

Use of nasal steroids in managing allergic rhinitis

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Intranasal steroids are highly effective drugs for treating patients with allergic rhinitis. First-line use of intranasal steroids is becoming increasingly common, and intranasal steroids can be used alone or in combination with other therapies to achieve optimal improvement in rhinitis symptoms. The major adverse effect of intranasal steroids is local irritation. This article reviews the mechanism of action of corticosteroids, the effects of intranasal steroids on chemical mediators of inflammation, and the risks and benefits associated with their use. (J Allergy Clin Immunol 1999;103:S388-94)

Corticosteroids are generally considered the most effective medications for the management of inflammatory diseases including asthma and allergic rhinitis. At the present time several nasal corticosteroids are available for treating patients with allergic rhinitis including beclomethasone dipropionate, flunisolide, triamcinolone acetate, budesonide, fluticasone propionate, and mometasone furoate. With the exception of beclomethasone, these drugs are quickly metabolized to less active metabolites, have minimal systemic absorption, and have been associated with few systemic side effects. In addition, the intranasal corticosteroids provide equivalent or better efficacy with regard to reducing the influx of inflammatory cells into the nasal cavity than oral steroid preparations.¹ Double-blind placebo-controlled studies in patients with seasonal allergic rhinitis demonstrated that the effect of intranasal steroids on rhinitis symptoms is dependent on local activity.^{2,3} Although considered as second-line agents after antihistamines by many physicians, first-line use of intranasal steroids is becoming increasingly common, especially for patients with severe symptoms.

MECHANISM OF ACTION

Corticosteroids act by controlling the rate of protein synthesis. When administered either systemically or topically, the unbound steroid molecule passively diffuses across the target cell membrane and enters the cytoplasm, where it binds to a single glucocorticoid receptor.⁴ After the association of corticosteroid and receptor, the activated glucocorticoid receptor enters the cell nucleus, where it attaches as a dimer to specific binding sites (glucocorticoid response elements) on DNA in the 5'-upstream

Abbreviations used

EPR: Early-phase response
LPR: Late-phase response

promotor region of steroid-responsive genes. The effect of this interaction is to either induce or suppress gene transcription. The messenger RNA transcripts induced during this process then undergo post-transcriptional processing and are transported to the cytoplasm for translation by ribosomes, with subsequent production of new proteins. After post-translational processing occurs, the new proteins are either released for extracellular activity or retained by the cell for intracellular activity.⁵⁻⁷ The time required for messenger RNA translation and protein transcription may account for the lag phase between the administration and resulting clinical activity of the corticosteroids.

More recently, it has become apparent that activated glucocorticoid receptors may interact directly with other transcription factors in the cytoplasm, which in turn may greatly affect the steroid responsiveness of the target cell.⁸

In sensitized patients with allergic rhinitis, allergen exposure leads to cross-linking of IgE antibodies on the surface of mast cells, which triggers a cascade of biochemical events and results in mast cell degranulation and the release of both preformed and membrane-derived chemical mediators in the early-phase allergic response (EPR). The chemical mediators released in the EPR promote the migration of inflammatory cells from the peripheral blood that contribute to the late-phase response (LPR). This migration of inflammatory cells into the nasal mucosa is responsible for the chronic inflammatory nature of allergic rhinitis. Approximately 50% of patients with allergic rhinitis demonstrate increased sensitivity to antigen after repeated daily exposure, a priming effect first described by Connell.⁹ In allergen challenge studies this increased sensitivity was associated with significant increases in the release of histamine, kinins, and prostaglandin D₂ and increases in the number of basophils, neutrophils, and eosinophils.^{10,11}

The effectiveness of corticosteroids for the management of allergic rhinitis is most likely related to multiple pharmacologic actions. Corticosteroids have demonstrated specific effects on the inflammatory cells and chemical mediators involved in the allergic process. Chemical mediators that appear to be directly affected by corticosteroids include leukotrienes and prostaglandins, which

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Table. Dosage and administration schedules for commonly used intranasal steroid preparations

Corticosteroid/ trade names		Dosage and administration			Intranasal bioavailability
Beclomethasone					Unknown
Beconase AQ®,	1-2 sprays/nostril twice daily	168 to 336 µg/d	Adults and children		
42 µg per spray			6 yrs and older		
Vancenase 84AQ®,	1 or 2 sprays/nostril daily	168 to 336 µg/d	Adults and children		
84 µg per spray			6 yrs and older		
Flunisolide					40% - 50%
Nasalide® /Nasarel®,	2 sprays/nostril twice daily or	200 µg/d	Adults 15 yrs and older		
25 µg per spray	2 sprays/nostril 3 times daily	300 µg/d			
	1 spray/nostril 3 times daily or	150 µg/day	Children 6 to 14 yrs		
	2 sprays/nostril twice daily	200 µg/d			
Budesonide					20%
Rhinocort®,	2 sprays/nostril twice daily or	256 µg/d	Adults and children		
32 µg per spray	4 sprays/nostril daily		6 yrs and older		
Fluticasone					0.5%-2%
Flonase®,	2 sprays/nostril daily	200 µg/d	Adults and children		
50 µg per spray			12 yrs and older		
	1-2 sprays/nostril daily	100 to 200 µg/d	Children 4 to 11 yrs		
Triamcinolone					Unknown
Nasacort®,	2 or 4 sprays/nostril daily	220 to 440 µg/d	Adults and children		
55 µg per spray			12 yrs and older		
	2 sprays/nostril daily	220 µg/d	Children 6 to 11 yrs		
	2 sprays/nostril daily	220 µg/d	Adults and children		
Nasacort AQ®,			12 yrs and older		
55 µg per spray	1-2 sprays/nostril daily	110-220 µg/d	Children ages 6-12 yrs		
Mometasone					0.1%
Nasonex®,	2 sprays/nostril daily	200 µg/d	Adults and children		
50 mg per spray			12 yrs and older		

are synthesized from arachidonic acid through the lipoxygenase and cyclooxygenase enzymatic pathways, respectively. Corticosteroids increase the synthesis of a protein (lipocortin-1) that has an inhibitory effect on phospholipase A2 and therefore may inhibit the production of lipid mediators.¹²⁻¹⁴ Other mediators such as histamine, platelet-activating-factor, kinins, and substance P are affected indirectly by the inhibitory effects of the corticosteroids on inflammatory cells.

Corticosteroids reduce the number of circulating T lymphocytes and inhibit T-lymphocyte activation,¹⁵ IL-2 production,¹ IL-2 receptor generation,¹⁶ and IL-4 production.¹⁷ They reduce circulating numbers of eosinophils and eosinophil influx in the LPR,¹⁸ inhibit IL-5 mediated eosinophil survival,¹⁹ and inhibit GM-CSF production.²⁰ Corticosteroids reduced seasonally induced increases in nasal mast cells²¹ and histamine levels,^{1,22} reduced the number of circulating basophils, and inhibited neutrophil influx after allergen challenge.¹¹ Corticosteroids cause reductions in the numbers of circulating macrophages and monocytes and inhibit the release of cytokines including IL-1, IFN- γ , TNF- α , and GM-CSF.²³

CLINICAL USE

In the United States intranasal formulations of beclomethasone, flunisolide, budesonide, fluticasone, tri-

amcinolone, and mometasone are available under various trade names. The recommended dosage and administration schedules are displayed in the Table. After using these dosages for 1 to 2 weeks, the patient should be re-evaluated, and the dosage can be adjusted based on the clinical response. The goal of therapy should be to use the lowest dosage that provides effective relief of symptoms.

CLINICAL STUDIES IN ALLERGIC RHINITIS

The effectiveness of intranasal steroids in managing allergic rhinitis has been established in well-controlled, comparative, clinical trials. In a 4-week, double-blind, placebo-controlled crossover study²⁴ in patients with chronic perennial rhinitis, 100 µg intranasal beclomethasone dipropionate 4 times daily was compared with intranasal cromolyn sodium 2% solution 6 times daily, and both drugs were compared with placebo. Beclomethasone and cromolyn were both more effective than placebo; however, beclomethasone was significantly better than cromolyn sodium in relieving both nasal and non-nasal symptoms. In an 8-week, randomized, single-blind study,²⁵ standard intranasal dosages of beclomethasone, flunisolide, and cromolyn were compared with placebo in patients with seasonal allergic rhinitis. Although all 3 agents were superior to placebo in improving the total symptom score, the 2 corticosteroids were statistically

significantly more effective than cromolyn. In a 6-week, double-blind, randomized, parallel-group trial in patients with rhinoconjunctivitis, 400 µg/d beclomethasone nasal spray was superior to 10 mg/d astemizole and equivalent to a combination of 400 µg/d beclomethasone plus 10 mg/d astemizole.²⁶ Triamcinolone nasal spray 220 µg/d was more effective than 10 mg/d astemizole in reducing total nasal symptoms, nasal stuffiness, nasal itching, and sneezing in a 4-week double-blind trial in patients with seasonal allergic rhinitis.²⁷ In a 4-week double-blind trial, 200 µg fluticasone aqueous nasal spray once daily was superior to both 60 mg terfenadine twice daily and placebo in managing nasal symptoms in patients with allergic rhinitis. As measured by rhinomanometry, total nasal airflow was significantly improved in the fluticasone group compared with patients treated with terfenadine or placebo.²⁸ In a 4-week placebo-controlled trial in patients with seasonal allergic rhinitis, 200 µg/d intranasal triamcinolone was statistically superior to 10 mg/d oral loratadine in relieving nasal symptoms and demonstrated a trend for greater improvement in ocular symptoms.²⁹

ANTIALLERGIC/ANTI-INFLAMMATORY EFFECTS

Intranasal steroids influence all aspects of the nasal inflammatory response in which they have been studied. The inhibitory effects of intranasal steroids on early- and late-phase allergic responses have been demonstrated in several well-controlled clinical studies.

Early-phase effects

Initial studies of the effects of intranasal steroids on the EPR did not yield positive results.^{30,31} However, further studies demonstrated significant inhibition of the early response after allergen challenge in sensitized patients, and it appears that the duration of corticosteroid pretreatment is a factor in limiting the EPR. In a double-blind crossover study, a 1-week pretreatment with intranasal beclomethasone resulted in significant inhibition of increased nasal airway resistance compared with placebo after allergen challenge in patients with seasonal allergic rhinitis.³² In a large multicenter trial, a 2-week pretreatment with 400 µg/d intranasal beclomethasone significantly inhibited allergen-induced early-phase symptoms compared with placebo in patients with perennial allergic rhinitis.³³ In a double-blind placebo-controlled trial in patients with seasonal allergies, 100 µg or 400 µg budesonide nasal spray daily for 1 week significantly inhibited the immediate response to allergen challenge as determined by reductions in nasal secretions and nasal blockage measured objectively by rhinomanometry.³⁴ In a double-blind placebo-controlled trial,³⁵ 400 mg/d budesonide inhibited the early response to allergen challenge when administered either 48, 12, or 2 hours before or 2 hours after the initial challenge, with 48-hour pretreatment being the most effective in reducing symptom scores.

Late-phase effects

The inhibitory effect of intranasal steroids on the LPR is well established. In a placebo-controlled study 164 µg beclomethasone twice daily for 7 days significantly reduced sneezing, histamine levels, and TAME-esterase activity compared with placebo 24 hours after nasal allergen challenge in patients with allergic rhinitis.³⁶ In a placebo-controlled allergen challenge study by Pipkorn et al,³⁷ reductions in histamine, TAME-esterase activity, and kinins after 1-week pretreatment with intranasal flunisolide were statistically significant during the EPR, whereas the reductions during the LPR were significantly greater than during the early phase. In a placebo-controlled allergen challenge study, 400 µg/d budesonide significantly improved nasal symptoms and nasal blockage during the LPR in patients with seasonal allergic rhinitis.³⁸ A 6-week double-blind treatment with 400 µg/d fluticasone in patients with allergy to grass pollen resulted in almost complete inhibition of late-phase nasal symptoms after allergen challenge.¹⁵

Effects on inflammatory cells and mediators

In a study by Linder et al,³⁹ nasal secretions from patients with seasonal allergic rhinitis treated with 400 µg/d intranasal beclomethasone contained significantly lower levels of eosinophil cationic protein than secretions from untreated patients in a control group when sampled during the allergy season and after allergen-specific nasal challenge out of season. In a double-blind placebo-controlled study, 400 µg/d fluticasone significantly decreased eosinophil cationic protein and IL-5 levels during the LPR in patients with perennial allergic rhinitis.⁴⁰ Compared with placebo, pretreatment with 200 mg/d flunisolide significantly inhibited the influx of basophils, eosinophils, neutrophils, and mononuclear cells in the LPR to allergen challenge in patients with seasonal allergic rhinitis.¹¹ A 2-week pretreatment with 400 µg/d budesonide significantly decreased tryptase and leukotriene C4 release and the activation and infiltration of eosinophils in response to nasal allergen challenge in a randomized, parallel-group trial.⁴¹ After a 6-week treatment with either 200 µg intranasal fluticasone daily or placebo during the pollen season, nasal biopsy specimens from patients in the fluticasone group showed no significant increases in epithelial eosinophils, submucosal eosinophils, and epithelial mast cells, whereas these cell types were significantly increased in the placebo group. Fluticasone also suppressed IL-4 expression in the nasal submucosa.⁴² Fokkens et al⁴³ reported the results of 2 studies in which 200 µg/d or 400 µg/d intranasal fluticasone reduced the numbers of antigen presenting cells, eosinophils, and IL-4 and -5 in patients with allergic rhinitis. In a 3-month placebo-controlled study, intranasal fluticasone significantly reduced the numbers of antigen-presenting cells and T cells in the nasal mucosa of patients with allergic rhinitis.⁴⁴ In a placebo-controlled study a 1-week pretreatment with 168 µg/d intranasal beclomethasone significantly reduced the levels of chemokines (IL-8, macrophage inflammatory pro-

tein-1a, and RANTES) and cytokines (IL-1b and GM-CSF) in nasal secretions of allergic patients after allergen challenge.⁴⁵ Significant decreases in the recovery of IL-1b, IL-8, IL-6, GM-CSF, macrophage inflammatory protein-1a, and RANTES also were reported after a 1-week pretreatment with 200 µg/d fluticasone in a placebo-controlled study.⁴⁶

Results of studies of the humoral effect of intranasal steroids suggest a direct influence on the immune response to seasonal allergens by downregulation of allergen-specific antibody production. In a placebo-controlled study in patients with seasonal allergic rhinitis, continuous treatment with 336 µg/d beclomethasone or 440 µg/d triamcinolone reduced symptom scores and the anticipated increase in ragweed-specific IgE during the duration of the ragweed-allergy season.⁴⁷ In a similar study, 400 µg/d beclomethasone returned anti-birch pollen IgE levels to baseline values by the end of a 5-week treatment period.⁴⁸

ADVERSE EFFECTS

Local irritation is the most frequently observed adverse effect with intranasal steroids, with approximately 10% of patients having some form of nasal irritation, nasal burning, or sneezing after administration. Bloody nasal discharge occurs in approximately 2% of patients treated with intranasal steroids, and there have been a few reports of septal perforations^{49,50} and delayed hypersensitivity reactions.⁵¹ However, long-term use of intranasal steroids does not appear to cause a significant risk of adverse morphologic effects in the nasal mucosa. Electron microscopy examination of the nasal mucous membranes of patients treated with beclomethasone for 1 year for nasal polyps showed no change in the membrane surface structure.⁵² In a study of intranasal steroid treatment in 90 patients with perennial rhinitis, nasal biopsy specimens revealed a trend toward normalization of the nasal mucosa at the end of the 12-month study period.⁵³ In a recent study of 52 patients with perennial rhinitis treated with mometasone for 12 months, nasal biopsy specimens showed a decrease in focal metaplasia, no change in epithelial thickness, and no sign of atrophy.⁵⁴ The incidence of local irritation with intranasal steroids has been reduced by the development of aqueous formulations of these drugs,^{55,56} and the subsequent reduction in local irritation with these preparations has increased their use in children.

Systemic side effects are generally not considered a serious risk with intranasal steroids, although early studies showed that intranasal dexamethasone at doses commonly used in allergic rhinitis induced mild to moderate adrenal suppression^{57,58}; however, recent reviews of the clinical experience with intranasal fluticasone⁵⁹ and triamcinolone⁶⁰ have indicated no reports of systemic side effects. Bilateral posterior subcapsular cataracts have been reported in association with nasal aerosol or inhalation of beclomethasone; however, many of the patients had used higher than recommended dosages or had

received concomitant oral steroid therapy.⁶¹ In a case control study nasal glucocorticoids were not associated with an increased risk of ocular hypertension or open-angle glaucoma, whereas prolonged administration of high doses of inhaled glucocorticoids increased the risk for these adverse effects.⁶²

Risk/benefit ratio

Antihistamines with or without decongestants are typically recommended as first-line therapy for allergic rhinitis. If treatment with antihistamines fails to relieve symptoms or if the symptoms are debilitating, intranasal steroids usually provide significant relief of nasal symptoms. The efficacy of intranasal steroids exceeds that of oral antihistamines and cromolyn. Although a delayed onset of action with the intranasal steroids may occur in some patients, well-controlled studies⁶³⁻⁶⁶ have shown that many patients have a clinically evident onset of effect during the first day of administration. Some studies suggest that intranasal steroids can be used on an as-needed basis by many patients, but for some patients optimal effectiveness can only be achieved with regular use.^{67,68} Although it has been suggested that the major reason for the lack of efficacy appears to be the inability to gain access to the site of inflammation,⁵⁰ a pharmacokinetic evaluation of intranasally administered triamcinolone demonstrated no difference in pharmacokinetic parameters between patients with documented nasal inflammation and healthy volunteers after single-dose administration and over a 6-week treatment period.⁶⁹

Although systemic absorption is low, there are still concerns about systemic side effects with intranasal steroids. For intranasal steroids to produce systemic side effects, they must access the systemic circulation. This can occur through direct intranasal absorption or through gastrointestinal absorption of the swallowed fraction of the administered dose. Although very little is known about the intranasal bioavailability of the different steroid preparations, the oral bioavailability of most steroids has been studied. Because it is likely that approximately 80% of the administered intranasal dose is swallowed, the gastrointestinal tract could potentially be a large contributor to the total bioavailability of an intranasal dose of steroid.

Unlike the dose absorbed through the nose, the swallowed portion of steroid will undergo a degree of hepatic first pass metabolism before reaching the systemic circulation. The reported oral bioavailability of fluticasone propionate⁷⁰ and mometasone furoate⁷¹ is negligible compared with 23% for triamcinolone acetonide,⁷² 20% for flunisolide,⁷³ and 11% for budesonide.⁷⁴

Measurements of intranasal bioavailability are quite limited. That the nose is a capable organ for absorbing steroids was demonstrated by Edsbacker et al,⁷⁵ who showed that 100% of an intranasal dose of budesonide solution could be absorbed under very specific laboratory conditions. The total bioavailability of an intranasal dose of mometasone is reported at 0.1%⁷¹ and for fluticasone at 0.5%⁷⁶ to <2%.⁷⁷ The total bioavailability of

intranasal budesonide is reported to be 20%,⁷⁸ and that of flunisolide is reported to be 40% to 50%.⁷⁹ The intranasal bioavailability of intranasal triamcinolone acetate is unknown. It should be noted that bioavailability of inhaled steroids is scant, and direct comparisons of data produced by different methods may be inappropriate.

There are no reliable data regarding the bioavailability of beclomethasone by any route. Unlike other intranasal steroids, beclomethasone dipropionate is metabolized to an active metabolite beclomethasone-17 monopropionate and relatively inactive metabolites beclomethasone-21 monopropionate and beclomethasone.⁸⁰ This may partly explain why growth suppression in children is so easily demonstrated with beclomethasone, whereas this effect was not seen in a 1-year study with fluticasone.⁸¹

An inhibitory effect of beclomethasone on growth in asthmatic children has been reported in 4 recent studies.⁸²⁻⁸⁵ A small but statistically significant effect on growth was reported in a 12-month study in children 6 to 9 years of age treated with 336 µg/d intranasal beclomethasone; however, the authors suggested that the clinical importance of these findings must be determined.⁸⁶ It has also been demonstrated that intranasal budesonide suppressed short-term lower leg growth as measured by knemometry.⁸⁷ In a 2-week study of intranasally administered budesonide or fluticasone, serum osteocalcin levels decreased significantly with both treatments, and serum cortisol decreased after 1 week of treatment, whereas urinary cortisol was not affected until the second week of treatment. These effects were receptor-dependent and reversible, and, according to serum and urinary cortisol levels and insulin tolerance testing, left the hypothalamic-pituitary-adrenal function intact.⁸⁸ In a study of hypothalamic-pituitary-adrenal-axis activity involving 16 healthy adult volunteers, it was found that once-daily intranasal fluticasone (43% suppression) but not triamcinolone (23% suppression) or beclomethasone (21% suppression) produced significant suppression of overnight urinary cortisol compared with placebo; however, none of the compounds caused a significant suppression of the overnight cortisol/creatinine ratio.⁸⁹ It should be noted that the clinical significance of the previously described findings is unknown. Recently, the Food and Drug Administration's Pulmonary and Allergy Drugs and Endocrine and Metabolic Drugs Advisory Committees considered the issue of class labeling precautions regarding pediatric growth suppression with use of inhaled and intranasal corticosteroids.

Long-term use of intranasal steroids in patients with perennial allergic rhinitis who require treatment for many years, in patients who administer excessive intranasal doses, or in patients with rhinitis, asthma, or dermatitis whose combined dosages from inhaled, intranasal, or topical routes of administration may place them at risk for possible hypothalamic-pituitary-adrenal suppression. Patients previously treated for prolonged periods with systemic corticosteroids and transferred to topical corticosteroids should be carefully monitored for acute adren-

al insufficiency. Localized fungal infections have occurred rarely^{78,79} with intranasal steroids and may require discontinuation of therapy. However, with proper use of intranasal steroids, 60% to 90% of patients may have virtually complete relief of rhinitis symptoms.⁹⁰

CONCLUSION

Intranasal steroids are highly effective drugs for treating patients with allergic rhinitis, with efficacy exceeding that of antihistamines, decongestants, and cromolyn. There are several available formulations, all with approximately the same efficacy and safety characteristics. Although less effective than antihistamines in managing the acute symptoms including ocular symptoms of seasonal allergic rhinitis, intranasal steroids can be used in combination with other therapies to achieve optimal improvement in overall symptoms. Corticosteroid preparations have a delayed onset of action and require daily administration to achieve optimal results. The major adverse effect of intranasal steroids is local irritation, and although there has been a recent appreciation of the systemic bioavailability of the different intranasal steroid preparations, reports of systemic side effects are rare.

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