

Ideal pharmacotherapy for allergic rhinitis

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The characteristics of the "ideal" pharmacotherapeutic agent for managing the symptoms of seasonal allergic rhinitis and the advantages and disadvantages of the pharmacotherapeutic agents that are currently available are reviewed. Decongestants, mast cell stabilizers, anticholinergics, intranasal steroids, and oral antihistamines and their place in the therapeutic armamentarium of the clinician are discussed. (*J Allergy Clin Immunol* 1999;103:S386-7)

The ideal therapeutic agent for managing the symptoms of seasonal allergic rhinitis (SAR) would be one that effectively addresses the pathophysiology of both the early-phase reaction (EPR) and the late-phase reaction (LPR). This drug would antagonize histamine at the H₁-receptor sites of effector cells, managing the cardinal symptoms of SAR including nasal pruritus, sneezing, rhinorrhea, and nasal congestion. Because other chemical mediators are also released with mast cell degranulation, the ideal drug would have to counter these effects as well. The primary effect of these mediators is to recruit inflammatory cells from the nasal vasculature to the nasal mucosa, setting up the potential for an inflammatory reaction. These recruited inflammatory cells also release chemical mediators that contribute to non-H₁-mediated symptoms in LPR, particularly nasal congestion. The ideal drug would therefore inhibit mediator release from the mast cells with the subsequent effect of minimizing inflammatory cell recruitment, thereby reducing the potential for inflammation. So the ideal drug would not only treat the acute EPR symptoms of SAR but also affect the LPR by reducing inflammatory cell migration and the underlying process of inflammation.

To manage the acute symptoms of SAR, the ideal drug would have to be fast-acting with first-dose effectiveness. To ensure patient compliance, the drug should only have to be taken when the patient has symptoms with a dosing schedule of once or twice daily. The ideal drug would effectively manage the specific symptom(s) that a patient is having, with few or no side effects. For patients with multiple symptoms the ideal drug would effectively manage all of the symptoms, eliminating the need for concomitant medication. The drug would have a favorable side effect profile, which would also assist patient compliance. Delivering the drug directly to the nasal mucosa could minimize systemic effects and concentrate the drug where it could produce an optimal effect.

Abbreviations used

EPR: Early-phase reaction
LPR: Late-phase reaction
SAR: Seasonal allergic rhinitis

CURRENTLY AVAILABLE AGENTS

Decongestants (both the oral and topical formulations) constrict blood vessels and reduce blood supply to the nasal mucosa through a direct effect on α -adrenergic receptors.¹ Decongestants provide effective relief of nasal congestion but have minimal effects on the other symptoms of allergic rhinitis and therefore would be effective therapy for a patient whose only symptom was nasal congestion. Topical decongestants have the disadvantage of predisposing the patient to rebound congestion or rhinitis medicamentosa.² Oral decongestants are associated with dose-related central nervous system stimulating and pressor effects that may not be appropriate in some patients.³

Although the precise mechanism of action of mast cell stabilizers has yet to be determined, it is believed that cromolyn sodium inhibits the release of histamine and other mediators of inflammation by stabilizing mast cells.⁴ Cromolyn sodium is most effective when used in prophylactic form for symptoms of allergic rhinitis; hence it must be started before the allergy season begins. Therefore the biggest disadvantage of cromolyn sodium is that the product must be administered for several weeks before optimal relief of symptoms is realized, and patients must use it regularly, usually 4 times daily, to obtain maximal benefit.⁵ These 2 requirements frequently present compliance challenges to patients and may result in missed doses and less-than-optimal clinical results. Also, the response to intranasal cromolyn sodium varies, and it is generally less effective in severe cases of allergic rhinitis.⁶ After 3 weeks of treatment in patients with SAR⁷ and after 4 weeks of treatment in patients with perennial allergic rhinitis,⁸ intranasal corticosteroids demonstrated a superior therapeutic effect compared with cromolyn sodium. Therefore supplemental therapy with other pharmacologic agents is usually necessary for an acceptable response to be achieved,³ especially in a patient in whom congestion is a troublesome symptom.

Anticholinergic drugs (eg, ipratropium) are drugs that competitively inhibit the effects of acetylcholine by blocking its binding to receptors at neuroeffector sites on glandular tissue,⁹ resulting in a reduction in the volume of secretions from the nose.³ Ipratropium is not effective for the management of symptoms of rhinitis other than

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rhinorrhea.¹⁰ Therefore when a patient has rhinorrhea in the absence of other symptoms, ipratropium monotherapy is considered appropriate therapy. Likewise, ipratropium is also effective in the management of the rhinorrhea component of the common cold.¹¹

Although intranasal steroids are considered effective drugs for managing allergic rhinitis, symptomatic response to intranasal steroids may not be evident for several days after therapy is initiated, and some patients may require a therapeutic trial of 2 to 3 weeks to determine whether the treatment is satisfactory. For treatment with intranasal steroids to be effective, they must be used on a regular basis to maintain optimal therapeutic efficacy.¹² Despite the general consensus among clinicians that topically administered steroids are only minimally bioavailable, the safety of these drugs remains a concern, particularly in children and adolescents. Studies^{13,14} demonstrated that serum and urinary cortisol levels were statistically significantly decreased by the short-term use (up to 14 days) of several intranasal steroids (fluticasone, beclomethasone, budesonide, and triamcinolone) in therapeutic dosages. In a recent 12-month, placebo-controlled, double-blind study¹⁵ of 100 children (aged 6 to 9 years) who were receiving 168 µg beclomethasone twice daily, bone growth as measured by standing height was evaluated at 1-, 2-, 4-, 6-, 8-, 10-, and 12-month intervals. A significant ($P < .05$) decrease in bone growth was observed at the 1-, 6-, 8- and 12-month visits; however, the authors suggested that the clinical importance of these findings should be determined. Based on these and other findings, the Food and Drug Administration's Pulmonary and Allergy Drugs and Endocrine and Metabolic Drugs Advisory Committees has recently considered the use of class labeling for inhaled and intranasal steroids regarding the issue of pediatric growth suppression.

Oral antihistamines manage sneezing, nasal itching, and rhinorrhea associated with allergic rhinitis but are not as effective in relieving nasal obstruction.^{6,16} It is estimated that only 33% to 50% of patients with SAR have no symptoms with antihistamine therapy,¹⁷ suggesting that mediators other than histamine contribute to symptom development. Leukotrienes, prostaglandins, and kinins are known to contribute to the development of nasal congestion, which may explain the lack of effectiveness of antihistamines in managing congestion.¹⁸ Although antihistamines effectively manage the H₁-receptor-mediated symptoms of the EPR in patients with SAR, they have not been as effective in managing the symptoms of the LPR, particularly congestion, and the underlying inflammatory process of SAR. Therefore leukotriene antagonists (eg, zafirlukast, montelukast) used in combination with antihistamines may be appropriate therapy for patients with allergic rhinitis.

CONCLUSION

Optimal treatment of patients with SAR can be achieved only by managing both the EPR and LPR. The symptoms observed in EPR are most effectively managed by an H₁-receptor antagonist, whereas the effects of LPR are best managed with a corticosteroid. Therefore the ideal pharmacologic therapy would be a drug that possessed not only H₁-receptor antagonist activity but also anti-inflammatory activity. In addition, this drug would have a favorable safety profile, would not have to be taken in prophylactic form, and would be fast-acting and convenient to administer.

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