

The Role of Nasal Corticosteroids in the Treatment of Rhinitis

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KEYWORDS

- Allergic rhinitis • Vasomotor rhinitis • Nonallergic rhinopathy
- Intranasal corticosteroids • Corticosteroid pharmacology
- Rhinitis treatment

Intranasal corticosteroids (INSs) have been available for the treatment of rhinitis since 1974. They are extremely effective in reducing the nasal symptoms of sneezing, itching, rhinorrhea, and nasal congestion. It is evident that INSs are the appropriate first-line treatment choice for many patients with rhinitis, particularly those with persistent or more severe symptoms.¹ In addition to efficacy and safety considerations, patients may have a preference for one INS agent over another, which can influence their compliance with therapy. This article reviews the rationale for using INSs in rhinitis and examines the criteria that should be considered when selecting an INS treatment.

NASAL CORTICOSTEROID MECHANISMS OF ACTION

The mechanisms of action of INSs are related to their anti-inflammatory activities. It is important to understand these and the magnitude of INS effects to use them most appropriately.

T Lymphocytes

Corticosteroid therapy provides a modest reduction in the number of lymphocytes because of induction of programmed cell death or apoptosis.² Topical corticosteroid administration has been shown to inhibit T-lymphocyte activation, prevent increases

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in interleukin (IL)-4, IL-5, and local IgE, and inhibit eosinophil recruitment and activation,^{3,4} IL-2 production,⁵ and IL-2 generation.⁶

Eosinophils

Corticosteroids have well-recognized effects on the eosinophil component of the inflammatory process through direct induction of eosinophil apoptosis⁷ and inhibition of eosinophil recruitment and migration into the nasal airways. Cytokine production in the airways may trigger this cellular infiltration, and therefore inhibition of cytokine production is one of the most important effects of corticosteroid therapy.⁸ Corticosteroids are effective and potent inhibitors of cytokines such as tumor necrosis factor α (TNF- α) and IL-1, which induce secretion of the nonspecific endothelial activators.⁹ They also inhibit the release of IL-4 and IL-13, thereby preventing expression of specific endothelial cell adhesion molecules, which can bind basophils, eosinophils, monocytes, and lymphocytes.³

In addition, corticosteroid treatment has been shown to inhibit the expression of the chemokine RANTES in airway epithelial cells.¹⁰ Furthermore, corticosteroids inhibit the production of IL-3, IL-5, and granulocyte-macrophage colony-stimulating factor (GM-CSF)¹¹ and reduce eosinophil survival time.¹² Thus, corticosteroids have multiple effects on eosinophils: they reduce the number of eosinophils in the circulation, prevent recruitment of eosinophils to local tissue sites,¹³ reduce survival of eosinophils, and prevent production of cytokines that are responsible for, or involved in, all of these processes. Glucocorticosteroids inhibit the production of many cytokines.

Mast Cells and Basophils

Topical corticosteroids can reduce inflammation through affecting the infiltration of mast cells and basophils. Treatment can decrease the number of mast cells in the nasal mucosa.^{14,15} Corticosteroid treatment has also been shown to markedly reduce the number of basophils in nasal secretions.¹⁶ An associated reduction in the release of mast cell mediators has been shown after corticosteroid treatment, along with an interference of arachidonic acid metabolism associated with a subsequent decrease in mediator production.^{17,18} The reduction in the recruitment and activation of lymphocytes, eosinophils, and basophils and the associated decrease in the production of inflammatory mediators contribute to the value of corticosteroids in relieving the symptoms of rhinitis.

Neutrophils

Corticosteroids are able to inhibit the accumulation of neutrophils,¹⁹ possibly through preventing neutrophil adherence to vascular endothelium because of suppression of the release of endothelial-activating cytokines, for example, IL-1, IL-4, and TNF- α , and by preventing the release of factors that influence migration through the endothelial barrier, for example, IL-8, TNF- α , platelet-activating factor (PAF), and LTB₄.²⁰

Monocytes and Macrophages

Corticosteroids reduce the number of tissue macrophages and inhibit their release of IL-1, interferon gamma, TNF- α , and GM-CSF (**Table 1**).^{8,21}

Epithelial Cells

Human epithelial cells metabolize arachidonic acid. Arachidonic acid metabolites, such as leukotrienes, prostaglandins, thromboxane, and PAF, have several activities, including regulation of vascular tone and vascular permeability, stimulation of mucus secretion, chemotaxis, and regulation of cell proliferation. The cytokines produced by

Table 1
Effects of corticosteroids on inflammatory cells

Cells Affected	Corticosteroid Effect
<i>T lymphocytes</i>	Reduction of circulating cell number, apoptosis Inhibition of: T-lymphocyte activation IL-2 production IL-2 receptor generation IL-4 production Antigen-driven proliferation
Eosinophils	Reduction of circulating cell number, apoptosis Reduction of epithelial and mucosal cell counts Reduction of cell influx in late-phase response Inhibition of IL-4- and IL-5-mediated cell survival
Mast cells/basophils	Reduction of circulating cell counts Reduction of cell influx in late-phase response Reduction of mast cell-derived mediators after challenge Reduction of histamine content and release
Neutrophils	Reduction of cell influx after challenge
Macrophages/monocytes	Reduction of circulating cell counts Inhibition of release of: IL-1 Interferon- γ TNF- α GM-CSF

Data from Meltzer EO. The treatment of vasomotor rhinitis with intranasal corticosteroids. WAO Journal 2009;2:168.

epithelial cells can also mediate recruitment, activation, and survival of inflammatory cells in the airway.²² Corticosteroids interfere with the inflammatory response through blocking the production of arachidonic acid metabolites in many cells. This interference is accomplished through inducing the production of the anti-inflammatory protein, lipocortin, which inhibits phospholipase A2, an enzyme central to the arachidonic acid cascade, thereby preventing the generation of cyclooxygenase and lipoxygenase products.²²

Blood Vessels

Topical corticosteroids reduce blood flow and inhibit vascular permeability. The mechanisms for these actions include a reduction in the cyclooxygenase metabolites that maintain vascular beds, inhibition of phospholipase A2, and the subsequent formation of leukotrienes and PAF,²³ inhibition of the release of endothelial-derived relaxing factor, production of vasocortin (which reduces permeability), and enhancement of vasospasm by α -adrenergic stimulation.^{24,25}

Nerve Cells

Steroids have been reported to upregulate neutral endopeptidase that degrades neuropeptides²⁶ and inhibits neurogenic plasma extravasation.²⁷

THE GLUCOCORTICOID RECEPTOR

Corticosteroid activity is mediated by intracellular activation of the glucocorticoid receptor (GR).^{28,29} In its inactive state, the GR exists as a cytosolic protein bound to

two heat shock protein 90 chaperonin molecules. Binding to the corticosteroid ligand results in a conformational change that allows dissociation of the GR from the protein complex, and a quick translocation into the cell nucleus. The ligand-bound GR can modulate gene expression in the nucleus through binding to glucocorticoid response elements in promoter regions of responsive genes. The GR binds to the glucocorticoid response elements as a homodimer and acts as a transcription factor. It has also become evident that the GR can regulate gene expression unfacilitated by glucocorticoid response elements through direct interaction with transcription factors such as nuclear factor NF-kappa B and activating protein.^{28,30,31} The inhibition of these two factors leads to downregulation of the production of cytokines and other inflammatory molecules and is believed to be among the primary mechanisms for the anti-inflammatory effects of corticosteroids.^{28,29}

NASAL CORTICOSTEROID PHARMACOLOGY

Corticosteroid Molecules

In recent years, increased understanding of glucocorticoid receptor and corticosteroid pharmacology has enabled the development of molecules designed specifically to achieve potent, localized activity with minimal risk of systemic exposure. Currently, eight INS compounds are approved for the management of allergic rhinitis in the United States: beclomethasone dipropionate, budesonide, ciclesonide, flunisolide, fluticasone furoate, fluticasone propionate, mometasone furoate, and triamcinolone acetonide (**Table 2**).³²

Corticosteroid molecules are derived from the parent molecule, cortisol.³³ The carbon framework of each corticosteroid is made up of three 6-carbon rings (rings A, B, and C) and one 5-carbon ring (ring D).³² All anti-inflammatory corticosteroids have features in common with cortisol and with each other: a ketone oxygen at position 3; an unsaturated bond between carbons 4 and 5; a hydroxyl group at position 11; and a ketone oxygen group on carbon 20. The variations occurring off ring D at positions 16, 17, and 21 are the greatest differentiating factors between the individual molecules. Structure–activity relationship studies of this region led to the identification of chemical groups that enhance topical activity and reduce systemic adverse events.³⁴ For example, the furoate group of mometasone furoate was found to enhance molecular affinity for the glucocorticoid receptor binding site.

Other modifications have improved the activity of corticosteroid compounds. The 21-chloro-17 (2' furoate) group on the mometasone furoate structure improves anti-inflammatory activity, whereas the chloride at position 21 provides the additional benefit of inferring resistance to degradation by esterases.³⁴ Halogen substitutions at positions 6 and 9 are thought to increase potency, as are side-chain substitutions at position 17.³⁵

Pharmacodynamic Properties

Glucocorticoid potency can be measured in various ways, but is thought to be closely related to GR binding affinity.³² **Fig. 1** illustrates the relative GR binding affinities for most intranasal compounds. Relative receptor affinity studies are highly dependent on assay methodology and prone to error.³⁶ Although specific values vary between studies, most have shown a similar order of potency. An earlier study of INSs that used competition assay methodology reported a similar rank order of relative binding potency: mometasone furoate > fluticasone propionate > budesonide > triamcinolone acetonide > dexamethasone.²⁹

Corticosteroid potency also has been evaluated using the McKenzie assay, which compares the relative cutaneous vasoconstrictor and skin blanching responses of

Table 2
Available intranasal corticosteroids

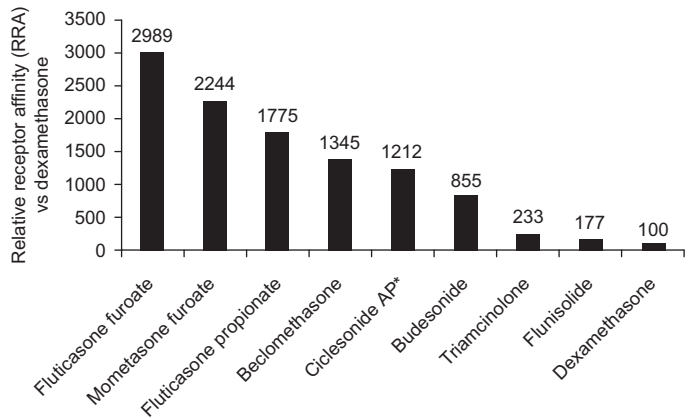
Generic (Proprietary) Name	Recommended Dosage
Beclomethasone dipropionate (Beconase AQ)	<i>Adults and children >12 years of age:</i> 1 or 2 sprays (42–84 µg) per nostril bid (total dose 168–336 µg/d) <i>Children 6–12 years of age:</i> 1 spray (42 µg) per nostril bid for total of 168 µg/d, or up to 2 sprays per nostril bid for total of 336 µg/d
Budesonide (Rhinocort Aqua) ^a	<i>Adults and children >6 years of age:</i> 1 spray (32 µg/spray) per nostril qd up to a maximum of 128 µg/d (6 to <12 years of age) or 256 µg/d (>12 years of age)
Ciclesonide (Omnaris)	<i>Adults and children >12 years of age:</i> 2 sprays (50 µg/spray) per nostril qd
Flunisolide (Nasarel)	<i>Adults:</i> 2 sprays (58 µg) per nostril bid, not to exceed 8 sprays per nostril per day (464 µg) <i>Children 6–14 years of age:</i> 1 spray (29 µg) per nostril tid or 2 sprays (58 µg) per nostril bid, not to exceed 4 sprays per nostril per day (232 µg)
Fluticasone furoate (Veramyst)	<i>Adults and children >12 years of age:</i> 2 sprays (55 µg) per nostril qd <i>Children 2–11 years of age:</i> 1 spray (27.5 µg) per nostril qd up to 2 sprays (55 µg) per nostril qd
Fluticasone propionate (Flonase)	<i>Adults:</i> 2 sprays (100 µg) per nostril qd or 1 spray (50 µg) bid <i>Adolescents and children >4 years of age:</i> 1 spray (50 µg) per nostril per day up to, but not in excess of, 2 sprays (100 µg) per nostril per day
Mometasone furoate (Nasonex)	<i>Adults and children >12 years of age:</i> 2 sprays (100 µg) per nostril qd <i>Children 2–11 years of age:</i> 1 spray (50 µg) per nostril qd
Triamcinolone acetonide (Nasacort AQ)	<i>Adults and children >12 years of age:</i> 2 sprays (110 µg) per nostril qd <i>Children 6–12 years of age:</i> 1 spray (55 µg) per nostril or 110 µg qd, up to 2 sprays (110 µg each) per nostril or 220 µg qd

^a Available in two strengths: 32 and 64 µg per spray.

Data from Derendorf H, Meltzer EO. Molecular and clinical pharmacology of intranasal corticosteroids: clinical and therapeutic implications. *Allergy* 2008;63:1297.

individual compounds.³⁷ Using this methodology, the rank order of potency was: fluticasone propionate > mometasone furoate > budesonide > flunisolide > triamcinolone acetonide (Table 3).^{8,38} This vasoconstriction phenomenon, which occurs in all subjects, has been suggested to partly explain the glucocorticosteroid effect on the nasal mucosa. In a randomized double-blind crossover study, using the 133Xe wash-out method as a measure of nasal mucosal blood flow, the effect of topically administered budesonide was compared with placebo. No difference between the groups was found to occur. A more complex activity than vasoconstriction seems likely to be responsible for the clinical effect of INSs.³⁹

Results of studies using another marker of corticosteroid potency, transactivation potency, correlate with receptor binding affinity results. One study found mometasone furoate the most potent GR ligand, requiring the lowest concentration to affect 50% of the maximum level of transcription activation of a glucocorticoid response element reporter gene in cells.²⁹ Overall rank of potency using this methodology



*Ciclesonide active principle (active metabolite)

Fig. 1. Relative glucocorticoid receptor affinity of intranasal corticosteroids. (From Derendorf H, Meltzer EO. Molecular and clinical pharmacology of intranasal corticosteroids: clinical and therapeutic implications. Allergy 2008;63:1294; with permission.)

was: mometasone furoate > fluticasone propionate > triamcinolone acetone > budesonide > dexamethasone.

No evidence is available of a linear association between glucocorticoid potency and clinical response, nor does a known “plateau” exist beyond which greater potency does not add additional benefit. Likewise, no evidence shows that the compound with the highest receptor affinity will have superior clinical efficacy. Although increased potency at intranasal sites would seem desirable, the possibility of greater potency at other sites could theoretically increase the risk of systemic adverse effects, because GRs are similar throughout the body.

Pharmacokinetic Properties

Because the goals of INS therapy are to deposit drug at the site of action, have it remain there as long as possible, and limit the amount that leaves the site and enters the systemic circulation, the pharmacokinetic features of particular interest are lipophilicity and systemic availability.

Table 3 Potency of topical corticosteroids based on receptor binding affinity and the skin-blanching test		
Corticosteroid	Receptor Binding Affinity	Skin Blanching Potency
Flunisolide	1.8	330
Triamcinolone acetone	3.6	330
Beclomethasone dipropionate	0.4	600
Budesonide	9.4	900
Fluticasone propionate	18.0	1200

Data from Meltzer EO. The treatment of vasomotor rhinitis with intranasal corticosteroids. WAO Journal 2009;2:169.

Lipophilicity

The more highly lipophilic compounds are absorbed more quickly and thoroughly by the nasal mucosa and retained longer in nasal tissue, increasing exposure to the GR.⁴⁰ Lipophilicity also contributes to increased plasma protein binding. In this sense, lipophilicity is a desired characteristic. In the event of systemic absorption, lipophilicity may contribute to the accumulation of drug in other tissues, possibly contributing to unwanted side effects. Thus, the ideal combination of features would include a high degree of lipophilicity coupled with low systemic absorption and rapid clearance.

The order of lipid solubility for corticosteroids has been reported as: mometasone furoate > fluticasone propionate > beclomethasone dipropionate > budesonide > triamcinolone acetonide > flunisolide.⁴⁰ Ciclesonide and des-ciclesonide have greater lipophilicity than fluticasone propionate.⁴¹ The furoate (mometasone) and propionate (fluticasone) ester side chains are pharmacologically similar moieties that contribute greatly to the lipophilicity of their associated compounds.⁴² The lipophilicity of fluticasone propionate has been reported as being three times higher than beclomethasone dipropionate, 300 times more than budesonide, and at least 1000-fold greater than flunisolide and triamcinolone acetonide.³⁸

Absorption/Bioavailability

After intranasal administration, a drug can enter the systemic circulation through direct local absorption in the nasal mucosa or after gastrointestinal absorption of swallowed material. A large proportion of intranasally administered drug is quickly cleared from the nose into the throat and swallowed, becoming available for absorption in the gastrointestinal tract. A high rate of first-pass metabolism will inactivate the absorbed drug, but direct absorption into the systemic circulation through the nasal tissues bypasses the protective hepatic first-pass mechanism.

Systemic absorption rates are highest among the relatively older compounds, flunisolide, beclomethasone, and budesonide (**Fig. 2**). One-third to one-half of an intranasally administered dose of the older agents may reach the systemic circulation. For budesonide, systemic exposure is primarily through absorption through the nasal

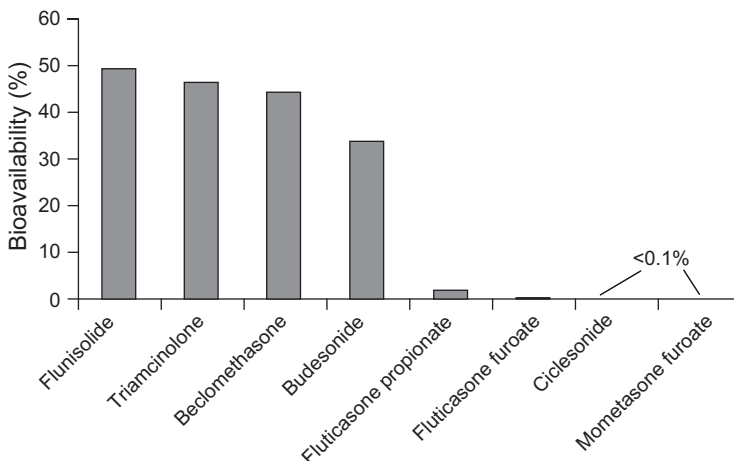


Fig. 2. Systemic absorption rates of intranasal corticosteroids. (From Derendorf H, Meltzer EO. Molecular and clinical pharmacology of intranasal corticosteroids: clinical and therapeutic implications. *Allergy* 2008;63:1294; with permission.)

mucosa.^{43,44} The newer compounds, fluticasone propionate, and mometasone furoate, are more lipophilic³⁴ and undergo rapid and extensive first-pass metabolism after oral administration, contributing to their negligible systemic absorption.³⁸ A pharmacokinetic study of ciclesonide in both healthy subjects and patients with seasonal allergic rhinitis found that serum levels of ciclesonide and the active metabolite des-ciclesonide were below the lower limits of quantification (25 and 10 pg/mL, respectively) in most subjects.⁴⁵

CLINICAL CONSIDERATIONS

Onset and Duration of Action

It was traditionally accepted that INSs should be used for days or weeks to achieve significant benefits, and because these agents were used primarily to control chronic symptoms, few studies focused on onset of action.⁴⁰ Symptom improvement has been noted within 1 to 2 days after administration of most newer agents.⁴⁰ A clinical study of ciclesonide nasal spray in patients with seasonal allergic rhinitis reported a significantly greater effect of treatment on total nasal symptom scores compared with placebo as early as hour 12.⁴⁶ In subjects with seasonal allergic rhinitis, mometasone furoate nasal spray significantly improved nasal symptom scores compared with placebo in as little as 7 hours after a single 200- μ g dose.⁴⁷ It is not uncommon for patients to use intranasal medications intermittently on an “as-needed” basis,⁴⁰ and this use may be justified given the potential for a more rapid onset of action than was previously ascribed to these medications.

Lipid conjugation, or fatty acid esterification, is a process through which a corticosteroid molecule forms a reversible chemical bond with fatty acids in the nasal tissues. These drug-lipid complexes serve as a slow-release drug reservoir that holds the corticosteroid within the target area, increasing the local residence time. As the binding process is reversible, the retained corticosteroid remains available for binding to local GRs. This binding process may be partly responsible for the once-daily duration of efficacy of many INSs. Lipid conjugation has been reported for budesonide⁴⁸ and des-ciclesonide.⁴⁹

Clinical Efficacy in the Therapy of Allergic Rhinitis

The design of topically active INS formulations has provided a much better therapeutic ratio than oral corticosteroids.²⁵ The pharmacodynamic and pharmacokinetic properties of these agents play an important role in facilitating local anti-inflammatory activity with a low rate of side effects. However, whether the often-subtle pharmacodynamic and pharmacokinetic differences between the compounds distinguish them in a clinical setting remains to be confirmed. Based on currently available data, no clear evidence shows that any INS is superior to any other for allergic rhinitis symptom relief,^{40,50} despite their pharmacologic differences. All have shown efficacy in both seasonal and perennial allergic rhinitis in a large number of well-controlled studies. The possibility exists that the degree of anti-inflammatory activity required for allergic rhinitis symptom relief is low enough that relief is easily achieved with agents of varying potencies, or that GR saturation or near-saturation occurs with all of the preparations.^{40,51} These considerations have not been well studied in the treatment of vasomotor rhinitis, also known as nonallergic rhinopathy.

INSs are the single most effective class of medications for allergic rhinitis, and therefore are recommended as first-line therapy by both national and international task forces for those with moderate-to-severe or persistent allergic rhinitis.^{52,53} They improve each of the nasal and ocular symptoms of allergic rhinoconjunctivitis. They

are superior to oral antihistamines in terms of both total nasal symptom scores and congestion scores.^{54,55} They also produce greater symptom relief than oral leukotriene antagonists^{56,57} and, despite limited information, INs are equivalent⁵⁸ or even superior^{59,60} to combinations of antihistamines and antileukotrienes. Although intranasal antihistamines have a more rapid onset of benefit compared with INs, the data are insufficient to conclude that intranasal antihistamines are therapeutically equivalent to INs, especially after a 14-day treatment period.⁶¹ In addition, INs show greater effectiveness than intranasal H1 antihistamines in improving nasal blockage.⁶² For the most part, the addition of an oral antihistamine to an IN does not seem to confer additional clinical benefits over the use of an IN alone.^{63,64} However, adding an intranasal antihistamine to an IN does seem to provide greater efficacy than the monotherapies.⁶⁵

Formulation characteristics may also influence the efficacy and tolerability of INs. These characteristics can affect patient preference and adherence to allergic rhinitis therapy.⁶⁶ All currently available INs are delivered in aqueous preparations, and beclomethasone and ciclesonide are under development in hydrofluoroalkane nasal aerosol solution formulations. Although IN preparations may vary in the volume emitted per actuated spray and sensory attributes (such as perceived runoff, discomfort, taste, and smell), and thus patient acceptance and adherence, no clear clinically relevant differences in efficacy have been seen between them.⁴⁰

Clinical Efficacy in the Therapy of Nonallergic Rhinopathy

Beclomethasone dipropionate was first reported to be effective for vasomotor rhinitis in 1976. In Sweden, 39 men and women aged 19 to 66 years (average, 39 years) with perennial nasal obstruction, drip, itching, and sneezing were studied in a randomized, double-blind, placebo-controlled, 4-week treatment period, crossover-designed trial. Intracutaneous specific aeroallergen testing for these subjects was negative. Nasal secretion eosinophilic cells were estimated to be less than 10%. The dosage was one aerosol-delivered puff into each nostril three times daily (300 µg of beclomethasone dipropionate per day during the active period). No difference was seen in the response of the groups on the first day of treatment. However, a significant reduction in the total symptom score was observed during the second week of the beclomethasone dipropionate treatment period. This effect remained throughout the remainder of the treatment period. For the individual nasal symptoms, a significantly lower score was registered for sneezing during the first week, for nasal drainage during the second week, for nasal itching during the third week, and for nasal blocking only during the fourth week of beclomethasone dipropionate treatment. After the beclomethasone dipropionate treatment period, 4 patients considered themselves free of trouble, 25 had improved, 10 were unchanged, and none had worsened; 74% considered themselves free of symptoms or greatly improved. After the placebo period, none was free of trouble, 12 had improved, 20 were unchanged, and 7 patients had worsened; 31% considered themselves free of symptoms or greatly improved. Of the 39 patients who completed the study, 25 preferred the beclomethasone dipropionate period, 5 preferred the placebo period, and 9 found no difference between the periods. The authors concluded that the results were encouraging, because approximately 75% of the patients considered themselves free of trouble or improved when treated with the intranasal corticosteroid.⁶⁷ In a small study of nonallergic patients aged 20 to 68 years, budesonide nasal aerosol was found to be significantly more effective than placebo in reducing the symptoms of nasal obstruction, nasal drainage, and sneezing at twice-daily dosing of 50, 200, and 800 µg. Budesonide, in dosages of 200 and

800 µg daily, significantly reduced the methacholine-induced secretions compared with the placebo treatment.⁶⁸

Of the currently available INS preparations in the United States, only fluticasone propionate has an indication approved by the U.S. Food and Drug Administration (FDA) for the treatment of perennial nonallergic rhinitis (PNAR), regardless of the presence of nasal eosinophilia.⁶⁹ In a large study of patients with PNAR, administration of fluticasone propionate at 200 µg (two sprays per side, once daily) was as effective as 400 µg once daily, and both doses were statistically better than placebo in achieving symptom reduction over 4 weeks.⁷⁰ A separate study in patients with vasomotor rhinitis showed that fluticasone propionate, 200 µg once daily, was significantly superior to placebo in reducing symptoms of nasal obstruction and decreasing inferior turbinate hypertrophy as assessed via CT scan.⁷¹ However, a study of individuals with PNAR showed that treatment with mometasone furoate, 200 µg (2 sprays per side once daily) for 6 weeks, did not show any significant improvement in rhinitis symptoms compared with placebo.⁷² Furthermore, another study showed that fluticasone furoate, administered as 110 µg (2 sprays per side once daily) to 699 subjects with vasomotor rhinitis triggered by weather or temperature, was not superior to placebo in reducing congestion, rhinorrhea, or postnasal drip during the 4-week study period.⁷³

The evidence for benefit of INSs in nonallergic nasal disease is somewhat inconsistent, probably reflecting the heterogeneous nature of these conditions. Nonetheless, studies to date in the treatment of vasomotor rhinitis, also known as nonallergic rhinopathy, suggest that INS treatment for nonallergic rhinopathy may be of some therapeutic value and should, for now, be considered for first-line therapy.⁷⁴

Safety

Differences in safety between INSs are more theoretical than evidence-based, with the greatest concern being systemic exposure and effects on adrenal function in all patients, and on growth in children. Pharmacokinetic studies confirm that the newer agents, mometasone furoate, fluticasone propionate, fluticasone furoate, and ciclesonide, exhibit negligible systemic absorption and would be expected to pose fewer risks. One could also argue that their greater potency could pose safety risks, even if they were absorbed to only a small degree. To date, these concerns have not been realized. Binding to proteins such as albumin and other biologic material can occur at the local site of action, and also in general circulation if a corticosteroid is systemically absorbed. Most INSs have a high degree of protein binding, ranging from 71% (triamcinolone acetonide) to 99% (ciclesonide, des-ciclesonide). Only free drug is pharmacologically active, and therefore a high degree of serum protein binding for these compounds is desirable to limit potential systemic adverse events.⁷⁵

Special caution is warranted in treating individuals who may be using concomitant corticosteroid therapy for other medical conditions, such as asthma. The safety of overlapping corticosteroid therapy has not been well studied, but combined treatments may be a concern because of the increased total systemic corticosteroid load. Despite potential concerns, the use of INSs at recommended doses does not seem to have a significant effect on the hypothalamic-pituitary-adrenal axis.⁷⁶ Osteocalcin, a marker of bone turnover, and eosinophilia were both unaffected by intranasal budesonide, mometasone, and triamcinolone, suggesting that the systemic glucocorticoid burden was clinically insignificant.⁷⁷ These results seem to be corroborated by the finding of no increased likelihood of bone fractures among octogenarians using intranasal corticosteroids, regardless of the dose used.⁷⁸ The effects of these agents on bone growth and height have also been evaluated in numerous studies, with

knemometry considered the most reliable and sensitive indicator.⁷⁹ Studies with budesonide, mometasone furoate, and fluticasone propionate using knemometry have not shown significant changes in lower leg growth velocity.^{79–81} Among studies based on stadiometry measurements, only one reported a small but significant reduction in height among children treated with intranasal beclomethasone for 1 year compared with placebo.⁸² One-year studies involving mometasone furoate, fluticasone propionate, budesonide, triamcinolone, and ciclesonide did not report any significant negative effects on height.^{83–87}

Common local side effects of INSs include dryness, stinging, burning, and epistaxis, the frequencies of which are similar in the various compounds. These side effects occur in 5% to 10% of patients, with the exception among the aqueous preparations of flunisolide, which, because of its excipients, causes a higher incidence of discomfort.⁸⁸ The administration technique of aiming the spray away from the septum is important because it seems to reduce the incidence of epistaxis.

Nasal mucosal atrophy is a concern with chronic topical steroid use. A long-term study with mometasone furoate found no evidence of atrophy or metaplasia after 12 months of intranasal use.⁸⁹ Similar studies with fluticasone propionate did not identify indications of atrophy, and noted only a nonsignificant increase in metaplasia in one patient.⁹⁰ Clinically apparent nasal candidiasis, occasionally seen with orally inhaled corticosteroids, is extremely rare with INSs.

SUMMARY

Allergic rhinitis, which has a well-known pathophysiology, and nonallergic rhinopathy, which is less well understood, are common conditions that affect millions of individuals worldwide. INSs diffuse across the respiratory membrane, bind to the intracellular glucocorticoid receptor, and, after transportation to the nucleus, can reduce inflammatory reactions. Their risk/benefit ratio is the best of the pharmacotherapeutic options. Therefore, INSs should be the first-choice treatments for patients with these nasal diseases to improve symptoms and quality of life.

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