the mucosa, corresponding to dermal atrophy, after prolonged use of INCS has not been observed.[132,133]

Because a proportion of intranasally applied corticosteroids end up in the gastrointestinal tract and is systemically absorbed, the risk of systemic adverse effects has been a concern for this class of drugs. However, these compounds, especially the

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