

Antihistamines and nasal blockage

Van Cauwenberge P, Wang D. Antihistamines and nasal blockage.
Allergy 1997; 52 (suppl 40): 35–38. © Munksgaard 1997.

Paul van Cauwenberge,
Deyun Wang

Department of Otorhinolaryngology, University
Hospital, University of Ghent, Ghent, Belgium

Introduction

At present, antihistamines are among the most widely used pharmacological agents in the treatment of allergic diseases. It is known that they are effective for the relief of nasal symptoms, such as itching, sneezing and rhinorrhea caused by allergic rhinitis. Especially the second-generation H_1 -antihistamines are strong H_1 -receptor antagonists, and most of them have a rapid onset of action. However, antihistamines have only little effect on nasal obstruction, probably because of the complex underlying pathophysiological mechanisms. Various mediators and other inflammatory components are known to play an important role in the formation of mucosal oedema and vasodilation.

In recent years, considerable attention has been paid to the treatment of the underlying inflammation of the nasal mucosa. Anti-inflammatory agents, such as topical corticosteroids, have proven to be very effective in the treatment of nasal allergy and hyperreactivity, especially in eosinophil-dominated nasal inflammation (1). Although it has been claimed, it has not been proven that the *in vitro* anti-inflammatory properties of the second-generation H_1 antihistamines also have an additional clinical effect.

It is generally accepted that at this time there is no cure for allergic rhinitis. The aims of pharmacotherapy for allergic rhinitis are therefore not always the same, and they depend on the specific goals that the physician and the patient want to achieve, i.e. (a) relief of nasal symptoms, (b) down-regulation of mucosal inflammation, (c) prevention of new exacerbations, and (d) improvement of quality of life. All the anti-allergic drugs have their specific advantages and disadvantages according to their efficacy and tolerance profiles.

Pathophysiology of allergic rhinitis

Allergic rhinitis is an inflammatory disease of the nasal mucosa. The pathophysiology is complex and involves many different cell types, inflamma-

tory mediators, cytokines and cell-adhesion molecules. At the cellular level, the mechanism of allergic reactions may consist of the following stages:

- (a) Airborne allergens deposit in the nose and interact with cell-bound IgE attached to high-affinity receptors on mast cells and low-affinity receptors on T lymphocytes, Langerhans cells, and eosinophils.
- (b) Allergen binding causes IgE molecules to cross-link, which triggers a membrane and cytoplasmic "cascade" leading to mast cell degranulation and release of inflammatory or immunological mediators. These include pre-formed mediators, i.e. histamine, heparin, tryptase and other chemotactic factors for eosinophils and neutrophils. Newly generated membrane-derived lipid mediators, such as arachidonic acid metabolites (i.e. prostaglandins and leukotrienes), and platelet-activating factor, also participate in the allergic inflammation. These inflammatory changes are evidenced in relationship with the onset of immediate nasal symptoms, such as sneezing, itching, rhinorrhea and nasal obstruction (2). The onset of itching and sneezing may occur as early as 30 seconds after nasal allergen challenge. A peak concentration of histamine (after 1 minute), tryptase (after 5 minutes) and LTC₄ (after 5 minutes) can be observed after allergen challenge (3).
- (c) Release of mediators, cytokines and granule constituents from mast cells and other inflammatory cells (i.e. lymphocytes and macrophages) can directly cause inflammation or activate the local vascular endothelium to further enhance the recruitment of leukocytes through the expression and function of adhesion molecules.
- (d) The increased mucosal accumulation and activation of leukocytes can further enhance mucosal inflammation and responsiveness to specific and nonspecific stimuli. In particular,

the formation of oedema, vasodilation and vascular reactions such as extravasation, result in a late-phase reaction that is especially characterized by nasal blockage which continues for several hours after allergen challenge and exposure.

A better understanding of the mechanisms of the allergic response has aided the development of more effective treatment modalities.

Histamine and the effect of histamine antagonists

Histamine released by mast cells and basophils is an important mediator in the pathophysiology of allergic rhinitis. The role of histamine in the nasal symptomatology is confirmed by the reproduction of nasal symptoms after nasal provocation with histamine. These symptoms can be inhibited by the application of histamine antagonists. In addition, the increase in histamine concentration in the nasal secretions of atopic patients after a nasal allergen challenge and during a natural allergen exposure is confirmed by several studies (4–6). More recently, increased expression of histamine H_1 -receptor mRNA in allergic rhinitis has been demonstrated (7).

To this date, three histamine receptors have been recognized: H_1 -, H_2 - and H_3 -receptors (8). It has been demonstrated that the nasal effects of histamine are predominantly mediated via H_1 -receptors and that H_1 -receptor antagonists reduce the clinical expression of nasal itching, sneezing and rhinorrhea. H_1 -antihistamines (Table 1) are relatively ineffective in the treatment of nasal obstruction (9, 10).

While it is completely unknown whether H_3 -receptors play any role in the human nose, there is good evidence that vascular H_2 -receptors are of some importance (11). The dilatation of nasal capacitance vessels, responsible for histamine-induced increase in nasal airways resistance, is mediated via both H_1 - and H_2 -receptors, while only H_1 -receptors are of importance for plasma exudation and oedema formation. Therefore, it

was not surprising to note that a combination of H_1 - and H_2 -receptor antagonists is more effective than H_1 -blockers alone in reducing histamine-induced nasal congestion (12, 13).

Some studies have demonstrated additional so-called anti-allergic effects of the newer antihistamines: inhibition of mediator release from mast cells, a decrease in local inflammatory cell influx and a decrease in the allergen-induced upregulation of ICAM-1 expression in epithelial cells in both the early and the late phase after nasal allergen challenge (14–19). However, the exact biologic effects of these antihistamines on mast cell degranulation and mucosal inflammation are not fully understood. Other studies have failed to show that H_1 -histamine antagonists have additional anti-inflammatory properties (13, 20–22). Whether the non- H_1 -receptor activities of the second-generation drugs, shown in experimental studies, have any clinical significance is not known.

Antihistamines, especially the first-generation antihistamines, may often have a sedative effect. This effect is CNS dependent and partly related to their anti-emetic effect and their ability to reduce motion sickness. The majority of these antihistamines have affinity for muscarinic receptors and have varying degrees of anticholinergic activity. In addition, some antihistamines may have local anaesthetic and antiserotonin properties.

Oral antihistamines

Most antihistamine drugs are taken orally, e.g. acrivastine, astemizole, cetirizine, loratadine, terfenadine and azelastine. They will provide a systemic effect that can be beneficial for the relief of symptoms of coexisting allergic diseases, such as rhinitis, conjunctivitis, mild asthma and urticaria. They may, however, also cause systemic side-effects, such as sedation (especially the first-generation H_1 -antihistamines). The second-generation H_1 -antihistamines are less or non-sedating and are free of anticholinergic activity. At a normal dose, they are generally safe and without severe side-effects.

Most newly developed H_1 -antihistamines have a rapid onset of action (except astemizole) and a duration of activity of up to 24 hours. Therefore, most of them have a once-daily regimen that benefits with patients' compliance. It is known that these H_1 -antihistamines can differ greatly from one to the other with regard to metabolism and pharmacokinetics. Because many of their metabolites are active H_1 -antagonists, the plasma half-life of the parent drug is poorly predictive of the duration of action (23). Cetirizine differs from other antihistamines in that it is not metabolized in the

Table 1. Classification of H_1 -antihistamines

First generation	Second generation
Chlpheniramine	Acrivastine
Diphenhydramine	Astemizole
Hydroxyzine	Cetirizine
Promethazine hydrochloride	Loratadine
Triprolidine	Terfenadine
Azelastine (oral and topical)	
Levocabastine (topical)	

liver, and no active metabolites are generated, so it is mainly excreted in the urine (24). Astemizole has a very long half-life (10 days in serum), reducing skin prick reactions to histamine and allergens for 6–8 weeks (25).

In a study of patients with seasonal allergic rhinitis during the pollen season, we found that 2 weeks' treatment with cetirizine (10 mg daily) caused a significant relief of subjective nasal symptom scores including itching, sneezing, rhinorrhoea and congestion (13).

When performing a nasal allergen challenge in the same patients, a dramatic reduction in the number of sneezing bouts (from a median number of 10.5 times to 0) was observed after the treatment. Meanwhile, significant increases in histamine, tryptase and leukotriene C_4 concentrations in their nasal secretions were evidenced after nasal allergen challenge before and after the treatment. When a combination of cetirizine and cimetidine was administered, a significant reduction in the nasal airway resistance and an increase of the nasal air flow were demonstrated after nasal allergen challenge. The effect on nasal symptoms of other oral antihistamines, such as terfenadine, loratadine, astemizole and azelastine, have been demonstrated by other investigators (14, 16, 17, 22, 25, 26).

Interestingly, a recent study performed by Bousquet et al. (27) demonstrated that treatment with cetirizine in patients with perennial allergic rhinitis not only reduced daily symptoms, but also improved quality of life in these patients. Allergic rhinitis is a disease causing variable restrictions on the physical, psychological and social aspects of the lives of patients, and it may have an impact on their business career. Therefore, successful treatment of allergic rhinitis should improve the quality of life of the patients.

Topical antihistamines

Some H_1 -receptor antagonists are effective when used in a topical form, e.g. a nasal spray. Kirkegaard et al. (28) demonstrated a topical effect of chlorpheniramine maleate on the relief of histamine-induced nasal symptoms. An advantage of an antihistamine nasal spray could be the more rapid onset of action and a stronger local effect, as these drugs are directly applied to the nasal mucosa and their concentration is high enough to exert an activity within minutes. However, there are few relevant data available about the qualitative and quantitative differences in the efficacy and onset of action between systemic and topical forms of H_1 -antihistamines. The exact clinical benefit of

topical antihistamines in the treatment of allergic rhinitis is still unknown.

In terms of safety, a topical treatment is preferable in particular to prevent systemic side-effects, which may be caused by systemic antihistamines. A drawback of a topical drug is that multiple daily applications are needed to maintain an effective concentration of the drug in the tissue. Another disadvantage of an antihistamine nasal spray is that it does not have a direct effect on co-existing allergic inflammations in other tissues, such as the conjunctiva and skin. In addition, it is quite difficult to reach a sufficient nasal mucosal surface in patients with severe nasal congestion and/or rhinorrhoea.

To date, two topical H_1 antihistamines are commercially available for the treatment of allergic rhinitis, i.e. levocabastine and azelastine. These two drugs have shown in clinical trials to be potent and highly specific H_1 -receptor antagonists. Levocabastine and azelastine nasal sprays offer quick relief of itching and sneezing; and, when used twice daily, they can prevent the development of these symptoms (23). They are as effective as oral antihistamines and it has been claimed, but not proven, that they may be more beneficial in relieving nasal obstruction (29–32).

Side-effects of antihistamines

With respect to efficacy and absence of sedation, the newer antihistamines show a favourable risk/benefit ratio. The most common side-effects of antihistamines, especially of the first-generation, are central nervous system suppression and sedation. In addition, increased appetite and weight gain can be a problem with cyproheptadine, ketotifen and astemizole (28). The possible, but extremely rare, cardiotoxic effects appear to be related in most cases, to an overdose, drug interaction or reduced hepatic metabolism of certain drugs, with abnormal accumulation and consequent effect on cardiac repolarization. The arrhythmogenic effects can be avoided, but require, like all drugs, careful case-by-case evaluation in order to recognize the possible contraindications (33).

Conclusion

Both systemic and topical H_1 antihistamines are efficacious and have proven to be effective in the treatment of allergic rhinitis. They give a rapid relief of the nasal symptoms, such as itching, sneezing and rhinorrhoea, but have less or no effect on nasal obstruction. Further studies on the biological mechanisms of different types of antihis-

tamines and their effects on different pathophysiological processes of allergic rhinitis have to be carried out in detail.

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