

Impact and modulation of nasal obstruction

Nasal obstruction, the leading symptom of allergic rhinitis, results from the combined activity of early- and late-phase allergic reactions. Desloratadine inhibits both early- and late-phase inflammatory mediators *in vitro*. Thus, double-blind, placebo-controlled, randomized, crossover trials were conducted to assess the efficacy of desloratadine against nasal obstruction, measured objectively and subjectively, during controlled exposure of patients with seasonal allergic rhinitis to allergen. Positive results were obtained in three single-dose studies; desloratadine 5 mg resulted in a greater improvement from baseline than did placebo in the total symptom score and the nasal obstruction symptom score ($P \leq 0.02$). Desloratadine was more effective than placebo in a multiple-dose study; desloratadine 5 mg was given once daily for 7 days, and a 6-h allergen challenge was administered at the end of treatment compared with placebo. Desloratadine treatment was associated with less deterioration from baseline in the mean nasal airflow ($P < 0.05$) and in the mean severity score for the symptom of nasal obstruction ($P < 0.03$). Desloratadine significantly reduces the severity of nasal obstruction in patients with seasonal allergic rhinitis.

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Nasal obstruction is caused by nasal mucosal congestion and mucus secretion. Nasal obstruction may be measured objectively as decreased nasal airflow and is a leading chronic symptom of allergic rhinitis. The pathophysiology of nasal obstruction is complex, involving both the early and late phases of the allergic reaction, and nasal obstruction is sustained by the numerous mediators associated with the late phase of the allergic reaction and by the chronic inflammatory process (1).

α -Adrenergic agents (e.g. pseudoephedrine) reduce nasal obstruction by stimulating α_1 - and α_2 -adrenoreceptors that increase arteriolar and venous tone within mucosal vessels (2). However, the usefulness of orally administered agents is limited by adverse effects and contraindications in some medical conditions. Topical nasal decongestants, such as oxymetazoline, act rapidly but have the potential for rebound congestion with prolonged use (3).

Alternatives to decongestants include nasal corticosteroids and histamine H_1 -receptor antagonists, which relieve most symptoms of seasonal allergic rhinitis (SAR) via anti-inflammatory and antihistamine actions, respectively. However, nasal corticosteroids also relieve nasal obstruction (4), whereas histamine H_1 -receptor antagonists are classically considered to be less effective against nasal obstruction than against other SAR symptoms (1).

Desloratadine, a new, selective, histamine H_1 -receptor antagonist, inhibits both early-phase and

late-phase inflammatory mediators *in vitro* (5). In multicentre, double-blind, placebo-controlled clinical studies, once-daily desloratadine relieved SAR symptoms, including nasal stuffiness and congestion (6–8).

In addition to a brief review of the pathophysiology of allergic nasal obstruction, this article presents results from a series of studies that assessed the efficacy of desloratadine against nasal obstruction, measured objectively and subjectively, during controlled exposure of patients with SAR to allergen.

Pathophysiology of allergic nasal obstruction

Allergic nasal obstruction is caused by inflamed and swollen mucosa, with engorgement of sinusoidal capacitance vessels, rhinorrhoea, and increased mucus production (9). The pathophysiology of allergic nasal obstruction is complex. Both the early phase and the late phase of the allergic reaction contribute to nasal obstruction, due to the involvement of histamine and inflammatory mediators (Fig. 1).

As described elsewhere in this Supplement, allergen challenge results in mast cell activation and the subsequent release of histamine; other preformed elements such as enzymes, hydrolases, and proteoglycans; and proinflammatory mediators such as prostaglandins (e.g. PGD_2), leukotrienes, platelet-activating factor (PAF), bradykinin, cytokines, and

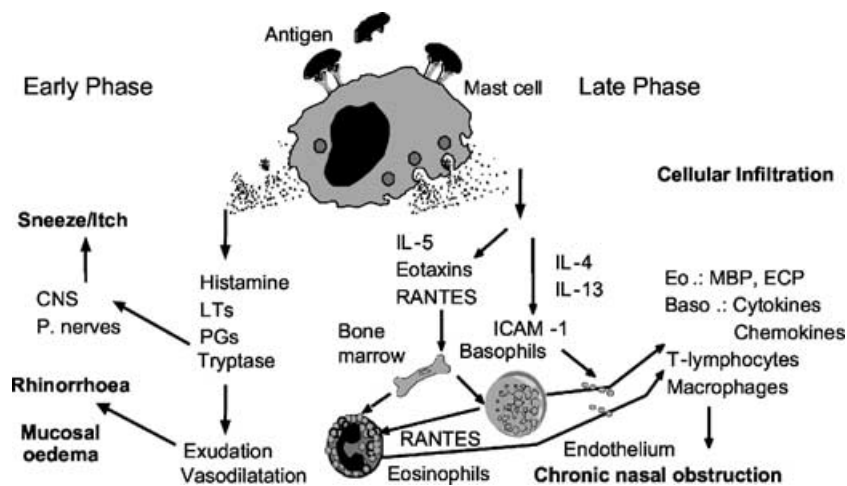


Figure 1 Nasal obstruction during the early and late phases of the allergic reaction. CNS, central nervous system; Eo, eosinophil; ECP, eosinophil cationic protein; ICAM-1, intercellular cellular adhesion molecule-1; IL, interleukin; LT, leukotriene; MBP, major basic protein; PG, prostaglandin; P. nerves, peripheral nerves; RANTES, regulated on activation, normal T cell expressed and secreted.

chemokines (10). Within minutes, histamine activates nerve endings located in epithelial tight junctions, resulting in the typical early-phase symptoms of sneezing and itching (1). Nerve stimulation also results in glandular secretion that contributes to rhinorrhoea and mucus production. Mucosal vessels become engorged, in part due to the effects of leukotrienes (11) and histamine (12). Engorgement leads to plasma exudation, which contributes to both nasal hypersecretion and obstruction. In addition, proinflammatory mediators initiate a complex inflammatory response, which includes contributing to activation of epithelial cells and the resulting increased expression of adhesion molecules (1). It is the complex network of inflammatory phenomena that is the driving force behind chronic nasal obstruction.

Early- and late-phase inflammatory mediators are inhibited by desloratadine *in vitro* (5). By inhibiting the release of early-phase mediators – histamine, tryptase, leukotriene C_4 , and PGD_2 – from mast cells and basophils, desloratadine may moderate early-phase allergic symptoms. *In vitro*, desloratadine inhibits many different cytokines, such as interleukins (IL-1 β , IL-3, IL-4, IL-5, IL-6, IL-10, IL-13, and IL-18), granulocyte monocyte colony-stimulating factor (GM-CSF), and tumour necrosis factor- α (TNF- α). Desloratadine also inhibits chemokines (i.e. RANTES (regulated on activation, normal T cell expressed and secreted) and IL-8), allergic cells (eosinophils and neutrophils), and adhesion molecules (i.e. P-selectin, intercellular adhesion molecule-1 (ICAM-1), vascular cellular adhesion molecule-1 (VCAM-1), and several clusters of differentiation including CD11a, CD11b, and CD134) (5,13,14). These mediators are linked to decreased activation, chemotaxis, recruitment, adhesion, and diapedesis of inflammatory cells. The *in vitro* actions of desloratadine against allergic inflammatory mediators have been demonstrated in a wide variety of cell preparations. However, before

apportioning clinical relevance to these actions, they should be demonstrated in the clinical setting.

Efficacy of desloratadine against nasal obstruction

A series of studies has demonstrated the efficacy of desloratadine treatment against nasal obstruction, assessed objectively and/or subjectively, in allergen-challenged patients with SAR. Subjects were at least 19 years of age, had at least a 2-year history of SAR, and had a positive IgE-mediated skin test response to the challenge allergen (either grass or ragweed pollen). Exclusion criteria included 1) recent use of corticosteroids, asthma medications, histamine H_1 -receptor antagonists, or antibiotics for respiratory tract infections without an adequate washout period and 2) a history of any clinically significant medical condition or clinically abnormal laboratory finding that might affect the patient's safety or the outcome of the study. The studies were conducted outside of the pollen season for the specified allergen, and the challenge was conducted in a sealed chamber in which levels of allergen were strictly maintained throughout the several hours of the testing period (9,15).

Three single-dose studies demonstrated the efficacy of desloratadine treatment for the relief of the symptom of nasal obstruction (termed congestion): a pilot study of desloratadine 5 mg ($n = 28$) and a dose-finding study of desloratadine 5 mg and 7.5 mg ($n = 36$), both of which were crossover in design with a washout period of at least 10 days, and a parallel-group comparison of desloratadine 5 mg and 7.5 mg ($n = 161$) (16). After baseline symptom evaluation, subjects were exposed to allergen and remained in the allergen chamber for an additional 5 h after administration of desloratadine or placebo. Patients scored nasal and non-nasal symptoms on a 4-point scale from 0 (none) to 3 (severe), and individual symptom scores were summed for a total symptom score. In all three studies, desloratadine

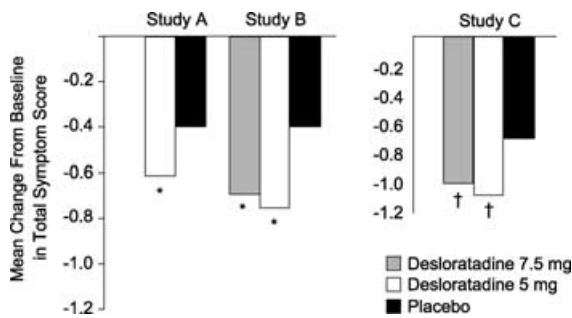


Figure 2 Mean change (improvement) from baseline in total symptom score after administration of a single dose of desloratadine 5 mg, desloratadine 7.5 mg, or placebo to allergen-challenged patients with seasonal allergic rhinitis (SAR). *P* values refer to comparison between desloratadine and placebo (**P* = 0.02; †*P* < 0.001) (16).

5 mg produced a significantly greater mean improvement from baseline compared with placebo in the total symptom score (*P* < 0.01; Fig. 2) and the nasal obstruction symptom score (*P* ≤ 0.02; Fig. 3). The 7.5-mg dose provided no additional benefit. Each of the seven individual rhinitis symptoms – nasal obstruction, sneezing, nasal discharge, itchy nose, itchy eyes, tearing, and itchy ears or palate – was significantly improved from baseline as compared with placebo (*P* < 0.05 for each).

These single-dose studies in relieving the symptom of nasal obstruction were followed by a multiple-dose, crossover study to show the efficacy of desloratadine treatment in preventing nasal obstruction, experienced subjectively as a symptom and recorded objectively as nasal airflow (ml/s) by active anterior rhinomanometry immediately before (baseline) and every 30 min during allergen exposure (9). Desloratadine 5 mg was compared with placebo, each administered once daily for 7 days separated by a 10-day washout. Prior to the first treatment, each person underwent a controlled 2-h exposure to grass pollen allergen to document adequate nasal allergic response. This was defined as 1) no or mild subjective nasal obstruction (symptom

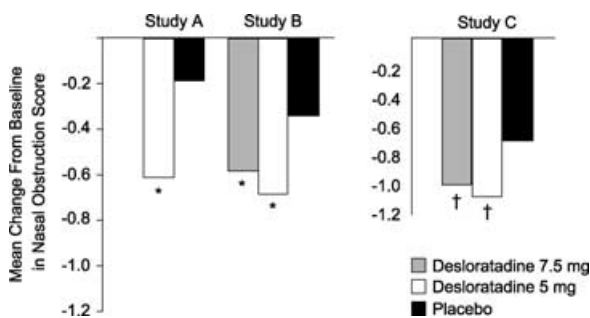


Figure 3 Mean change (improvement) from baseline in nasal obstruction symptom severity score after administration of a single dose of desloratadine 5 mg, desloratadine 7.5 mg, or placebo to allergen-challenged patients with seasonal allergic rhinitis (SAR). *P* values refer to comparison between desloratadine and placebo (**P* = 0.02; †*P* < 0.01) (16).

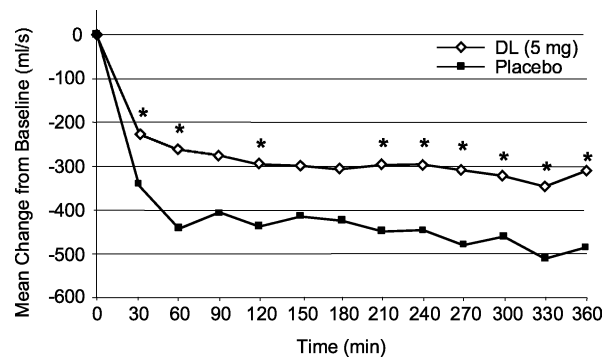


Figure 4 Mean change (decrease) from baseline in nasal airflow (in ml/s) in response to allergen exposure after treatment with desloratadine 5 mg (DL) or placebo every morning for 7 days. *P* values refer to comparison between desloratadine and placebo (**P* < 0.05). Reproduced with permission from (9).

score ≤ 1) at entry to the allergen exposure chamber, which increased to at least moderate upon allergen exposure (symptom score ≥ 2) and 2) an increase in objectively measured nasal obstruction, documented by a 30% or greater decrease in airflow. On day 7 of each treatment period, patients underwent 6 h of continuous allergen exposure with periodic assessments of objective nasal obstruction, nasal secretions (collected with sealed, preweighed packets of absorbent paper tissues), and nasal and non-nasal SAR symptom severity. The primary endpoint was the between-group comparison of the mean change (decrease) from baseline in nasal airflow after the start of the 6-h allergen challenge.

A total of 47 patients participated in the multiple-dose study. The mean change (decrease) from baseline in nasal airflow was significantly less with desloratadine than with placebo at most assessment times (*P* < 0.05; Fig. 4). Furthermore, the mean change (increase) from baseline in the severity score for the symptom of nasal obstruction was also

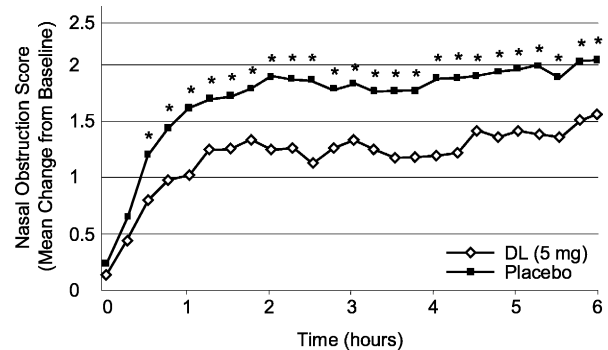


Figure 5 Mean change (increase) from baseline in nasal obstruction symptom severity score in response to allergen exposure after treatment with desloratadine 5 mg (DL) or placebo every morning for 7 days. *P* values refer to comparison between desloratadine and placebo (**P* < 0.03). Reproduced with permission from (9).

significantly less with desloratadine than for placebo at all assessment times ($P < 0.03$; Fig. 5).

Conclusions

Nasal obstruction is produced by a complex network of inflammatory phenomena during the early and late phases of the allergic reaction and is sustained by a chronic inflammatory process and by numerous mediators. Thus it responds only partially to antagonism of histamine H_1 -receptors.

In addition to antagonizing H_1 -receptors, desloratadine inhibits numerous other early- and late-phase

inflammatory mediators, including tryptase, PGD_2 , leukotriene C_4 , cytokines, adhesion molecules, chemokines, and allergic cells, *in vitro*. Desloratadine 5 mg significantly reduces the severity of nasal obstruction documented objectively (as nasal airflow measurement) and subjectively (using symptom scores) in allergen-challenged patients with SAR. The efficacy of desloratadine against nasal obstruction, in combination with its favourable pharmacokinetic and safety profiles and intriguing *in vitro* inhibitory effects on allergic mediators (6), makes desloratadine an important new option for the treatment of SAR.

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