ORIGINAL ARTICLE

Evaluating the Safety of Intranasal Steroids in the Treatment of Allergic Rhinitis

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Given that intranasal corticosteroids (INCs) are widely considered first-line therapies for treatment of rhinitis, it is important for the clinician to be comfortable with the side-effect profile and be able to discuss potential safety concerns regarding these therapies. Among the safety concerns with the use of INCs are the potential for growth suppression both short and long term, the potential for hypothalamic-pituitary-adrenal axis suppression, ocular safety, and the use of INCs concomitantly with inhaled corticosteroids in asthma patients. As all clinicians are aware, each patient can have individual responses to both efficacy and safety; however, the data reviewed suggest that the benefits outweigh the potential risks. Understanding the potential concerns and the data behind these concerns should give clinicians the information to be able to discuss this with patients and parents to incorporate appropriate therapy for those with allergic rhinitis.

Key words: *allergic rhinitis, intranasal corticosteroids, safety, treatment*

Allergic rhinitis (AR) affects almost 94 million Europeans, 50 million Americans, and 10 million Canadians.[1] Because it is so prevalent, almost all primary care physicians will encounter this disease. Health Canada estimates that nonfood allergies are "the most common chronic condition in Canadians 12 years of age and older."[1] In one study, 42% of children were diagnosed with AR by the age of 6 years. The prevalence of AR has increased dramatically in the past 30 years and continues to increase. Children with one component of atopy (AR, asthma, eczema) have a threefold greater risk of developing a second component.[2]

In 1998, the Joint Task Force on Practice Parameters in Allergy, Asthma, and Immunology defined rhinitis as "inflammation of the membrane lining the nose, characterized by nasal congestion, rhinorrhea, sneezing, itching of the nose and/or post-nasal drainage."[3] AR is the nasal symptoms that result from a hypersensitivity reaction to specific allergens occurring in sensitized patients, which is mediated by IgE antibodies, in which the end result is inflammation. Management of AR is important for preventing the symptoms but also for preventing potential complications of the disease. The options for treatment include allergen avoidance, pharmacotherapy, and immunotherapy.[4]

Pharmacotherapy options for AR include antihistamines (oral and intranasal), oral leukotriene receptor antagonists, and INCs. Treatment guidelines for AR support the use of INCs as first-line therapy. The Joint Task Force on Practice Parameters in Allergy, Asthma, and Immunology concluded that "extensive clinical and toxicological studies have generally demonstrated that nasal corticosteroids have an excellent benefit/risk profile in long term usage in children"[3] INCs are approved for use as low as age 2 years in pediatric patients. Given that INCs are widely considered first-line therapies for treatment of rhinitis, it is important for the clinician to be comfortable with the-side effect profile and be able to discuss potential safety concerns regarding these therapies. Among the safety concerns with the use of INCs are the potential for growth suppression both short and long term, the potential for hypothalamic-pituitary-adrenal (HPA) axis suppression, ocular safety, and the use of INCs concomitantly with inhaled corticosteroids in asthma patients.

Growth

An early study that examined the effect of the use of beclomethasone dipropionate (BDP) in AR raised concerns about the potential for growth suppression with INC

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use.[5] In this study, 100 children aged 6 to 9 years of age were studied for 1 year to measure the effect of INCs on growth. One group (51 children) received BDP 168 μg twice daily and the other (49 children) a placebo nasal spray in a double-blind fashion. The children were prepubertal and had normal growth prior to the study. During the study, the children had their heights measured by stadiometry at months 1, 2, 4, 6, 10, and 12 of treatment. They also had their HPA axis assessed via 8 AM cortisol and cosyntropin stimulation testing. The results showed that the mean change in height was 5.0 cm/yr in the BDP group compared with 5.9 cm/yr in the placebo group ($p < .01$). The mean overall rate of growth was 0.14 mm/d for BDP versus 0.16 mm/d for placebo ($p < .01$). There were no differences in the 8 AM cortisol or response to cosyntropin stimulation. This study was one of the first to show a negative effect on growth in pediatric patients with INC use. In addition, the HPA axis was not affected in these patients. To date, this is the only study that shows an effect on growth with INC therapy.

Subsequent studies with other INCs have not shown a similar effect on growth, suggesting that the effect with BDP was specific to that molecule, perhaps owing to its metabolite, beclomethasone monopropionate, with high systemic bioavailability or to the twice-daily dosing regimen. Murphy and colleagues examined the effect of once-daily therapy with budesonide (BUD) aqueous nasal spray on growth velocity in children with perennial AR.[6] They studied 229 children ages 4 to 8 years. The mean growth velocity was 5.91 cm/yr in the BUD-treated children versus 6.19 cm/yr in the placebo-treated patients (p = not significant).

Two newer-generation corticosteroids that have high first-pass metabolism and low systemic bioavailability have also been studied. Schenkel and colleagues examined the effect of intranasal mometasone furoate (MF) on growth.[7] They studied 49 children treated with MF and 49 with placebo over 1 year. The children treated with MF had a mean change of 6.95 cm/yr versus 6.35 cm/yr in the placebo. Allen and colleagues did a similarly designed double-blind, parallel-group, multicentre study in children with perennial AR using the corticosteroid fluticasone propionate (FP).[8] In this study, 74 children were treated with FP and 76 with placebo for 1 year. The children treated with FP had a mean change of 6.4 cm/yr versus 6.4 cm/yr in the placebo. Taken together, these studies are reassuring regarding a lack of any effect on growth with the newer-generation, low-bioavailability INCs in pediatric patients.

Knemometry is an alternative way to measure growth in studies. It is more useful as a method to measure short-term growth and has been reported as being a more sensitive indicator of systemic bioactivity compared with urinary cortisol measurement. Appropriately used, it can measure changes as small as 0.1 mm over 1 week in lower leg length; however, the use of knemometry on final adult height or long-term (ie, greater than 6 months) growth has not been conclusively established. In addition, few studies have examined the correlation between short-term changes in knemometry and long-term changes in growth. Nonetheless, knemometry provides additional useful information regarding effects on growth. Skoner and colleagues examined growth as measured by knemometry in 49 pediatric patients treated with either placebo, triamcinolone acetonide (TAA) at doses of 110 μg and 220 μg, and FP 200 μg for 2 weeks in a four-way crossover study.[9] The study predetermined that a 50% reduction in lower leg growth velocity was clinically significant. The magnitude of treatment effect was −19.6% for TAA 110 μg, −21.7% for FP, and −32.6% for TAA 220 μg. The authors concluded that there was no statistically significant difference in lower leg growth between any of the treatments and placebo. Owing to the short nature of the study and the large variability inherent in knemometry, these large treatment effects did not reach the predetermined values of 50% that the authors considered clinically significant.

Newer-generation INCs have also been examined using knemometry. Gradman and colleagues studied fluticasone furoate (FF) over 2 weeks of treatment compared with placebo in 53 children and found the change in lower leg growth to be 0.42 mm/wk in the placebo group versus 0.40 mm/wk in the FF group.[10] There was no statistical difference. Agertoft and Pedersen studied oral inhaled ciclesonide (CIC) at doses of 40, 80, and 160 μg in a similar design in 24 children.[11] Note that this was an asthma medication inhaled into the lung; however, the data still provide useful information about medication safety. In this study, there was a trend toward an effect but no statistical significance. The placebo group grew 0.412 mm/wk, CIC 40 μg grew 0.425 mm/wk, CIC 80 μg grew 0.397 mm/wk, and CIC 160 μg grew 0.370 mm/wk. These short-term growth studies also provide the clinician with reassurance regarding a lack of effect on growth with newer-generation corticosteroids.

HPA Axis

Suppression of the HPA axis is one of the methods used to determine if steroids have potentially negative effects. Reviewing the types of studies and methods used to

measure the HPA axis is beyond the scope of this article; however, they have been elegantly reviewed by Allen.[12] Galant and colleagues performed a randomized, double-blind, placebo-controlled study to evaluate the effects of FP 200 μg daily on HPA axis function measured by 12-hour urinary free cortisol levels in children 2 to 3 years of age after 6 weeks of treatment.[13] FP was equivalent to placebo with respect to effects on HPA axis function measured by 12-hour urinary free cortisol. Grossman and colleagues studied FP in 250 children aged 4 to 11 years with seasonal AR.[14] They found that the morning plasma cortisol concentrations and frequency of drug-related adverse events were similar in the FP and placebo groups.

Furthermore, Wilson and colleagues studied 20 patients in a single-blind, randomized, four-way crossover design and compared the systemic bioactivity of aqueous formulations of BUD, MF, and TAA in terms of adrenal gland, bone, and white blood cell markers.[15] The individual treatments were separated by 7-day washout periods. After 5 days of treatment at steady state, serial blood and urine samples were taken for 24 hours. Collective and fractionated measurements (daytime, overnight, and 8 AM) were done on plasma cortisol and urine cortisol/creatinine excretion. Plasma osteocalcin and blood eosinophil counts were measured at 8 AM. The authors found that there was no significant difference between placebo and the active treatments with any of the markers of adrenal suppression.

The newer INCs have also been studied with regard to HPA axis suppression and safety. In a 6-week study in children 2 to 5 years of age with perennial AR, daily doses of 200, 100, and 25 μg of CIC nasal spray were compared with placebo nasal spray.[16] The CIC-treated groups had a numerically (but not statistically) greater decline in 24-hour urinary free cortisol and plasma cortisol compared with the placebo treated group. In a 12-week study in children 6 to 11 years of age with perennial AR, daily doses of 200, 100, and 25 μg of CIC nasal spray were compared with placebo nasal spray. The CIC-treated groups had a numerically (but not statistically) greater decline in 24-hour urinary free cortisol compared with the placebo-treated group. The mean morning plasma cortisol value did not show any consistent treatment effect with differences from placebo.

Another newer-generation INCs, FF has also been evaluated with respect to HPA axis function. Allen and colleagues measured serum cortisol after a single dose of nasal FF and compared this with placebo.[17] They reported a ratio of FF to placebo in serum cortisol. The ratios (95% confidence interval) for FF 50, 100, 200, 400, and 800 micrograms were 1.00 (0.89–1.13), 1.04 (0.94–1.16), 1.05 (0.96–1.14), 1.06 (0.95–1.19), and 0.92 (0.82–1.04), respectively. Tripathy and colleagues measured serum cortisol levels after 6 weeks of therapy with FF in children aged 2 to 12 years with perennial AR.[18] The ratio of end of treatment to baseline was 0.98 in the placebo group and 0.94 in the FF-treated group. Patel and colleagues reported a similarly designed study in adults (age 12 years and above), which included an additional arm of prednisone 10 mg daily for the last 7 days of treatment.[19] The ratio of end of treatment to baseline was 0.99 for placebo, 0.97 for FF, and 0.49 for prednisone 10 mg groups. These data suggest a minimal HPA axis effect with FF. The prescribing information for FF provides additional data on urinary cortisol levels from these studies. With the urinary cortisol data, there was a large degree of variability in the measured results.[20] Likely owing to this variability in urinary cortisol values, a more conservative conclusion was reached by the US Food and Drug Administration (FDA). According to the FDA, "when the results of the HPA axis assessments described above are taken as a whole, an effect of intranasal FF on adrenal function cannot be ruled out, especially in pediatric patients."[20]

Ocular Safety

Another potential safety concern is ocular side effects. Derby and Maier conducted a retrospective observational cohort study of cataract incidence among users of oral and INCs identified from the United Kingdom–based General Practice Research Database with a nested case-control analysis to control for confounding factors.[21] The study population included 286,078 subjects aged less than 70 years old drawn from 350 general practices in England and Wales. Patients were classified as users of only INCs, users of only oral corticosteroids, and nonusers of either medication. They found that the incidence rate of cataract (1.0 per 1,000 person-years) among users of INCs was similar to the incidence rate among nonusers. However, oral corticosteroid users were at higher risk of cataract (2.2 per 1,000 person-years). In this study, approximately 70% of INC exposure was to BDP only; the event rate in this group was similar to that in the unexposed group. Cataract risk did not increase with the number of prior prescriptions for INCs. The authors concluded that the use of INCs was not associated with an increased risk of cataracts in this study population.

Another ocular concern is development of glaucoma or increased intraocular pressure. Medication class warnings suggest that nasal and inhaled corticosteroids may result in

the development of glaucoma and/or cataracts. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.

Specific data with CIC suggest minimal ocular effects. The risk of glaucoma was evaluated by assessments of intraocular pressure in three studies, including 943 patients. Of these, 390 adolescents or adults were treated for up to 52 weeks and 186 children ages 2 to 11 years received treatment for up to 12 weeks. In these trials, no significant differences in intraocular pressure changes were observed. Additionally, no significant ophthalmologic differences between CIC nasal spray 200 μg and placebo-treated patients were noted during the 52-week study of adults and adolescent patients in whom thorough ophthalmologic assessments were performed, including evaluation of cataract formation using slit lamp examinations.[16]

Glaucoma and cataract formation with FF was evaluated using intraocular pressure measurements and slit lamp examinations in one controlled 12-month study in 806 adolescent and adult patients aged 12 years and older and in one controlled 12-week study in 558 children aged 2 to 11 years.[20] Intraocular pressure remained within the normal range ($<$ 21 mm Hg) in $\geq$ 98% of the patients in any treatment group in both studies. However, in the 12-month study in adolescents and adults, 12 patients, all treated with FF, had isolated intraocular pressure measurements that increased above normal levels ($\geq$ 21 mm Hg). In the same study, which had a 3:1 (FF to placebo) randomization schedule, seven patients (six treated with FF and one treated with placebo) had cataracts identified during the study that were not present at baseline.[20] Further longer-term (more than 1 year) studies are needed with regard to ocular safety.

Concurrent Use of Inhaled and Intranasal Corticosteroids

Given that many patients with AR also have asthma, another potential concern is the use of INCs with concomitant therapy for asthma such as inhaled steroids. Few studies have examined this specific question. Sheth and colleagues reported that the concurrent use of intranasal FP with orally inhaled FP for the treatment of rhinitis and asthma does not increase the risk of HPA axis abnormalities.[22] This analysis of two double-blind, randomized, placebo-controlled, parallel-group safety and efficacy studies included evaluation of the HPA axis effects of concurrent treatment with intranasal and orally inhaled FP. In the first study, patients with asthma who were $\geq$ 12 years of age were assigned randomly to receive twice-daily doses (either 88 or 220 μg) of orally inhaled FP delivered from a metered-dose inhaler (MDI). In the second study, patients were assigned randomly to receive either orally inhaled FP 250 μg or orally inhaled FP 250 μg/salmeterol 50 μg delivered via the Diskus device. In both studies, patients with rhinitis were allowed to continue the use of intranasal FP at their usual dosing. Treatment periods were 26 weeks and 12 weeks for the MDI and Diskus studies, respectively. HPA axis effects were assessed using response to short cosyntropin stimulation testing. The number and percentage of patients with an abnormal cortisol response, defined as a morning plasma cortisol of $<$ 5 μg/dL, a poststimulation peak of $<$ 18 μg/dL, or a poststimulation rise of $<$ 7 μg/dL, were summarized in two subgroups: patients who used intranasal FP and those who did not. The concurrent administration of intranasal FP and orally inhaled FP via an MDI or Diskus or via Diskus with salmeterol was not associated with HPA axis effects compared with orally inhaled FP alone.

Conclusion

INCs are first-line therapy for treatment of AR in both children and adults. Safety concerns with the use of INCs were examined in this article. As newer-generation INCs are developed, more sophisticated studies examining safety have been performed. As all clinicians are aware, each patient can have individual responses to both efficacy and safety; however, the data reviewed suggest that the benefits outweigh the potential risks. Based on many of the articles reviewed in this article, INCs appear to be safe to use in appropriate patients. As newer-generation INCs become available, they, too, will need to meet or exceed the safety standards set by the currently available therapies for AR. Understanding the potential concerns and the data behind these concerns should give clinicians the information to be able to discuss this with patients and parents to incorporate appropriate therapy for those with AR.

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