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RHINITIS, CONJUNCTIVITIS, AND SINUSITIS (JJ OPPENHEIMER AND J CORREN, SECTION EDITORS)

Safety of Intranasal Steroids: an Updated Perspective

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Abstract

Purpose of Review Intranasal corticosteroid sprays have been available as over-the-counter (OTC) medications since 2013. As such, clinicians need to be up-to-date with the risks and the safety of INS, as patients may have concerns and detailed questions. The following is a review of the recent medical literature regarding the safety profile, adverse reactions, and special populations using INS.

Recent Findings The latest research on intranasal steroid sprays (INS) continue to confirm that INS rarely have significant local side effects, such as severe and persistent epistaxis. Recent studies looking at systemic side effects such as hypothalamic pituitary axis suppression, growth effects, and ocular effects do not indicate any new concerns nor have found significant differences from the past literature. The use of combination INS and topical antihistamine medications did not reveal any new safety issues. Use of INS with topical decongestants found some limited effects of tachyphylaxis and rebound congestion. Studies continue to support the use of newer INS for children and continued monitoring of growth in this population. The HIV population should avoid use of INS with the prescription of ritonavir, given demonstration of adrenal suppression.

Summary This updated perspective has found that newer generation INS should be used at the lowest effective dose for the selected population, that clinicians can inform patients using the OTC INS preparations that there are very few safety concerns, and that regular follow-up visits can provide further reassurance with physical examinations and address patient's questions. Future research regarding the safety of INS should study newer preparations when developed and if used in combination with other topical agents.

Keywords Allergic rhinitis · Rhinitis · Intranasal steroid spray · Side effects · Safety · Special populations

Introduction

Allergic rhinitis is a common disease, with a worldwide prevalence of up to 25% [1] and an associated economic burden of billions of dollars [2, 3].The mainstay of treatment is allergen avoidance and pharmacotherapy. For the latter, intranasal steroid sprays (INS) are essential [3, 4•, 5–7, 8•, 9] medications which have been used for management of this condition since 1973 [10]. Non-allergic rhinitis, without infections, is a large group of nasal disorders, having some symptoms similar to allergic rhinitis. Some non-allergic rhinitis conditions, such as non-allergic rhinitis with eosinophilia syndrome, idiopathic rhinitis, and hormonally induced rhinitis, are managed with INS. Acute and chronic rhinosinusitis are additional medical treatments where INS are recommended [11, 12]. These disorders have some overlapping symptoms (nasal congestion, nasal drainage, and occasionally sneezing) which have led to the effective use of similar medications, namely, INS (Table 1).

INS medications first became available over-the-counter (OTC) in 2013. Triamcinolone acetonide and fluticasone propionate were the first two preparations approved by the FDA for non-prescription use. Prior to the OTC approval, several concerns were brought up by professional societies in the fields of both allergy/immunology and otolaryngology [13].

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Table 1 First- and second-generation INS preparations

First-generation intranasal steroids				
Generic name	Brand name	Prescription only or OTC		Minimum age approval
Budesonide	Rhinocort Aqua	OTC		Age 6
Beclomethasone dipropionate	Beconase, QNasl	Prescription only		Age 6
Triamcinolone	Nasacort	OTC		Age 2
Flunisolide	Nasalide	Prescription only		Age 6 and up
Second-generation intranasal steroids				
Generic name	Brand name	Prescription only or OTC	Minimum age approval	Other considerations
Mometasone furoate	Nasonex	Prescription only	Age 2	Safe in pregnancy
Fluticasone furoate	Flonase Sensimist, Veramyst	OTC	Age 4	Safe in pregnancy, caution in HIV*
Fluticasone propionate	Flonase	OTC	Age 4	Safe in pregnancy, caution in HIV*
Ciclesonide	Omnaris	Prescription only	Age 6	

Tables indicate commonly prescribed and recommended INS medications in the USA

* See text

These concerns included the lack of clinician-provided instructions on use of the INS, lack of long-term monitoring, and potential safety issues of the various preparations. Despite these concerns [14], these medications were approved for OTC use. With individuals having OTC access to previously prescribed INS, it is all the more critical for clinicians to be able to provide patients the most up-to-date information regarding safety and the proper use of these medications.

The majority of clinicians are familiar with the side effect profile of oral corticosteroids, which include hypothalamic pituitary axis suppression, suppression of normal growth in children, and ocular disorders like glaucoma and cataracts. The risks of these systemic side effects have led to similar concerns about local glucocorticoids such as the INS medications that are the subject of this review. In this article, such risks will be investigated in detail. It is important to keep in mind, however, that the INS medications were designed, successfully it turns out, to minimize adverse steroid effects by delivering the drug directly to the target tissue, thereby lowering systemic exposure and associated side effects.

Molecular Mechanisms and Pharmacokinetic Considerations

INS work locally in the nose by reducing mast cell degranulation and act ultimately to dampen the effector immune cell response to allergen contact [15].This occurs at the cellular level by steroids binding to glucocorticoid receptors in the cytoplasm, with subsequent transport to the nucleus where the steroids interact with gene sequences to exert their downstream effects [16]. The culmination of these effects is overall decreased nasal eosinophils and a trend toward normalization of the nasal mucosa [13], with no adverse effect on the epithelial integrity of the nasal mucosa [17].

There are two important pharmacokinetic considerations at play with these medications. The first is the overall systemic bioavailability. After being sprayed in the nose, these medications are absorbed in the gastrointestinal tract [1]. Newer generation INS medications are almost completely inactivated via first-pass metabolism, in the liver and the gut, leading to negligible systemic bioavailability [18], and thus much lower potential for systemic side effects. The second, and related, consideration relates to the lipophilicity of a given INS medication. Lipophilic INS medications stay in the nasal tissues longer, binding with greater affinity to local glucocorticoid receptors [18]. Highly lipophilic medications are more likely to lead to local side effects, but less likely to lead to systemic side effects. Older INS medications (budesonide, beclomethasone, triamcinolone, flunisolide) are less lipophilic and more bioavailable [1, 18, 19•, 20]. Newer INS medications (mometasone, fluticasone furoate, fluticasone propionate, betamethasone, and ciclesonide) are more lipophilic, less bioavailable [1, 18, 19•], and thus overall less likely to lead to significant side effects [5, 6, 21].

The ultimate metabolic pathway of each INS varies. Older INS medications like beclomethasone undergo less efficient first-pass metabolism in the liver [16, 19•]. In contrast, newer INS medications like fluticasone, mometasone, and ciclesonide are almost completely metabolized in the liver on the first pass, with resultant oral bioavailability of these medications estimated at < 1% [16, 19•].

Local Effects

Given the above discussion regarding the pharmacokinetics of these medications, it is perhaps not surprising that most side effects of nasal steroids are local [21]. General local effects are mild and include epistaxis, throat irritation, nasal dryness, and

burning and stinging sensation in the nose [20, 21]; additionally, some patients strongly dislike the physical sensation of medication "dripping down the throat" [3].

Epistaxis is a common side effect voiced by patients and, anecdotally, often attributed to the steroid's direct effect on the nasal septum. Interestingly, this is most likely actually secondary to local trauma from administration of the medication; in several studies the rates of epistaxis and other such local effects are similar between treatment and control groups [1, 3, 16, 21]. Though this problem is usually mild, there have been reports of severe and persistent epistaxis. Potentially severe adverse effects are septal ulceration and/or perforation, found only as isolated case reports associated with INS MDI formulations [22, 23]. The risk for these rare adverse events can be reduced with proper technique, instructing the patient to administer the medication spray away from the septum, after nasal insertion[24•]. Nasal atrophy remains a concern for clinicians but is quite rare in reality [21, 25•]. Two studies of chronic INS use (looking at beclomethasone, budesonide, flunisolide, fluticasone, mometasone, and triamcinolone specifically) have not shown any development of nasal atrophy, adverse effects on mucociliary clearance, or negative changes to olfactory function [26•, 27].

In addition to the abovementioned concerns, the package insert for a prototypical INS, such as fluticasone propionate, cites additional concerns for candidal infection, impaired wound healing, and hypersensitivity reactions including anaphylaxis. We note that in our review of the literature, we found no reports of these problems occurring in actual patients with the exception of very rare anecdotal reports of bronchospasm with medication administration [24•, 28].

Hypothalamic Pituitary Axis Suppression

Because of the nonselective effect of corticosteroids in general, their impacts on the HPA have been extensively evaluated and reviewed in the literature [6, 16, 25•, 29, 30]. The relevant studies have employed various methodologies to this end, from the simple (serum cortisol/urine cortisol levels) to the complex (ACTH stimulation studies). The strong consensus of these studies is that intranasal steroids used at FDA-recommended dosing ranges do not lead to significant adrenal insufficiency. In contradiction, more potent delivery vehicles, such as the mucosal atomization device (MAD) system advocated for by some otolaryngologists, have been linked with possibly higher risks of adrenal suppression [29]. One study found an association between intranasal fluticasone propionate and a reduction in urinary cortisol levels in children [31]; however, subsequent studies have not found any convincing evidence of adrenal suppression in these medications [32, 33] even when concurrently used with inhaled steroids [16, 25•, 34]. In a more recent study performed in evaluating the safety of a novel intranasal steroid (SFDAC), there was no evidence of clinically significant hypothalamic pituitary axis suppression [6].

Growth Effects

Long-term use of oral steroids has long been known to impair normal linear growth in children, for reasons that are not entirely clear [9]. As such, the issue of the degree to which INS medications affect the child's growth and development has been examined in several research studies. The literature in this area has generally relied on measurements of lower leg bone length (knemometry), which is useful in the evaluation of short-term maladaptive effects, and measurements of standing height (stadiometry) which are easier to track in longer-term studies.

It is notable that some of the older INS medications have been associated with adverse effects on growth velocity. For example, beclomethasone has been shown to be associated with decreased growth in children 6–9 years of age [35]. In this small study of 90 children treated with beclomethasone, Skoner and colleagues found significant differences in baseline age and height between placebo and treatment groups, although later research contradicted these findings [36]. Other older INS medications such as triamcinolone [37] have not been associated with these issues. Perhaps unsurprisingly, newer generation INS medications like mometasone [19•, 29, 32], fluticasone furoate [38], and ciclesonide [39] have been thoroughly examined for adverse effects on growth and have been demonstrated to be safe, although there is some indication that there may be clinically small but statistically significant decreases in growth for children on fluticasone (decrease of 0.27 cm/year compared with placebo) and triamcinolone (decrease of 0.45 cm/year compared with placebo) in more recent studies [25•].

For allergists treating children, the newer INS medications should be considered first-line for children with noninfectious rhinitis. Based upon the cumulative literature, past and present, we recommend that when treating children with INS, the older generation INS be avoided, specifically beclomethasone, due to its potential effects on growth. We also recommend that any child using INS on a regular basis be checked for growth, following CDC growth curves; this practice can be done by the child's pediatrician (a standard practice for pediatricians) and/or the allergist. This recommendation should be discussed with the caretakers of children using INS.

Ocular Effects

Despite a known link between oral corticosteroids and increased risk of cataracts and glaucoma, multiple studies of

INS medications have confirmed their ophthalmic safety. Although clinicians sometimes worry about ocular effects, based on the well-known experience with oral steroids, high-quality studies have suggested that these are generally not a concern with INS [8•, 21, 25•].

This safety record is even borne out in longer-term studies. LaForce and colleagues found that over a 2-year study period, there were no detrimental changes in lens opacification, intraocular pressure, visual acuity, and fundoscopic cup-to-disk ratio in a large cohort of over 500 subjects [40]. In a cross-sectional analysis of the novel MAD formulation of budesonide by Manji et al., the authors found increased rates of elevated intraocular pressure in 6% of the patients [29]. This finding is not surprising, however, given that the authors studied a MAD delivery device specifically designed to deliver a more concentrated formulation of medication as well as employing an older generation INS.

In the first long-term study of ocular safety with respect to fluticasone furoate specifically, LaForce and colleagues found that over the 2-year study period, there were no detrimental changes in lens opacification, intraocular pressure, visual acuity, and fundoscopic cup-to-disk ratio [40].

Lightman and Scadding conducted a thorough review of the literature regarding ocular safety of the various INS products and noted that the majority of evidence demonstrates that these medications are quite safe from the standpoint of glaucoma and cataracts [8•]. They do note that it is not advisable to use these medications, however, in patients who have herpes keratitis, steroid-related glaucoma, or central serous retinopathy.

All in all, it is reasonable to conclude that significant ocular side effects are quite rare when these medications are used as typically prescribed in the allergy community.

Other

Oral corticosteroids are known to increase the risk of osteoporosis and fractures in adult patient via several mechanisms, including decreased absorption and increased excretion of calcium, parathyroid-driven bone resorption, inhibition of osteoblastic activity, and reduced estrogen production by the adrenal cortex [26•]. Fortunately, these effects have not been seen with INS use. A 30-year review by Edelman and van Os found that therapeutic doses of intranasal beclomethasone have not been associated with osteoporosis or risk of fractures [26•]. In reviews of studies evaluating the long-term use of other INS, there was no effect on bone mineral density or increased risk of fracture, even in children [1, 16, 26•].

Several studies have evaluated the safety of combinations of INS and other classes of topical medications and found them to be quite safe. Prior to the approval of fluticasone furoate and azelastine (Dymista), Allen and colleagues investigated the safety of prototype combination medication (fluticasone furoate and levocabastine) and found that the antihistamine component did not increase the detectable levels of the steroid component [15]—indeed > 99% of the fluticasone concentrations were undetectable, and the most common adverse effect reported from the study subjects was mild to moderate headache. In a study by Meltzer et al. of the combination of mometasone furoate plus oxymetazoline, a topical decongestant medication, the most common side effect noted was headache (approximately 2% across groups), and the incidence of epistaxis in the study cohort was quite low (0.7–1.4% across groups) [41]. The study authors note that while they were concerned about tachyphylaxis and rebound congestion from the oxymetazoline component of this combination medication, none of the study subjects actually developed this problem. While the study results were informative, we would advise caution in recommending more than a few days of consecutive use of topical decongestants as the risk of tachyphylaxis is well-established in the literature [42].

Special Populations

Children

Allergic rhinitis is the most common chronic condition in children, thought to affect up to 40% worldwide [43••]. INS are first-line therapy for allergic rhinitis in children, as in adults. Beclomethasone, triamcinolone, budesonide, flunisolide, fluticasone propionate, and mometasone are all currently approved for use in children. For children under age 6, the options are limited to mometasone furoate, fluticasone propionate, and fluticasone furoate [37]. Because of intolerability of adverse developmental and other effects in the pediatric age group, there been special research emphasis on establishing the safety of these medications in this population.

Generally, INS are well tolerated in children. The most common pediatric adverse effects include nasal irritation, sneezing, epistaxis, burning sensation, and dry sensation in the nose [18]. Epistaxis is usually mild and intermittent. Although patients frequently report epistaxis, a study in children aged 6 to 9 years of mometasone use for 1 year showed that rates of epistaxis were only slightly higher in the treatment group than the placebo group [32].

The potential effects on growth and the preference for the new INS medications to minimize this risk were previously discussed. Regarding the effect on the HPA axis, one study found an association between intranasal fluticasone propionate and a reduction in urinary cortisol levels in children after 2 weeks of use [31]. This finding contradicted prior studies that did not show any effect on urinary cortisol excretion or plasma cortisol levels with fluticasone use. Other studies have demonstrated no HPA axis suppression with beclomethasone,

triamcinolone, budesonide, or mometasone [37, 43••]. Few studies have evaluated the effect on bone metabolism in children, but of those that have, there has been no evidence of changes to bone metabolic markers [43••] or bone mineral density [1]. Anderson et al. found no clinically significant changes in hemoglobin, hematocrit, AST, and urine uric acid with budesonide use in children aged 6 to 17 years [10]. Ocular effects in children aged 6 to 11 years were evaluated in a 12-month study of mometasone use by Dibildox. No significant changes from baseline intraocular pressure that would be suggestive of glaucoma or posterior subcapsular cataracts were detected at the end of the study period [44].

Pregnant Women

All INS were initially labeled as category "C" based on the US FDA's five-letter pregnancy risk classification system until December 2014, when FDA made labeling changes. After a large Swedish case-control study from 1995 to 2001 showed reassuring safety data with budesonide use during pregnancy, the FDA upgraded this drug to category "B." A more recent study from 2016 [45] found an association between the use of triamcinolone in pregnancy and congenital respiratory defects (malformations of the respiratory tract) and is not recommended for use during pregnancy. Though other older INS, specifically beclomethasone and budesonide, have fared well in safety studies [46•], the association of triamcinolone use and malformations of the developing respiratory tract calls into question the general safety of older INS. Newer INS mometasone and fluticasone have shown no association with congenital malformations making them favorable choices during pregnancy [21, 46•].

HIV Positive

Intranasal fluticasone should be avoided in patients taking ritonavir, an antiretroviral medication used in HIV treatment. As ritonavir is a potent inhibitor of the CYP3A4 enzyme, there have been cases of significant adrenal suppression with resultant exogenous Cushing syndrome in patients taking the combination of these two medications, with onset of symptoms occurring as late as 18 months after initiation. Fortunately, this interaction has not been observed with the other intranasal corticosteroids [47•].

Elderly

There are few studies assessing the safety profile of INS in elderly patients. Specific concerns for elderly patients are decreased hepatic metabolism and increased incidence of glaucoma, cataracts, and osteoporosis. Though a few case studies suggest a potential increased risk of glaucoma, Garbe and colleagues performed a large case-control study of patients age 66 years and older. This study showed that with the use of INS, there was no increased risk of ocular hypertension or open-angle glaucoma [48]. Another study, a randomized controlled study of 334 patients (aged 65 years and older) treated with INS for a 3-month period, showed no increased adverse effects in the treatment group compared with the placebo [49]. The most common adverse effects were epistaxis, headaches, and pharyngitis. No serious treatment-related adverse events or clinically meaningful changes in electrocardiograms, vital signs, or laboratory test results occurred. Of the studies that have been performed, there is consensus that adverse effects are similar to those found with adult patients.

Considerations for Use

INS are generally well-tolerated and require minimal monitoring. Prior to initiation, evaluation of personal or family history of glaucoma would be reasonable for the cautious physician [25•]. For such patients, monitoring for visual changes and regular eye exams should be recommended. While taking the medication, patients should undergo periodic nasal exams to evaluate for mucosal changes and epistaxis. If this occurs, consider decreasing the dose [26•]. In children, growth should be followed and compared with standard CDC growth curves. If growth slows, consider decreasing the dose or discontinuation.

Practical Advice for Patients

INS have been over-the-counter since late 2013, with triamcinolone/Nasacort first receiving approval by the US FDA, followed by fluticasone/Flonase in early 2014. The FDA has required the OTC INS package inserts to include the information that the growth rate of some children might be slower, as well as talking to the physician if there has been nasal surgery or ulcers, nasal lesions that have not healed, and allergic reactions to any of the ingredients. Eye conditions such as cataracts and glaucoma are also mentioned as possible side effects. As these are topics that patients may bring up in office visits, we suggest physicians being comfortable providing specific advice.

Other topics that we have addressed with our patients include how to use INS, how soon will the medication be effective in relieving rhinitis symptoms, and how long can INS be used safely. The authors have created a video trigger that you can view and use with your patients (<<INSERT LINK>>). The INS package inserts give directions on how to use the medication, and some (like fluticasone propionate/Flonase) provide video triggers on their websites. Following 2017 practice guidelines for the treatment of allergic rhinitis [4•], we recommend that INS be used continuously, meaning daily,

but there is some evidence that intermittent use can also be beneficial [50•]. Regarding the duration of use of INS, studies have followed INS use for a few weeks up to 5.5 years. Two studies performed nasal mucosal biopsies after continuous use of INS (mometasone and budesonide) and found that long-term use of these two INS did not cause any adverse histopathological mucosal changes [51, 52].

Another commonly asked question by patients is which OTC product is the best to use. With regard to effectiveness, a Cochrane ENT review assessed the different types of first- and second-generation INS preparations in the treatment of chronic rhinosinusitis. First-generation INS include beclomethasone, triamcinolone, flunisolide, and budesonide and second generation INS are ciclesonide, fluticasone furoate, fluticasone propionate, mometasone, and betamethasone. The authors concluded that there was not enough evidence to support the use of one INS preparation in terms of effectiveness for patients being treated for chronic rhinosinusitis [53].

To answer this question in a personalized manner, the healthcare provider will need to ask the patient some more questions in the effort to identify patient preferences. INS preparations definitely differ in smell, taste, spray volume and amount, and cost. Patients may have a preference with their past use and prefer to continue the same medication or brand. Unpleasant local effects directly affect medication tolerability and thus adherence. , Past studies comparing triamcinolone to other options (beclomethasone and fluticasone) have shown that it is among the better-tolerated options in the array of INS medications [54•]. One study, published in 2005, compared patient preferences of four different INS (beclomethasone, budesonide, fluticasone, and mometasone). In this single-blind crossover study of 114 patients, study subjects preferred mometasone because the medication did not have a strong odor and strong aftertaste [55•]. The subjects also perceived that it was less irritating. In the end, patients' choice of preferred INS may be determined by ease of obtaining the INS and overall cost.

One precaution to mention to patients is the FDA maximum recommended number of daily sprays to use, which is two sprays daily in each nostril. The saying "more is better" does not apply to the use of INS, and, with INS being OTC, there is little to no regular examination of the nose to monitor possible local adverse side effects. Increased number of daily sprays of INS has been recommended in the treatment of nasal polyps (Nasonex package insert).

Conclusion

The side effects of INS are usually mild and self-limited, especially for newer generation nasal steroids when used at the lowest effective dose. Given the low systemic bioavailability of the newer generation INS, and the lack of significant HPA suppression, the FDA decision to make INS medications OTC has not been associated with adverse clinical outcomes. Certain populations require special consideration while on these medications, including children, the elderly, pregnant women, and HIV positive patients. In the majority of cases, regular clinical follow-up will ameliorate potential problems before they become a real issue. Patients who use INS on a daily and long-term basis should still be consulting with their healthcare providers to monitor for the potential side effects and to ensure effective clinical outcomes for the treated diseases.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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