

Intranasal Corticosteroid

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Siriraj Med J 2008;60:90-95

E-journal: <http://www.sirirajmedj.com>

Rapidly metabolized intranasal corticosteroid (INS), with high topical potency and low systemic bioactivity, was introduced for perennial rhinitis in 1974 and found to be as effective as corticosteroids administered systemically. These second-generation INSs include beclomethasone dipropionate (BDP), budesonide (BUD), flunisolide (FLU), fluticasone propionate (FP), triamcinolone acetonide (TAA), mometasone furoate (MF), and fluticasone furoate (FF). Although these INSs represent improvements relative to earlier topical corticosteroids, they do vary from one to the other in potency and systemic bioactivity. For example, MF is equal in potency to FP and is considered to be the most potent INS to date and has almost undetectable systemic availability. FF, the most recently introduced INS, is a novel, enhanced-affinity glucocorticoid with potent anti-inflammatory activity administered in a unique side-actuated device. Among the therapeutic indications for INS are seasonal and perennial allergic rhinitis, nonallergic rhinitis, acute and chronic rhinosinusitis, rhinitis medicamentosa, and nasal polyposis.

Mechanism of action

Corticosteroids are highly effective in mitigating inflammation. The ability to modulate the expression of various arms of the immune response has led to widespread use in various inflammatory states. Corticosteroids act primarily by regulating protein synthesis. Whether administered topically or systemically, the unbound steroid molecule enters the cytoplasm of corticosteroid-responsive tissues by passively diffusing across the cell membrane. In the cytoplasm, it binds to a glucocorticoid receptor forming a complex that undergoes a conformational change. In addition, corticosteroids stabilize lysosomal membranes, block the effect of migratory inhibitory factor, decrease permeability, and inhibit pro-inflammatory cytokine production, including that of interleukin (IL)-1, IL-2, the IL-2 receptor, interferon (IFN)- α , tumor necrosis factor (TNF), and various colony-stimulating factors (CSFs) such as IL-3. Even in very low concentrations, corticosteroids can inhibit the synthesis of a variety of pro-inflammatory enzymes, including the macrophage products, collagenase,

elastase, and plasminogen activator. Furthermore, lymphocyte proliferation and delayed type hypersensitivity are also inhibited by corticosteroids *in vitro*.

The role of corticosteroids in the management of allergic rhinitis is influenced by their effect on the inflammatory cells and chemical mediators that are released in the early- and late-phase allergic responses. The early-phase allergic response is characterized by an initial period of sensitization to a specific allergen. Subsequent exposure to the inciting allergen causes cross-linking of IgE antibodies located on the surface of mast cells residing in the nasal mucosa, which results in mast cell degranulation and the release of various chemical mediators, such as histamine. These mediators cause the infiltration of inflammatory cells in the peripheral blood to the site of exposure. The ensuing cascade of events is termed the late-phase allergic response and is characterized by hyper-reactivity of the nasal mucosa.

Pharmacokinetics

Pharmacokinetics are the processes that ultimately determine the concentration of the drug at the receptor site. The volume of distribution is the fluid volume required to contain the entire drug at the same concentration existing in the blood and is a measure of relative tissue uptake. Clearance is the rate of elimination by all routes relative to the concentration of drug in the blood and is a measure of the elimination capacity. The half-life is the relation between volume of distribution and clearance and is the time it takes for the plasma concentration to be reduced by 50%. Factors included in half-life are the time to reach steady state and the decay rate from steady-state concentrations. Bioavailability is the amount of drug that reaches the systemic circulation. In the case of drugs that are administered locally, such as the INS, the term systemic availability is more appropriate. A reference formulation is used to calculate the extent of systemic availability. The term absolute systemic availability is used when intravenous dosing is used as the standard. These kinetic properties are described as the absorption, distribution, metabolism, and excretion properties of the drug. Although INS is applied topically, a significant portion can be absorbed systemically. The goal of INS design is to achieve a high ratio of topical to systemic activity because this increases the potential for desired therapeutic effects relative to undesired systemic effects (therapeutic ratio).

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Delivery device

Delivery devices have evolved to meet specific requirements for efficacious and tolerable delivery of INS. The Freon-propelled aerosols first used to deliver INS distributed the drug poorly. Metered-dose pump sprays were used to deliver FP solubilized in polyethylene glycol and propylene glycol, although this approach caused nasal stinging. Aqueous pump sprays and pure powder formulations are now the more common methods of delivery because the intranasal distribution of drug is more favorable than with a pressurized aerosol. Delivery of aqueous suspensions by pump spray provides better drug deposition at the ciliated mucous membrane rather than the nonciliated anterior when compared with pressurized aerosol. Studies with TAA indicate greater systemic levels when administered in an aqueous rather than aerosol formulation for allergic rhinitis.¹ Actual quantitative comparisons of drug delivered by different devices are complicated by the large amounts of drug deposited in the nozzle of pressurized aerosols. However, there appears to be approximately the same degree of symptom reduction by pressurized aerosols and aqueous pump sprays.² After intranasal administration, there is nasociliary clearance of the drug into the throat. Approximately 80% of the drug is available for absorption at the nasal mucosa. Significant amounts of drug (10% to 20%) remained in the target areas of the frontal cavity and turbinates for up to 1.5 hours.³

Absorption

There are two aspects of absorption regarding the INS. One is topical absorption at the target site (the nose) that determines therapeutic efficacy and the other is systemic absorption (Fig 1). Systemic absorption either occurs from the fraction of INS swallowed and subsequently absorbed through the gastrointestinal tract or from the fraction absorbed into the blood at the nasal mucosa. The amount of drug reaching target tissues and exerting a therapeutic effect relative to the amount reaching the systemic circulation is a measure of safety for topically applied drugs, such as the INS.

Some corticosteroids (e.g. BUD) are well absorbed through the nasal mucosa directly into the systemic circulation. In contrast, FP and MF are believed to be

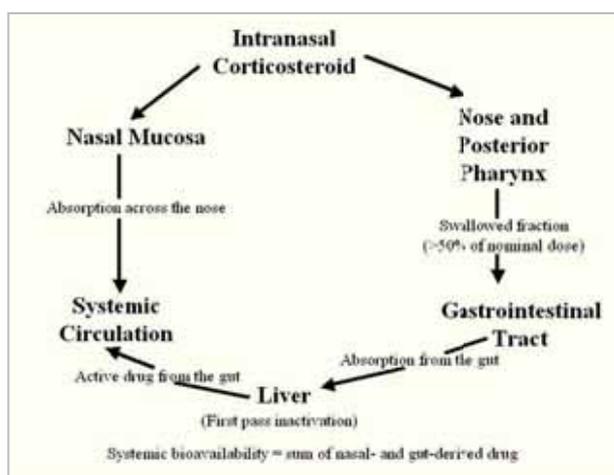


Fig 1. The fate of intranasal corticosteroid. The amount of intranasal corticosteroid that reaches the systemic circulation is the sum of the nasal and oral bioavailable fractions. The majority of the drug is swallowed, and systemic bioavailability is determined by the absorption from the gastrointestinal tract and the degree of first-pass hepatic inactivation.

TABLE 1. Systemic availability after intranasal corticosteroid administration

Drug	Dose	Systemic availability (%)
Budesonide	100 µg	100
Flunisolide	117 µg	49
Fluticasone propionate	800 µg	1.8
Mometasone furoate	400 µg	< 0.1

poorly absorbed into the systemic circulation because of their lipophilicity. When the area under the concentration-time curve after intranasal administration is compared with that for intravenous administration, the absolute systemic availability can be calculated⁴ (Table 1). For both FP and MF, the systemic availability is very low. It is important to remember that, in many cases, the plasma concentration of the drug was below the limit of quantification of the assay used (50 ng/L).

Distribution

Once in the systemic circulation, many corticosteroids are highly bound by plasma albumin. The degree of plasma protein binding for several corticosteroids has been determined, including TAA (71%), FLU (80%), BDP (87%), BUD (88%), FP (90%), and MF (>90%).⁵ Binding to plasma proteins, primarily albumin, is generally greater with the more lipophilic corticosteroids. The volume of distribution is a classic pharmacokinetic parameter derived from intravenous drug administration. It reflects the tissue distribution of the drug, with higher amounts indicating greater amounts of drug either protein bound or in peripheral tissue outside of the systemic circulation. As the lipophilicity of a corticosteroid increases, so does the volume of distribution.

Metabolism

BDP is a prodrug metabolized by many tissues, including the nose, into the more active metabolite, beclomethasone monopropionate (BMP). Compared with a corticosteroid receptor affinity of 1 for dexamethasone, the relative binding affinity of BDP is 0.53, whereas that of the metabolite, BMP, is almost 25-fold greater.⁵ In a study that compared the relative binding affinities of MF, FP, BUD, and TAA with dexamethasone (dexamethasone binding affinity was defined as 100), all of the corticosteroids had greater binding affinity than did dexamethasone. MF showed the highest affinity for the corticosteroid receptor with a relative binding affinity, followed by FP, BUD, and TAA.⁵

Systemic absorption of the swallowed portion of the dose may be inactivated by the first-pass effect (i.e., metabolism of the drug by the liver before entering the systemic circulation). Rapid inactivation in the gastrointestinal tract minimizes systemic activity from the swallowed portion. As a result, the oral bioavailability of FP is low because of poor absorption from the gastrointestinal tract and an extensive first-pass metabolism. MF also undergoes extensive metabolism in the liver; consequently, systemic absorption is extremely low (Fig 1).⁶

Elimination

Half-life is a function of clearance rate and volume. After multiple doses of a drug, the plasma concentration rises until it reaches a steady-state concentration. As a general rule, it takes about 5 half-lives for a drug to reach its steady-state concentration during repeated dosing. The greatest half-life value currently reported is for FP. MF

has the second-greatest half-life, followed by BUD, FLU, and TAA.⁵

Most pharmacokinetic analyses are performed on healthy adults, and few data exist for children. When the pharmacokinetic parameters of BUD were investigated in children (10 to 13 years of age), the half-life (1.5 hours) was shorter and the weight-adjusted clearance was approximately 50% higher than those values previously reported for adults.⁷ The authors postulate that this finding may be the result of a higher hepatic blood flow in children. Assuming that this suggestion is correct, more rapid systemic elimination in children compared with adults would be expected for other high clearance drugs, including the other second-generation INS.

Implications of pharmacodynamics

Pharmacokinetic parameters such as systemic availability, clearance, and half-life can be used to assess the relative systemic exposure to INS. The expectation that low systemic exposure results in minimal adverse systemic effects has been examined by monitoring sensitive systemic indexes, such as hypothalamic-pituitary-adrenal (HPA) axis effects. The second-generation INS causes minimal systemic effects at recommended doses, with the possible exception of FP, which showed significant suppression of overnight urinary cortisol when compared with TAA and BDP. Reviews of intranasal administration of BDP, BUD, FLU, FP, and MF indicate no detectable effects on measures of HPA axis function at recommended doses, which is in agreement with rapid hepatic metabolism of these INSs.⁴ Therefore, the improved pharmacokinetic parameters of the second-generation INS maximize efficacy relative to systemic availability.

Clinical use of INS

1) Allergic fungal sinusitis

Atopy, continuous antigenic exposure, and inflammation all play roles in the perpetuation of the disease. The mainstay of any combination treatment for allergic fungal sinusitis remains surgical removal of the allergic mucin and fungal elements along with creation of the sinuses. As a single modality, functional endoscopic sinus surgery results in a high rate of recurrence, and therefore medical therapy is mandatory. This intervention can occur preoperatively in the form of corticosteroid administration to decrease the intranasal polyposis and inflammation. In addition, corticosteroids should be administered postoperatively both topically and systemically, but the duration and optimal dosing remain unclear. Multiple studies⁸⁻¹¹ have shown improvement in symptoms as well as increased time to recurrence and improvement in overall recurrence rates with corticosteroid administration, and the data seem to support a longer period than a shorter one.

2) Allergic rhinitis

Allergic rhinitis is a hypersensitivity to inhaled allergens, with symptoms including congestion, rhinorrhea, sneezing, and nasal itching. Corticosteroids are the most potent preparations available for relief of the symptoms of nasal allergy since they alter the course of both the early and late phases of allergic rhinitis and reduce hyperactivity of nasal mucosa. They minimize allergic inflammation by decreasing capillary permeability, stabilizing lysosomal membranes, blocking the effect of migratory inhibitory factors, and suppressing portions of the arachidonic acid cascade. INS is then a first line of treatment for allergic rhinitis especially in patients with moderate-to-severe allergic

rhinitis or when nasal congestion is a major component and may be an alternative to antihistamines. Clinical data show that INS is highly effective in treating the symptoms of seasonal and perennial allergic rhinitis and non-allergic rhinitis and in preventing the onset of symptoms in such patients.¹² INS is significantly more effective than leukotriene-receptor antagonists alone or leukotriene-receptor antagonists combined with antihistamine in the treatment of grass pollen-induced rhinitis.¹³ In agreement with this finding, meta-analyses of 11 randomized controlled trials show that leukotriene-receptor antagonists did not differ from antihistamines and were less effective than INS in reducing nasal symptoms and improving rhinoconjunctivitis quality of life of patients with allergic rhinitis.¹⁴ INS has also been shown to relieve ocular symptoms in patients with allergic rhinoconjunctivitis.¹⁵ One likely mechanism is probably the modulation of a naso-ocular neurogenic reflex. Rhinitis therapy has been reported to improve the subjective and objective measures of asthma. Data from a large managed care organization collected to analyze patients with asthma and concomitant rhinitis revealed patients who used INS had a significantly lowered risk of both asthma-related emergency department treatment visits and hospitalizations.¹⁶ Nonsedating antihistamine use showed no significant trend toward reduced visits in this study. Patients using both INS and second generation antihistamines had a further reduction over patients using INS alone. However, the efficacy of INS on asthma outcomes in patients with rhinitis and asthma was recently evaluated by meta-analyses of 14 randomized controlled trials.¹⁷ INS tended to improve asthma symptoms and forced expiratory volume in one second (FEV₁), but the results did not reach significance.

3) Rhinosinusitis

Rhinosinusitis is defined as inflammation of the paranasal mucous membranes, which leads to nasal obstruction, poor drainage, and nasal infection. Classic symptoms of acute rhinosinusitis include nasal congestion, purulent discharge, fever, headache, facial pain, and post-nasal drip. Being an anti-inflammatory drug, INS appears to be a rational approach to relieve nasal and possibly sinus ostial obstruction in rhinosinusitis. Study data indicate that concomitant administration of INS with antibiotic in the treatment of acute rhinosinusitis is more effective, in terms of symptom relief, than antibiotic therapy alone.^{18,19} Moreover, in patients with acute, uncomplicated rhinosinusitis, INS alone produced significant symptom improvements versus amoxicillin and placebo, without predisposing the patient to disease recurrence or bacterial infection.²⁰

Chronic rhinosinusitis (CRS) is broadly regarded as inflammation of the nose and paranasal sinuses lasting longer than 12 weeks. Neutrophils, macrophages, lymphocytes, and eosinophils are among the characteristic inflammatory cells infiltrating the sinus mucosa in CRS. Ultimately, the inflammatory process leads to fibrosis, thickening of the mucosa, and obstruction of the ostiomeatal complex. In the treatment of CRS, INS is a staple of treatment. Steroids in topical and systemic forms have been used widely in the treatment of CRS. Their use should improve patency of the ostiomeatal complex by way of reduction in mucosal swelling. The myriad actions of corticosteroids, and especially their ability to reduce airway eosinophil infiltration by directly preventing increased viability and activation of eosinophils and indirectly to reduce secretion of chemotactic cytokines by nasal mucosa, make them an

TABLE 2. Treatment with intranasal corticosteroid in persistent rhinosinusitis without nasal polyposis

Study	Drug	Number	Time	Effect on symptoms	Other effects
Lund et al ²⁵ (2004)	Topical budesonide	134	20 weeks	Significant improvement in total symptom score	Significant improvement in peak nasal inspiratory flow
Lavigne ²² (2002)	Intranasus budesonide	26	3 weeks	Total symptom score significantly improved	T cells, eosinophils mRNA for IL-4, and IL-5 significantly improved
Parikh ²³ (2001)	Fluticasone propionate	22	16 weeks	Not significant	Acoustic rhinometry, not significant
Cuenant ²¹ (1986)	Tixocortol irrigation	60	11 days	Nasal obstruction significantly improved	Maxillary ostial patency significantly improved
Sykes ²⁴ (1986)	Dexamethasone & tramazoline	50	4 weeks	Discharge, obstruction, and facial pain significantly improved	Plain radiograph and nasal airway resistance and mucociliary clearance significantly improved

obvious choice. To date, five randomized control trials have investigated the use of topical corticosteroids in CRS.²¹⁻²⁵ Two of these trials involved intranasus installation.^{21,22} The other three involved topical treatment.²³⁻²⁵ Four of the five trials demonstrated significant improvement in symptoms with no evidence of increased infection (Table 2).

Another common problem in CRS is olfactory dysfunction. Rather than being only an obstructive phenomenon from mucosal edema or polyps (transport disorder), hyposmia or anosmia resulted in part from the direct effects of inflammatory processes on the olfactory epithelium, the surface of the olfactory receptors, or the olfactory mucus bathing the receptors (sensory disorder). Aside from decreasing edema and improving the nasal airway in CRS, systemic steroids also seem to affect olfactory neuron function in certain cases, perhaps by decreasing inflammatory cytokines. The side effects of systemic steroids make their prolonged use impractical for continuous treatment of olfactory loss. Unfortunately, INS, which is safe for long-term daily use, does not have equivalent beneficial effects on olfaction.²⁶ In supporting this concept, approximately 50% of anosmic patients with CRS undergoing sinus surgery alone would have a persistent postoperative olfactory deficit. They were unresponsive to INS, but most of these patients' sense of smell was restored with oral steroids.²⁷ In recalcitrant rhinosinusitis, new intranasal/intranasus catheters have recently been developed to allow the direct application of steroid formulations into the maxillary sinus.²⁸ Intranasal applications of steroids have been shown to decrease the levels of inflammatory mediators in the local milieu of the sinus as well as in serum.²⁹

4) Nasal polyp

Nasal polyposis is a disease of the nasal and paranasal mucous membranes. It is characterized by edematous, semi-translucent masses arising from the mucosal lining of the middle nasal meatus. The presenting symptoms of nasal polyposis are nasal congestion, difficulties in breathing, post-nasal drip, and loss of sense of smell. The etiology is multifactor, and the exact pathophysiology is unknown. However, T-cells and their cytokine profiles in nasal polyps are of clinical significance, since the use of topical anti-inflammatory agents, such as corticosteroids, may have a beneficial effect because of their ability to down-regulate

the genome of all inflammatory cells. This decreases cytokines and chemokines known to be derived from lymphocytes, eosinophils, and other inflammatory cells that are part of the inflammatory events in nasal polyposis.³⁰ These resulted in reduced symptoms of rhinitis, improved nasal breathing and reduced size and number of polyps, although INS appears to have less effect on improving the sense of smell. Thus, corticosteroids form the mainstay of medical treatment. Surgery is reserved for severe and non-responding nasal polyposis patients.

Systemic (oral, intramuscular, or intravenous) corticosteroids can reduce the size of nasal polyps to an extent that is comparable with surgery. Often a systemic burst is used to shrink large obstructive polyps to provide more area to apply INS therapy. Treatment with topical steroid nasal drops in patients who had nasal polyposis and CRS also had improved symptom scores, improved nasal airflow, decreased polyp volume, and obviated the need for surgery in about half of the treated patients.³¹ INS reduces polyp recurrence and the requirement for repetitive sinonasal surgery and should be used in the long term.^{32, 33}

The patient with the tetrad of symptoms including nasal polyps, asthma, aspirin intolerance, and CRS has been classified as having ASA triad or Samter's triad. These patients have often had multiple polypectomies, and the aggressive postoperative medical management of these patients is paramount to delay recurrence of polyposis. Clinical experience has generally shown a good response to oral steroids in these patients. The need for oral steroids may be offset by using a higher concentration of nasal steroid drops or sprays.

5) Eustachian tube dysfunction and/ or otitis media with effusion

Eustachian tube dysfunction and / or otitis media with effusion (OME) is common and may cause hearing loss with associated developmental delay in children. The use of topical flunisolide has been reported to accelerate the return of normal eustachian tube function in allergic children.³⁴ Recently, the effectiveness of INS in promoting the resolution of effusions has been assessed by meta-analyses of randomized controlled trials. It was found that INS alone or in combination with an antibiotic lead to a quicker resolution of OME in the short term. However, there is no evidence of a long term benefit from treating OME or associated hearing loss with INS.³⁵

6) Posttraumatic olfactory dysfunction

Although injury to the olfactory neurons or their cortical projections cannot be treated medically, some posttraumatic conductive olfactory deficits can. Direct trauma to the sinonasal region may lead to mucosal edema or hematoma formation. Local administration of steroids improves olfaction in some cases.^{36, 37}

To yield the greatest benefit, INS must be delivered into a relatively patent airway. Thus, if large polyps, severe septal deviation, or marked mucosal edema are present, the sprays are less effective. Once treatment is begun, the patient must continue the therapy for at least 1 to 2 weeks (the time required for maximum effect to be evident) and often longer. Intermittent or as-needed dosages are less effective. Evaluation of patients at regular intervals by the treating physician is necessary to detect undesirable local or systemic corticosteroid effects.

Use of INS in children

There has been a rise in INS usage with the recognition that long-term treatment is beneficial for seasonal and perennial rhinitis. Although the use of INS to treat allergic rhinitis is generally thought to be associated with minimal serious adverse events in adults, increased long-term use in children has raised concerns about the potential for pediatric-specific effects, such as growth suppression. A 1-year study showed that use of 168 µg BDP aqueous nasal spray twice daily resulted in a significant suppression of growth in children compared with placebo.³⁸ However, other similar studies have shown no suppression of bone growth in children after 1 year of treatment with the recommended pediatric dose of MF nasal spray (100 µg daily)³⁹ or with BUD (200 µg twice daily).⁴⁰

Adverse effects

A. Systemic adverse effects

1) Effects on the HPA axis

The vast majority of data in the literature indicate that therapeutic doses of INS have very minimal effects on the HPA axis function. The time of administering the dose has demonstrated a variable effect on the HPA axis. A few studies have shown that doses administered in the late afternoon and evening affect the normal and nocturnal decrease in plasma cortisol concentrations.⁴¹ From a practical viewpoint, the long-term clinical history of INS therapy is informative. Clinically significant suppression of the HPA axis because of INS therapy alone appears to be exceedingly rare. Detectable suppression of childhood growth was observed when an INS with relatively poor first-pass inactivation was administered twice daily continuously throughout the year.⁶ Of note, most currently available INS preparations are given once-daily in the morning and thus, do not have significant adverse effects on the circadian rhythm of the HPA axis.⁴² A major concern to clinicians is prescribing INS to children. Several studies have demonstrated a similar safety profile of INS with respect to the HPA axis, as that observed in adults.^{43,44} These

studies corroborate results from those seen in adults and demonstrate that use in children (age > 3 years) is safe and effective.

2) Effects on growth and bone metabolism

Studies have shown that INS administered at recommended doses is not associated with impairment in growth and subsequent final adult height. However, these studies are limited since there have been no prospective, long-term data analyzing the effect of regular INS use on final adult height.⁴⁵ This is currently being facilitated by gradually lowering ages of approval for the use of INS by the Federal Drug Administration (Table 3).⁴⁶

The effects of INS on bone metabolism are a specific concern in certain patient groups such as children, the elderly, postmenopausal women, and those receiving steroids for other concurrent conditions. These patients are more susceptible to the potential adverse effects of steroid use as their thresholds may more readily be reached or exceeded. However, current studies that have evaluated the effects of INS on bone metabolism have also been limited by the lack of long-term studies. As with growth effects, it is difficult to assess the effects of INS on bone, due to confounding factors such as nutritional status and underlying disease. Short-term studies in both children and adults, however, demonstrate no significant effect on bone mineral metabolism.⁴⁵

3) Ocular changes

The risk of ocular side effects appears to be negligible due to the low systemic bioavailability of most available INS preparations.

4) Infection

Use of INS has not been associated with infectious complications^{23,47} although other forms of inhaled steroids (such as those used in asthma) are associated with oropharyngeal candidiasis and have infrequently been associated with infectious complications.⁴⁸⁻⁵⁰

B. Local adverse effects

INS has been associated with several local side effects such as epistaxis, dryness, and burning. These local side effects occur in approximately 5% to 10% of patients and occur with most available INS preparations. Studies have focused on the effects of these drugs on the nasal mucosa. Initial concerns regarding atrophy of the nasal mucosa with chronic topical steroid use were addressed in a study evaluating the long-term effects of the newer generation, more potent INS on nasal mucosa histology. The use of MF and FP over a 12-month period demonstrated no evidence of atrophy or metaplasia.^{51,52} There have been a few case reports of septal perforations associated with INS use⁵³, but this complication occurs mostly with the very early preparations and can be avoided with appropriate use of these agents. The general recommendation is to spray the contents toward the lateral nasal wall as opposed to the septum to maximize the anti-inflammatory action on the nasal mucosa while avoiding the potential dryness, crusting, and bleeding from the septum.

TABLE 3. Lower age limits for licensed prescription of intranasal corticosteroid

Active component	Trade name	Lower age limit
Beclomethasone dipropionate	Beconase®	6 years
Budesonide	Rhinocort Aqua®	6 years
Triamcinolone acetonide	Nasacort®	4 years
Fluticasone propionate	Flixonase®	4 years
Mometasone furoate	Nasonex®	2 years

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