

Intranasal corticosteroids topical characteristics: Side effects, formulation, and volume

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ABSTRACT

Background: Guidelines from throughout the world recommend intranasal corticosteroids (INSs) as first-line treatment for most patients with moderate to severe allergic rhinitis. In general, limited comparative studies between different INSs have not indicated that one particular steroid moiety is more effective than another in controlling symptoms of allergic rhinitis. However, there are numerous formulations available with different ingredients that may influence a patient's adherence to treatment.

Methods: This article looks at topical features with these agents, specifically, formulations, vehicles (aqueous vs aerosol), and side effects such as epistaxis and nasal septal perforation.

Results: Topical side effects are minimal with INSs with the exception of epistaxis. There are major differences in formulations, volumes, and vehicles between INSs, which could affect adherence.

Conclusion: Physicians need to be aware of the different INS attributes to try to match patients' preferences in order to achieve better adherence and improve outcomes in sufferers of allergic rhinitis.

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For over 30 years, intranasal corticosteroids (INSs) have been a mainstay for treatment of allergic rhinitis in the United States. In 1981, the Food and Drug Administration (FDA) approved beclomethasone in a chlorofluorocarbon metered-dose inhaler (CFC-MDI) for allergic rhinitis. Thereafter, numerous other corticosteroids in both CFC-MDIs and aqueous formulations were developed and released in the United States. With the advent of the Montreal Protocol on Ozone Depletion in 1987, CFC-MDIs were completely removed from the U.S. market by July 2003. In April 2004, triamcinolone in a hydrofluoroalkane (HFA), a gas friendly to the ozone layer, was approved by the FDA but never marketed in the United States. In 2012, two HFA-MDIs were approved and marketed in the United States, beclomethasone and ciclesonide and the first combination product, fluticasone dipropionate, an INS, with an intranasal antihistamine, azelastine. Presently, in the United States, we have seven different steroid moieties for treatment of allergic rhinitis with different topical properties as seen in Table 1.

Because studies fail to show that one particular INS is more effective than another in the treatment of allergic rhinitis, it is important to determine if the topical qualities of these agents may matter in patient adherence.^{1,2} Because allergic rhinitis is a chronic condition for many patients it is paramount to have good adherence to achieve successful outcomes in our patients. We looked at some of the topical properties in the different marketed INSs. Understanding the differences may improve our abilities to target which INS may be the best fit for a particular patient.

SAFETY AND EFFICACY OF INS

Allergic rhinitis is associated with specific histopathological changes in the nasal mucosa including local eosinophilia and squamous metaplasia.³ Minshall *et al.* undertook a multicenter, open-label study to evaluate, by nasal biopsy, the tissue changes associated with

intranasal mometasone furoate use (200 µg/day) in patients with perennial rhinitis during a 12-month treatment period. They had 52 patients complete 12 months of treatment. Then, nasal biopsy specimens were found to have no sign of atrophy, a decrease in focal metaplasia, and no change in epithelial thickness. Their analysis of the nasal biopsy specimens revealed a significant decrease in tryptase-positive mast cells and major basic protein-positive eosinophils in the lamina propria and the epithelium. Mometasone furoate appears to decrease the inflammatory process by reducing the extent of inflammatory cell infiltration, particularly of eosinophils.³ This study indicated that long-term administration of intranasal mometasone furoate was not associated with adverse tissue changes in the nasal mucosa of patients with perennial rhinitis.

Lindqvist *et al.* performed a long-term safety study of intranasal administered budesonide. This multicenter study included 104 patients with perennial rhinitis, allergic or nonallergic, and followed them for 12 months. Their analysis revealed no histopathological changes of the nasal mucosa, no clinically significant changes in the blood chemistry or hematologic parameters, as well as no signs of atrophy or candidiasis. All nasal symptom parameters assessed by the patients were significantly reduced from baseline during the follow-up period.⁴

TOPICAL SIDE EFFECTS

Intranasal administration of corticosteroids is associated with various topical side effects in 5–10% of patients regardless of the formulation.⁵ The most common of these adverse side effects include dryness, burning, hoarseness, sneezing, and aftertaste. Other less common side effects include headache, nausea, local infections (especially with *Candida albicans*), epistaxis, candidiasis, and nasal septal perforation.⁶ Although this is not an exhaustive list of the possible side effects from INS, these are pertinent and in this article we will focus on the epistaxis, candidiasis, and nasal septal perforation.

In 2008 Benninger performed a study to find the incidence of epistaxis and see if there was a relationship with the handedness of the patient. He included 559 consecutive patients using an INS for >3 months. He found that 28 patients (5%) reported epistaxis within the prior 2 months. Of their recorded 32 sides of bleeding (unilateral and bilateral combined), 78% (25 episodes) were on the same side as the hand used to apply the INS.⁷ This study found a strong correlation between the side of bleeding and both the hand used to administer INSs and the handedness of the patient, suggesting that patient-induced trauma, instead of specific formulations, was the cause of the

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Table 1 INs available in the United States

Beclomethasone dipropionate	AQ and AERO
Budesonide	AQ
Ciclesonide	AQ and AERO
Fluticasone furoate	AQ
Fluticasone propionate	AQ
Mometasone furoate	AQ
Triamcinolone acetonide	AQ

AQ = aqueous INs; AERO = aerosolized INs; INs = intranasal corticosteroids.

epistaxis. Therefore, technique is a major factor influencing the incidence of epistaxis seen with INs and why education on the proper administration of these agents is paramount.

Candidiasis appears to be a very rare complication of INs although it is listed in the package insert with all INs. Webb *et al.* reported one patient with nasal candidiasis with prolonged use of intranasal beclomethasone aqueous.⁸ They reported a 62-year-old woman with 1.5 years of intranasal steroid use for vasomotor rhinitis. On physical exam she was found to have white plaques in her nose and a positive culture but a negative candida skin test. She was found to have chronic lymphocytic leukemia as the underlying cause of her anergy. She was treated with ketoconazole.

Kyrmizakis *et al.* reported on the successful treatment of three patients with acute erythematous candidiasis of the pharynx, which was the result of the use of INs.⁹ Pharyngeal candidiasis may be asymptomatic (acute pseudomembranous form) or may give rise to severe pain with dysphagia (acute erythematous form). Clinically, it can give rise to small white patches or to more generalized red lesions and/or slight congestion. Therefore, despite this being a rare side effect, it is important to always be diligent and mindful of this possible complication while performing a physical exam on patients with allergic rhinitis.

Nasal septal perforation is an important side effect to be aware of when considering use of INs. This very rare occurrence has been attributed to the vasoconstrictor activity of the corticosteroid molecules.¹⁰ There are relatively few reports in the literature of nasal septal perforation with INs. Cervin and Andersson in 1998 reviewed potential side effects to INs reported to the Swedish Medical Products Agency. They reviewed their personal department data and found that over a 5-year period 32 patients were found to have nasal septal perforations (21 women and 11 men). The most common risk factor for septal perforation was INs treatment. Of their 32 cases, 11 cases (10 women and 1 man) had been on INs. This cohort's average age was 33 years (range, 19–49 years). They concluded that septal perforation due to INs is an underreported side effect and that perforations are most likely to appear during the first 12 months of treatment and more likely in young women.¹¹

Nasal septal perforation has also been reported in a patient with allergic bronchopulmonary aspergillosis and rhinitis who was on long-term intranasal and oral corticosteroids.¹² Lanier *et al.* reported on cases of nasal septal perforation reported to the FDA from January 1, 1997 through December 31 2006. Over this time period, around 50 cases were reported to the FDA in patients using not only INs but also intranasal decongestants and antihistamines.¹⁰

During the pivotal studies for FDA approval of intranasal ciclesonide HFA for seasonal allergic rhinitis, 2 of 884 subjects treated with the 74- μ g dose were reported to have nasal septal perforation. The first one was in a 58-year-old woman. Her nasal perforation was discovered on required nasal examination on day 16. However, it was discovered that this subject had a remote history of nasal polyps, nasal septal perforation, and recurrence of nasal polyps postsurgery. This information was omitted from study documentation and the subject was randomized in error.¹³ The other case was in a 34-year-old

woman. She was found to have a 2-cm perforation noted on nasal examination on day 13 that had not been observed at baseline. This patient was unaware of the lesion and her lesion had well-healed edges. Two months later when she was assessed by an ear, nose, and throat specialist, this lesion was well healed and was considered to be a preexisting lesion.¹⁴ It appears unlikely that either case was caused by the intranasal ciclesonide. In a 6-month long-term study with intranasal ciclesonide HFA, no nasal septal perforations were observed.¹⁵ The other dry aerosol INs, beclomethasone, did not report any nasal septal perforations in their clinical trials for FDA approval¹⁶ (beclomethasone prescribing information).

SPECIFIC FORMULATION COMPONENTS

Overall, INs have a good safety profile.¹⁷ The previously mentioned significant topical side effects are rare. However, one of the problems that can affect long-term successful treatment is adherence. One very important factor that affects adherence is the specific formulations of the different INs.

Meltzer in 2007 reviewed several components found in different aqueous INs. One commonly used additive is benzalkonium chloride (BKC), which is a cationic surfactant commonly used as a preservative in INs. *In vitro*, BKC was ciliotoxic. However, *in vivo* studies suggested that normal ciliary movement was maintained because of the findings that BKC did not alter saccharin transport time.¹⁸ Also, BKC has been associated with increased nasal hypersecretion, nasal irritation, and burning sensation. BKC is present in fluticasone furoate, fluticasone propionate, mometasone furoate, and triamcinolone as seen in Table 2.

Potassium sorbate is an additive that has been found to inhibit microbial growth. It is most commonly used in food preservatives, because it has a neutral taste and is physiologically inert.¹⁸ So far, the literature reports that potassium sorbate in INs has not been associated with adverse effects in humans. Potassium sorbate is used as a preservative in budesonide and ciclesonide.

Alcohols are additives that can be used to enhance the sensory attributes of INs sprays. Fluticasone propionate contains phenylethyl alcohol. This additive confers both smell and taste to foods and perfumes. Although using alcohol may potentially mask the unpleasant sensory attributes of an INs, this additive may cause drying of the nasal mucosa and irritation, which could lead to epistaxis.¹⁸

Polysorbates are nonionic surfactants and emulsifying agents that are used as additives in lotions, shampoo, and food. Polysorbates are found in most of the commercially available INs (budesonide, fluticasone propionate, fluticasone furoate, mometasone, and triamcinolone). The literature does include case reports that described contact allergy or sensitivity to polysorbates, most often polysorbate 80. Studies have also found that polysorbate 80 reversibly inhibited ciliary beat frequency in cultured human nasal epithelial cells.¹⁸ This additive has also been associated with hypersensitivity (erythema, pruritus, and orofacial angioedema).

Most commercially available INs contain thixotropic agents, such as carboxymethylcellulose (CMC), because they increase viscosity. Because all INs suspensions with this additive have a high viscosity, they must be shaken before use. This action decreases the viscosity of the suspension, which allows the INs to be administered as a mist to the nasal mucosa. After the INs suspension dries, the steroid and the thixotropic agent remain as a residue that can exert a drying effect on the nasal mucosa.¹⁸ This result could contribute to the increased rates of epistaxis in patients receiving INs. There are rare cases of anaphylactic reactions to CMC that have been reported with injections of corticosteroids containing CMC. Of the seven INs available in the United States, only triamcinolone acetonide does not contain CMC¹⁸ (Beconase INs prescribing information; GlaxoSmithKline, Philadelphia, PA).

Propylene glycol is an agent commonly used in antifreeze and deicing solutions and used as a wetting agent when combined with polyethylene glycol.¹⁸ This is only present in flunisolide and has often

Table 2 Formulation components of aqueous INS products

INS	BKC	Potassium Sorbate	Alcohol	Polysorbate	Propylene Glycol	CMC
Ciclesonide	—	+	—	—	—	+
Fluticasone propionate	+	—	+*	+	—	+
Triamcinolone acetonide	+	—	—	+	—	—
Flunisolide	+	—	+ [#]	+	+	+
Mometasone furoate	+	—	—	+	—	+
Budesonide	—	+	—	+	—	+
Fluticasone furoate	+	—	—	+	—	+

Source: Ref. 18.

*Phenylethyl alcohol.

[#]Sorbitol.

BKC = benzalkonium chloride; CMC = carboxymethylcellulose; INS = intranasal corticosteroid; — = negative; + = positive.

Table 3 Total daily volumes of AQ INS

Budesonide	200 μ L
Fluticasone furoate	200 μ L
Ciclesonide	280 μ L
Fluticasone propionate	400 μ L
Triamcinolone acetonide	400 μ L
Mometasone furoate	400 μ L
Fluticasone propionate/azelastine	548 μ L

AQ = aqueous INS; INS = intranasal corticosteroid.

been reported to cause irritation or burning. However, because flunisolide is no longer available, no further discussion will be provided in this article.

TOPICAL CHARACTERISTICS AND ADHERENCE

Another very important factor that affects adherence is the total volume of spray that patients are required to deliver into their nasal cavity. Too high a volume of INS can result in runoff that can cause irritation.⁶ In the Allergies in America study, patients reported that run down the back of the throat and out the nose were two of the major side effects seen with aqueous INSs.¹⁹ Table 3 shows the maximum daily spray volume for adults with the major INSs.

Sensory attributes are important in affecting adherence to INSs. Mahadevia *et al.* performed a cross-sectional study having respondents choose between pairs of hypothetical INSs differing in sensory attribute composition (taste, aftertaste, smell, nose run-out, throat rundown, and feel of spray in nose or throat). These patient's preferences were measured for three intensity levels of each sensory attribute (*e.g.*, strong taste, weak taste, and no taste). Patient preferences for INSs were found to decrease with increasing intensity levels of each sensory attribute. In this study they found that aftertaste was the most important attribute in 28% of patients, taste in 19%, throat rundown in 18%, nose run-out in 12%, smell in 11%, and feel of spray in 7%.²⁰ Mahadevia reported that if patients were instructed to take an INS daily for 3 months, 77% of patients stated that they would definitely be able to follow their physician's advice (willingness to adhere) if given one containing the lowest level of each sensory attributes versus only 4% if given an INS that had moderate levels of the sensory attributes.

Currently, in the United States the FDA has approved two intranasal HFA aerosol corticosteroids: beclomethasone and ciclesonide. They both are approved for once-daily dosing. Luskin *et al.* theorized that an HFA INS may lead to improved adherence because of its ease of use and no anterior run-out of the nose or posterior runoff that can lead to throat irritation.⁶ Hankin *et al.* also reported their study in which they compared CFC-propelled pressurized MDIs to aqueous INSs. They found there was better compliance and lower health care costs in the groups using the pressurized MDIs.²¹

With many choices available for treatment of allergic rhinitis it is important to consider what type of patient may benefit from aerosolized versus aqueous INS. Table 4 lists types of patients that may have increased benefit from HFA INSs. These include patients with nasal polyps and pre- and post-sinus surgery patients where the dry aerosol spray may have a different spray distribution pattern that could be beneficial.⁶ The postsurgery patient also may have the added benefit of the aerosolized spray slowing the return of disease or inflammation. In addition, a presurgery patient may benefit from the drying effect of the aerosolized spray before a sinus surgery. Children and adolescents also may be more accepting of the different feel of the aerosolized spray and its volume and be more likely to get a full dose of medication because of ease of use. Other patients who suffer from "wet" allergic rhinitis (profuse rhinorrhea) may benefit from the "drying" effect and sensation of an aerosolized INS. Also, the difficult scenario of a patient who previously failed an aqueous INS or who could not tolerate the side effects from an aqueous INS may tolerate using the dry aerosol, thereby increasing adherence with the prescribed regimen.

In addition to considering the potential positive effects of aerosolized INS one must also consider the potential risks of this delivery option as well. With increased pressure one could argue it may be too forceful or the increased pressure could possibly have a damaging effect on the nasal mucosa and cause epistaxis more easily than an aqueous solution. However, data from studies with CFC-propelled aerosolized INS and clinical experience with them did not support this hypothesized risk.⁶ Studies comparing the aqueous and aerosol formulations did not report significant differences between the different formulations.

DISCUSSION

A group of experts from specialties that manage allergic rhinitis had a round table discussion in 2006 with the goal of developing a consensus to guide physicians in choosing between the different INSs. They felt that one must always consider nasal anatomy and physiology to optimize intranasal steroid deposition in the nose. Emphasis was placed on teaching patients proper technique for using intranasal steroid devices to prevent nasal injury and to help concentrate the drug effect on affected tissues.²² Studies have clearly taught us that patients can identify sensory characteristics of INSs that will establish their own individual product preferences.

With all the possible choices available for a physician to prescribe to their patients it can be difficult to decide which INS and which method of delivery to use for a particular patient. For some patients their insurance dictates which medication is covered and with good education and proper use, most patients should find benefit. However, for some patients many options are available.

Currently, no study exists comparing all of the INSs to see if one truly is more efficacious than the other INSs. There also are no

Table 4 Patients who might benefit from aerosol INS

Polyps	Distribution pattern of spray
Olfactory disorder (mild hyposmia of AR)	Distribution pattern of spray
Postsurgery	Distribution into paranasal sinuses; may slow return of disease/inflammation
Presurgery	Drying effect and distribution of spray
Children and adolescents	Spray volume and feel
Wet AR (profuse rhinorrhea)	"Drying" effect and sensation
Previously failed AQ product	Distribution and preference may contribute to success
Bothered by side effects or can not tolerate AQ product	Preference may enhance compliance

AR = allergic rhinitis; AQ = aqueous INS; INS = intranasal corticosteroid.

laboratory tests or genetic studies available that would suggest that a certain formulation would work better than a different formulation. Therefore, discussion with the patient and giving a trial of a various INSs with close follow-up to monitor improvement of symptoms, identifying side effects, and promoting proper technique is likely the best current option.

In conclusion, we should realize that INS will continue to be a major treatment for our patients with allergic rhinitis. The major topical side effects of INSs are rare for most patients even with chronic use. Adherence to INSs is impacted by their individual formulations. We need to assess each patient to determine which INS (aerosol versus aqueous) will achieve the best adherence and improve the outcomes for our patients.

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