

## Intranasal Corticosteroids for Allergic Rhinitis: Superior Relief?

Lars Peter Nielsen,<sup>1,2</sup> Niels Mygind<sup>2</sup> and Ronald Dahl<sup>2</sup>

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



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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.<sup>[1]</sup> Moreover, this prevalence seems to be increasing.<sup>[2,3]</sup> Although allergic rhinitis is not a life-threatening disease, it can severely impact on quality of life<sup>[4-6]</sup> and be associated with comorbidity from other diseases, for example, asthma and conjunctivitis.<sup>[7]</sup>

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.<sup>[8]</sup>

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<sub>1</sub>-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<sub>1</sub>-receptor antagonists.<sup>[9,10]</sup> In addition to H<sub>1</sub>-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.<sup>[11-19]</sup> However, other studies have been unable to confirm these findings.<sup>[20-23]</sup> 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<sub>1</sub>-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.<sup>[24-31]</sup> They are also effective for conjunctivitis and recent results seem to indicate some influence on lower airway symptoms.<sup>[32,33]</sup>

Moreover, the pharmacokinetic profile of second-generation antihistamines are advantageous when compared with the first-generation agents.<sup>[34]</sup> 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.<sup>[35]</sup> 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.<sup>[36-38]</sup> These effects seem to be enabled through a quinidine-like action, causing a prolongation of the QT interval.<sup>[39,40]</sup> 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.<sup>[41]</sup>

Astemizole can also act as an appetite-stimulant and result in increased bodyweight.<sup>[42,43]</sup> 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 astem-

izole 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<sup>[44]</sup> and cetirizine.<sup>[45]</sup> 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<sub>1</sub>-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.<sup>[46,47]</sup> 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,<sup>[46,48]</sup> whereas the occurrence of a short lasting perversion of taste has been described for azelastine.<sup>[49]</sup>

### 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.<sup>[50,51]</sup> 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<sup>[52]</sup> and response to histamine challenge.<sup>[53]</sup> 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.<sup>[54]</sup> 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<sup>[55,56]</sup> cetirizine,<sup>[56-58]</sup> ebastine,<sup>[57]</sup> loratadine,<sup>[55,59,60]</sup> mizolastine<sup>[59]</sup> and terfenadine.<sup>[58,60]</sup> No differences between agents were seen except that astemizole was more effective than loratadine for rhinorrhoea in 1 short-term study,<sup>[59]</sup> and cetirizine was better than ebastine according to the investigators' opinion in another study.<sup>[57]</sup> 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.<sup>[60]</sup>

#### 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,<sup>[61]</sup> as seen in the single-dose study,<sup>[51]</sup> 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.<sup>[62]</sup>

Several seasonal studies involving acrivastine,<sup>[63]</sup> astemizole<sup>[42,64]</sup> cetirizine,<sup>[64-69]</sup> ebastine,<sup>[67]</sup> fexofenadine,<sup>[68]</sup> loratadine,<sup>[42,70]</sup> mizolastine<sup>[69]</sup> and terfenadine<sup>[65,66,70]</sup> 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<sup>[71]</sup> or investigator preference of ebastine over cetirizine<sup>[72]</sup> 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,<sup>[73]</sup> while another claims ebastine to achieve maximum effect faster than cetirizine.<sup>[72]</sup> The use of other objective endpoints such as nasal peak flow<sup>[70]</sup> and inflammatory mediators in nasal lavage fluid<sup>[74]</sup> 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.<sup>[75]</sup> In another 4-week study in children with PAR, cetirizine was superior to loratadine according to parental assessment.<sup>[76]</sup>

#### 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,<sup>[77]</sup> whereas other studies have demonstrated azelastine to be equally effective as cetirizine,<sup>[78]</sup> ebastine,<sup>[79]</sup> loratadine<sup>[80]</sup> and terfenadine.<sup>[81]</sup> In 2 studies, intranasal levocabastine has been marginally more effective than terfenadine in relieving single symptoms, i.e. sneezing<sup>[82]</sup> and nasal itching,<sup>[83]</sup> whereas a third study did not show any difference.<sup>[84]</sup> In 1 study,<sup>[83]</sup> levocabastine given as eye drops were also judged superior to terfenadine for relieving ocular symptoms. A comparison of levocabastine and loratadine showed identical efficacy.<sup>[85]</sup>

#### 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.<sup>[68]</sup>

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.<sup>[82]</sup>



## 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.<sup>[86]</sup> 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.<sup>[87,88]</sup>

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.<sup>[89,90]</sup> Moreover, such treatment seems to impair their processing of antigen.<sup>[91]</sup> Similarly, the migration of basophils and mast cells to the nasal epithelium is inhibited by INCS.<sup>[91-94]</sup> Evidence suggesting an impact on the release of mast cell mediators, that is, histamine, has also been presented.<sup>[95]</sup> 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.<sup>[96,97]</sup> Moreover, formation of a number of cytokines and chemokines vital to eosinophil lifespan are inhibited, for example, interleukin (IL)-5 (formation),<sup>[98]</sup> IL-4 (adhesion)<sup>[99]</sup> and RANTES [Regulated on Activation, Normal T cell Expressed and Secreted] (chemotaxis).<sup>[100]</sup> Results demonstrating an inhibitory effect of intranasal corticosteroid on activated T cells in nasal epithelium have been presented.<sup>[101]</sup> In 2 studies, the allergen-induced increase of specific IgE in patients with PAR during season was abolished.<sup>[102,103]</sup> 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,<sup>[8]</sup> 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,<sup>[104]</sup> budesonide,<sup>[105]</sup> flunisolide,<sup>[106]</sup> fluticasone propionate,<sup>[107]</sup> mometasone<sup>[108]</sup> and triamcinolone.<sup>[109]</sup> In addition, some reports have indicated that INCS may have a beneficial effect towards bronchial hyperresponsiveness and asthma symptoms.<sup>[110-115]</sup>

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

The different potencies of INCS are important when considering comparative data. It is well established that fluticasone propionate is twice as potent as beclomethasone.<sup>[107]</sup> 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.<sup>[117]</sup>

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.<sup>[127]</sup>

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

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

newer fluticasone propionate and mometasone, have low systemic bioavailability, mainly because of their massive first-pass metabolism in the liver.<sup>[117]</sup> When used exclusively intranasally at therapeutic dosages, the drugs in this class do not seem to exhibit any influence on the hypothalamus-pituitary-adrenal (HPA)-axis.<sup>[134-137]</sup> However, a lack of HPA-axis suppression does not guarantee against other systemic adverse effects. Data demonstrating an inhibitory effect on the short term growth rate of children have been presented for beclomethasone and budesonide,<sup>[138,139]</sup> although the result for budesonide was only achieved by giving an adult dose of 200 µg twice daily. Moreover, this could not be reconfirmed in a recent study in which the impact on child growth, as measured by lower leg knemometry, of budesonide 400 µg daily was comparable to placebo.<sup>[140]</sup> Other systemic adverse effects, which have been linked to inhaled therapy, for example, cataract, glaucoma and dermal thinning, do not seem to occur in patients receiving treatment exclusively by the intranasal route.<sup>[141]</sup>

### 2.3 Comparative Effect of Intranasal Corticosteroids

#### 2.3.1 Perennial Allergic Rhinitis

As corticosteroids need continuous application to achieve maximum effect, single dose studies are, obviously, not very useful for comparing efficacy. Considering the many comparisons performed, not many have used a randomised, double-blind and eventually placebo-controlled design. Unless otherwise stated, the comparative studies discussed in this section (2.3) have used the drugs in standard recommended doses for allergic rhinitis.

Four placebo-controlled studies in patients with PAR have been published. Two studies<sup>[142,143]</sup> compared 1 dose of beclomethasone with 2 dose levels of fluticasone propionate in 183 patients for 12 weeks and in 466 patients for 26 weeks, respectively. The 2 remaining studies, each lasting 12 weeks, both considered mometasone. One was a comparison with beclomethasone at twice the standard daily dose in 387 patients<sup>[123]</sup> and the

other regarded an equi-nominal dose of fluticasone propionate in 459 patients.<sup>[144]</sup> None of these studies revealed any difference in the relief of symptoms of allergic rhinitis or in the physicians' assessment of treatment efficacy. Moreover, nasal cytology specimens were unable to demonstrate differences between treatments in 2 of the studies.<sup>[142,143]</sup>

One randomised, double-blind, 1-year study in 251 patients reported a significantly better effect with fluticasone propionate compared with an equi-nominal dose of beclomethasone on nasal congestion and secretion as well as relief of ocular symptoms.<sup>[145]</sup> These findings can partly be explained by the higher potency of fluticasone propionate. Of note, the difference was not reconfirmed by the 2 studies discussed in the previous paragraph.<sup>[142,143]</sup> A smaller randomised, double-blind, cross-over study comparing beclomethasone and flunisolide in 23 patients with perennial rhinitis, 15 of whom were allergic, did not show differences in efficacy for symptom relief or on more objective parameters of nasal blockage, that is, nasal peak flow and posterior rhinomanometry.<sup>[146]</sup>

In contrast, 2 studies comparing beclomethasone and budesonide with single-blind<sup>[147]</sup> or non-blind<sup>[148]</sup> design seem to favour the latter. Two single-blind studies have compared fluticasone propionate and budesonide. One study<sup>[149]</sup> demonstrated budesonide to be superior, especially for relief of nasal congestion. The other study,<sup>[128]</sup> which compared budesonide 200 and 400 µg daily given by turbuhaler to fluticasone propionate 200 µg daily, did not reconfirm this. One single-blind<sup>[150]</sup> and 1 non-blind study<sup>[151]</sup> have shown beclomethasone and flunisolide to be equally effective.

#### 2.3.2 Seasonal Allergic Rhinitis

Comparisons of efficacy between INCS in patients with SAR do not differ significantly from those in patients with PAR. Two randomised, double-blind, placebo-controlled comparisons of beclomethasone and mometasone, which both included >300 patients, over a period of 4 and 8 weeks, respectively,<sup>[152,153]</sup> did not demonstrate differences between the 2 agents. Similarly, no dif-



ference in treatment effect was seen in another study of similar design, which compared beclomethasone and fluticasone propionate in 313 patients for 2 weeks.<sup>[154]</sup> Only 1 randomised, double-blind study has shown a difference between 2 INCS, that is, beclomethasone and budesonide.<sup>[155]</sup> However, this 7-week study, which included 56 patients, had variable dose administration, ranging from 0 to 800 µg daily, and the difference was seen as less consumption of doses in the budesonide group.

No differences in treatment effect were seen in 1 non-blind<sup>[156]</sup> and 2 single-blind<sup>[157,158]</sup> comparisons of beclomethasone and flunisolide, even though 1 study used a rather low dose of beclomethasone.<sup>[158]</sup> Similarly, in single-blind comparisons, flunisolide was equivalent to budesonide<sup>[159]</sup> and triamcinolone was equivalent to fluticasone propionate.<sup>[160]</sup> Budesonide was superior to beclomethasone in relief of sneezing in 1 single-blind comparison<sup>[161]</sup> and for relief of sneezing, nasal secretion and itching in another.<sup>[162]</sup> In a single-blind study, 2 dose levels of budesonide were compared with 1 dose level of fluticasone propionate.<sup>[163]</sup> This showed a marginally better effect of the higher dose of budesonide on sneezing but otherwise no differences between the 2 drugs.

### 2.3.3 Safety

The occurrence of adverse effects was similar in all of the comparisons of INCS discussed in this section (2.3), apart from 2 studies showing less nasal irritation with budesonide than flunisolide and beclomethasone, respectively.<sup>[155,159]</sup> Only 3 studies have compared the systemic impact of INCS in patients with allergic rhinitis. Two of these have been mentioned already, one comparing budesonide and fluticasone propionate in adults<sup>[128]</sup> and the other budesonide and mometasone in children.<sup>[140]</sup> The first was unable to disclose differences in urine cortisol levels, while the second did not reveal any differences in short term leg growth rate. The third study considered the influence of budesonide, mometasone and triamcinolone on plasma and urine cortisol levels as well as serum osteocalcin levels and blood eosinophil counts.<sup>[137]</sup> It applied

a single-blind, cross-over, placebo-controlled design with treatment periods of five days in 20 patients with allergic rhinitis. No differences between treatments were seen for any of the parameters.

## 3. Comparing Antihistamines and Intranasal Corticosteroids

### 3.1 Perennial Allergic Rhinitis

A number of studies have compared antihistamines and INCS in patients with allergic rhinitis (table I and II).

Few studies have been performed in patients with PAR. Two 4-week studies compared terfenadine to beclomethasone<sup>[164]</sup> and astemizole with budesonide,<sup>[165]</sup> respectively. Both demonstrated that the INCS was superior for the relief of nasal symptoms. One small (n = 8) 12-week study of astemizole and beclomethasone was unable to show differences between the 2 drugs.<sup>[166]</sup>

Topical antihistamines and INCS have also been compared, with no demonstrable differences shown between azelastine and beclomethasone for relief of symptoms, physicians assessment of efficacy or nasal blockage, as measured by rhinomanometry.<sup>[167]</sup> However, when azelastine was compared with budesonide, the INCS was significantly superior for all nasal symptoms.<sup>[168]</sup> A single-blind comparison of levocabastine and beclomethasone, which was a follow-up on a double-blind comparison of levocabastine and placebo, demonstrated that beclomethasone provided better relief of nasal obstruction.<sup>[169]</sup>

### 3.2 Seasonal Allergic Rhinitis

Several comparisons of antihistamines and INCS have been conducted in patients with SAR, almost all being randomised and double-blind studies (table I and II).

The results of 14 comparative studies of oral antihistamines, in a total of >2500 patients, have been presented (terfenadine vs beclomethasone<sup>[170,171]</sup> and fluticasone propionate;<sup>[20,172,173]</sup> loratadine vs beclomethasone,<sup>[174]</sup> triamcinolone<sup>[175,176]</sup> and fluticasone propionate,<sup>[177,178]</sup> astemizole vs beclometh-

Table 1. Comparative studies of oral antihistamines and intranasal corticosteroids in patients with allergic rhinitis.

Reference	Study design	No. of pts.	Active treatments (daily dose)	Duration (weeks)	Comparative efficacy <sup>a</sup>
<b>Perennial allergic rhinitis</b>					
Robinson et al. <sup>[164]</sup>	r,db,co	18	Terfenadine 120mg/beclomethasone 400µg	2x4	Beclomethasone > terfenadine
Bunnag et al. <sup>[165]</sup>	r,db	67	Astemizole 10mg/budesonide 400µg	4	Budesonide > astemizole
Sibbald et al. <sup>[166]</sup>	nb,co	8	Astemizole 10-30mg/beclomethasone 400µg	2x12	NS
<b>Seasonal allergic rhinitis</b>					
Bronsky et al. <sup>[20]</sup>	r,db	346	Terfenadine 120mg/fluticasone propionate 200µg	4	Fluticasone propionate > terfenadine
Beswick et al. <sup>[170]</sup>	r,db	49	Terfenadine 120mg/beclomethasone 400µg	4	Beclomethasone > terfenadine <sup>b</sup>
Lancer et al. <sup>[171]</sup>	r,db	18	Terfenadine 120mg/beclomethasone 400µg	8	NS
Danielli et al. <sup>[172]</sup>	r,db,p	214	Terfenadine 120mg/fluticasone propionate 200µg	6	Fluticasone propionate > terfenadine
van Bavel et al. <sup>[173]</sup>	r,db,p	232	Terfenadine 120mg/fluticasone propionate 200µg	2	Fluticasone propionate > terfenadine
Frolund <sup>[174]</sup>	r,db	60	Loratadine 10mg/beclomethasone 400µg	3	Beclomethasone > loratadine
Condemni et al. <sup>[175]</sup>	r,db	348	Loratadine 10mg/triamcinolone 220µg	4	Triamcinolone > loratadine
Schoenwetter and Lim <sup>[176]</sup>	r,db	274	Loratadine 10mg/triamcinolone 220µg	4	Triamcinolone > loratadine
Gehanno and Desfougères <sup>[177]</sup>	r,db	114	Loratadine 10mg/fluticasone propionate 200µg	4	Fluticasone propionate > loratadine
Jordana et al. <sup>[178]</sup>	r,db	240 <sup>c</sup>	Loratadine 10mg/fluticasone propionate 200µg	4	Fluticasone propionate > loratadine
Salomonsson et al. <sup>[179]</sup>	r,db	158	Astemizole 10mg/beclomethasone 400µg	5	Beclomethasone > astemizole
Wood <sup>[180]</sup>	r,db	74	Astemizole 10mg/beclomethasone 400µg	15	NS
Bernstein et al. <sup>[181]</sup>	r,db	209	Astemizole 10mg/triamcinolone 220µg	4	Triamcinolone > astemizole
Vervloet et al. <sup>[182]</sup>	r,db	238	Cetirizine 10mg/fluticasone propionate 200µg	3	Fluticasone propionate > cetirizine

a Statistically significant difference between active medications for one or more nasal symptoms.

b During high exposure.

c Adolescents.

co = cross-over; db = double-blind; nb = nonblind; NS = no significance; p = placebo-controlled; r = randomized; &gt; indicates significantly better than.

asone<sup>[179,180]</sup> and triamcinolone<sup>[181]</sup> and cetirizine vs fluticasone propionate.<sup>[182]</sup> With the exception of 2 studies,<sup>[171,180]</sup> all demonstrated the INCS to be more effective in the relief of nasal symptoms than the oral antihistamine.

Of the exceptions, 1 study, which compared astemizole to beclomethasone in 74 patients, dem-

onstrated similar effects on nasal symptoms.<sup>[180]</sup> A possible explanation could be that a very long study period of approximately 15 weeks for the grass pollen season was used, thereby imposing a risk of diluting differences depending on pollen exposure. In fact, the paper lacks pollen data for the last 17 days of the study period. Although the sec-



ond study did not demonstrate differences between the agents in symptoms, it showed the INCS to have a superior effect on an objective measure of nasal obstruction, that is, rhinomanometry.<sup>[171]</sup>

This difference in nasal obstruction measured objectively was also seen in 1 of the studies demonstrating a difference between an antihistamine and INCS in nasal symptomatology.<sup>[20]</sup>

In the 1 study in adolescents, fluticasone propionate was more effective than loratadine in the relief of nasal peak inspiratory flow rate in a subgroup of patients.<sup>[178]</sup> Two studies were able to demonstrate significant reductions in the number of nasal mucosal eosinophils only with INCS.<sup>[20,173]</sup>

Conjunctivitis is often a major problem in patients with SAR. One of the reasons for using oral antihistamines rather than INCS has been because of the anticipated better effect on ocular symptoms. However, only 2 of the studies discussed in this section have confirmed this.<sup>[174,180]</sup>

The apparent superiority of INCS to oral antihistamines on relief of nasal symptoms was confirmed by a recent meta-analysis of 16 studies in-

volving 2267 subjects,<sup>[183]</sup> which demonstrated that INCS were more effective in relief of nasal obstruction, secretion, itching and sneezing as well as total nasal symptom score. Moreover, the meta-analysis was unable to demonstrate any difference between the 2 drug classes on ocular symptoms.

Data on the comparative efficacy of topical antihistamines and INCS in patients with SAR are also available (table II). Azelastine has been compared with beclomethasone in 2 studies, one of which showed beclomethasone as more effective in relieving nasal symptoms,<sup>[184]</sup> and the other revealed fewer eosinophils in nasal lavage but no difference on nasal symptoms.<sup>[185]</sup> Two small non-blind studies comparing azelastine to budesonide were unable to discriminate between treatments.<sup>[186,187]</sup> Three studies involving levocabastine have been reported, 1 compared this agent with budesonide<sup>[188]</sup> and 2 with fluticasone propionate.<sup>[189,190]</sup> All 3 studies demonstrated the INCS was superior in the relief of nasal symptoms. Moreover, fluticasone propionate reduced the number of eosinophils in nasal lavage fluid in both studies,<sup>[189,190]</sup> as well as

Table II. Comparative studies of topical antihistamines and intranasal corticosteroids in patients with allergic rhinitis.

Reference	Study design	No. of pts	Active treatments (daily dose)	Duration (weeks)	Comparative efficacy <sup>a</sup>
<b>Perennial allergic rhinitis</b>					
Davies et al. <sup>[167]</sup>	r,db,p	130	Azelastine 560µg/beclomethasone 400µg	6	NS
Stern et al. <sup>[160]</sup>	r,db,p	195	Azelastine 560µg/budesonide 256µg	6	Budesonide > azelastine
van de Heyning et al. <sup>[189]</sup>	r,db	21	Levocabastine 800µg/beclomethasone 400µg	2 <sup>b</sup>	Beclomethasone > levocabastine
<b>Seasonal allergic rhinitis</b>					
Newson-Smith et al. <sup>[184]</sup>	r,db,p	243	Azelastine 1120µg/beclomethasone 400µg	2	Beclomethasone > azelastine
Pelucchi et al. <sup>[186]</sup>	r,db,p	38	Azelastine 560µg/beclomethasone 200µg	6	NS
Dorow et al. <sup>[187]</sup>	r,nb	36	Azelastine 560µg/budesonide 200µg	2	NS
Wang et al. <sup>[187]</sup>	r,nb	14	Azelastine 1120µg/budesonide 400µg	2	NS
Svensson et al. <sup>[188]</sup>	r,db,p	44	Levocabastine 400µg/budesonide 400µg	6	Budesonide > levocabastine
Di Lorenzo et al. <sup>[189]</sup>	r,db,p	24	Levocabastine 400µg/fluticasone propionate 200µg	6	Fluticasone propionate > loratadine
Ortolani et al. <sup>[190]</sup>	r,db,p	288	Levocabastine 400µg/fluticasone propionate 200µg	6	Fluticasone propionate > levocabastine

a Statistically significant difference between active medications for one or more nasal symptoms.

b Follow-up of double-blind comparison between levocabastine and placebo.

db = double-blind; nb = nonblind; NS = no significance; p = placebo-controlled; r = randomized; sb = single-blind; > indicates significantly better than.

Table III. Comparative studies on combinations of oral antihistamines and intranasal corticosteroids in patients with seasonal allergic rhinitis

Reference	Study design	No. of pts	Active treatments (daily dose)	Duration (weeks)	Comparative efficacy <sup>a</sup>
Juniper et al. <sup>[191]</sup>	r,db	80	Astemizole 10mg, beclomethasone 400µg, astemizole 10mg + beclomethasone 400µg	6	Astemizole + beclomethasone = beclomethasone > astemizole
Ratner et al. <sup>[192]</sup>	r,db,p	600	Loratadine 10mg, fluticasone propionate 200µg, loratadine 10mg + fluticasone propionate 200µg	2	Loratadine + fluticasone propionate = fluticasone propionate > loratadine
Simpson <sup>[193]</sup>	r,db,p	106	Terfenadine 120mg, budesonide 400µg, terfenadine 120mg + budesonide 400µg	3	Terfenadine + budesonide = budesonide > terfenadine
Brooks et al. <sup>[194]</sup>	r,db	60	Loratadine 10mg, beclomethasone 336µg, loratadine + beclomethasone 336µg	2	Loratadine + beclomethasone > beclomethasone = loratadine
Backhouse et al. <sup>[195]</sup>	r,db	99	Terfenadine 120mg, terfenadine 120mg + flunisolide 200µg	11	Terfenadine + flunisolide > terfenadine
Juniper et al. <sup>[196]</sup>	r,nb	61	Terfenadine 60-120mg (+fluticasone propionate prn) fluticasone propionate 200-400µg (+Terfenadine prn)	6	NS <sup>b</sup>

a Statistically significant difference between active medications for one or more nasal symptoms.

b Only expressed as quality of life.

db = double-blind; nb = nonblind; NS = no significance; p = placebo-controlled; prn = as required; r = randomized; sb = single-blind; = indicates equal to; > indicates significantly better than.

eosinophil and mast cell markers of nasal lavage in 1 study.<sup>[189]</sup>

### 3.3 Combination of Antihistamines and Intranasal Corticosteroids

A combination of an antihistamine and INCS is often used in clinical practice. Four studies have included a treatment arm of such combination therapy in addition to treatment arms of antihistamine and INCS monotherapy (table III). Three of these, including almost 800 patients, showed that the combination therapy, although better than antihistamine alone for relief of nasal symptoms, offered no advantages over INCS alone.<sup>[191-193]</sup> The fourth study in 60 patients demonstrated the combination of loratadine and beclomethasone as significantly superior to beclomethasone alone for the outcomes of sneezing and nasal itching.<sup>[194]</sup>

One study has compared the combination of terfenadine and flunisolide to terfenadine alone and demonstrated a better effect of the combination for relief of nasal symptoms and in the investigator

assessment of treatment.<sup>[195]</sup> Another study with a nonblind design, which assessed terfenadine and fluticasone propionate offering the opposite drug on an as needed basis, was unable to demonstrate any difference in quality of life measures.<sup>[196]</sup> This parameter was also applied in 2 other studies, where the INCS-containing treatments produced a better quality of life.<sup>[173,192]</sup>

### 3.4 Safety

In contrast to the differences demonstrated for efficacy between antihistamines and INCS in all these comparative studies, no quantitative differences were observed regarding occurrence of adverse effects. Minor qualitative differences can be observed, eg. nasal crusting for INCS and sedation for antihistamines. However, in general, occurrence of adverse effects is low in both treatments. This includes results of morning plasma cortisol levels, albeit not an ideal indicator of HPA-axis interference, which were performed in three studies.<sup>[20,173,190]</sup>



### 3.5 Cost Effectiveness

The cost effectiveness of treatments is naturally dependent on local prizes for the respective medications. However, two-cost analyses seem to favour INCS over oral antihistamines. In the US, fluticasone propionate was more cost effective than terfenadine, when medications were needed for more than 11 to 22 days,<sup>[197]</sup> when comparing direct costs of medication to effect upon nasal symptoms and patient overall assessment. In Canada fluticasone propionate was 2.5 and 5.7 times as cost effective, respectively, than terfenadine and loratadine, when comparing direct costs of medication to days without nasal blockage.<sup>[198]</sup>

The combination use of oral antihistamines and INCS, which appears to offer no or a marginal clinical benefit compared with the use of INCS alone, cannot be considered to be cost effective.

### 4. Conclusion

A recent review<sup>[199]</sup> was unable to conclude any differences of efficacy between oral second-generation antihistamines, when considering the results of the relatively few existing randomised, double-blind, placebo-controlled studies of patients with SAR. This view is largely supported by data from randomised, double-blind comparator studies over the last decade for both SAR and PAR. Moreover, no differences have been documented by comparisons of systemic and topical second-generation antihistamines, when the latter were given both via the nose and the eyes.

No striking differences in efficacy in patients with allergic rhinitis have been demonstrated in comparisons of INCS at recommended doses. Similarly, existing clinical evidence on adverse effects do not convincingly support the theoretically-based superiority of newer compounds, for example, fluticasone propionate and mometasone. On the other hand, beclomethasone and budesonide provide the greatest amount of experience accumulated during more than 20 years. In summary, the available clinical evidence does not support one drug among the available INCS as superior.

The currently available comparative data on the efficacy of INCS and antihistamines clearly support INCS as more effective in the relief of nasal symptoms in patients with allergic rhinitis. Moreover, this is substantiated by results for other study endpoints, that is, inflammatory parameters, acoustic rhinometry, rhinomanometry and quality of life assessments. Interestingly, present evidence does not support a difference between these 2 drug classes in effective control of ocular symptoms. No quantitative differences have been demonstrated between INCS and antihistamines regarding occurrence of adverse effects in safety data. The common clinical practice of combining INCS and oral antihistamines in the treatment of allergic rhinitis has no support in clinical evidence, as the combination has not provided effects beyond INCS alone and so it cannot be considered cost effective.

International consensus reports<sup>[41,200]</sup> recommend INCS as first-line treatment in SAR and in PAR (adults) for patients with moderate to severe disease with regular or daily symptoms. Antihistamines are recommended as first-line treatment in patients with mild disease with infrequent symptoms, and in children with PAR.

This review supports the notion that INCS offer superior relief for the symptoms of allergic rhinitis. As long term experience has shown the treatment to be very well tolerated, INCS have a high therapeutic index and can be recommended as an effective treatment for allergic rhinitis.

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Correspondence and offprints: Dr Lars Peter Nielsen, Department of Clinical Pharmacology, The Bartholin Building, University of Aarhus, DK-8000, Aarhus, Denmark.  
E-mail: lpn@dadlnet.dk