

Safety update regarding intranasal corticosteroids for the treatment of allergic rhinitis

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ABSTRACT

Intranasal corticosteroids (INSs) are the most efficacious medication for the treatment of allergic rhinitis. In 2006, the Joint Task Force of the American College of Allergy, Asthma, and Immunology, and the American Academy of Allergy, Asthma, and Immunology, published a white paper on the potential over-the-counter switch of INS (Bielory L, Blaiss M, Fineman SM, et al. Concerns about intranasal corticosteroids for over-the-counter use: Position statement of the Joint Task Force for the American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology. Ann Allergy Asthma Immunol 96:514–525, 2006). The concern of the paper was the safety of the use of these agents without oversight by a health care professional. The objective of this paper was to review published literature on the safety of INS since the publication of the task force white paper. Recent studies, which evaluated topical and systemic adverse events associated with ciclesonide (CIC), fluticasone furoate (FF), mometasone furoate (MF), triamcinolone acetonide, fluticasone propionate, budesonide, and beclomethasone dipropionate were summarized. In general, no significant topical or systemic complications were observed in these studies, although none were >1 year in duration. The newer formulations of topical corticosteroids for allergic rhinitis, such as CIC, FF, and MF, which have less systemic bioavailability, may be safer for long-term use. New studies continue to add to the reassurance of the safety of INSs in the treatment of allergic rhinitis but still do not answer the question if these agents are appropriate for long-term use without oversight by a health care professional.

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In 2006, The Joint Task Force for the American Academy of Allergy, Asthma, and Immunology, and the American College of Allergy, Asthma, and Immunology was charged with developing a position paper regarding the potential release of intranasal corticosteroids (INSs) for over-the-counter (OTC) use.¹ The sole purpose was to evaluate the safety of using INSs without physician oversight. Their review of the literature before 2006 examined at possible topical and systemic adverse events and concluded that these agents should remain by prescription only. Their conclusion was reached based on the evidence that corticosteroids administered by any route, including the intranasal route, have the potential to cause adverse effects, that these adverse effects could be insidious, and there is a potential for overuse without oversight by a health care professional.

The purpose of this review is to evaluate articles published from 2006 to the present on INSs, which

have assessed safety by evaluating local and systemic side effects (Table 1) in patients with allergic rhinitis. Although most of these published articles did not have safety as their primary focus, they do add to our understanding of potential side effects.

CICLESONIDE

The newest INS approved for use in the United States is ciclesonide (CIC). This molecule is a prodrug that is broken down by intracellular esterases in the nasal mucosa to a more active moiety, desisobutyryl CIC. In a 1-year safety study in adolescents and adults, important information in assessing potential topical and systemic side effects was obtained on this agent.² Over 400 subjects were on CIC at 200 µg/day and >200 subjects were on placebo. In assessing topical side effects, 10% of the patients on CIC had epistaxis with 7.2% in the placebo group. Epistaxis was defined as a few flicks of blood to frank bleeding. This level of epistaxis is not much different from that seen in the general population.³ Benninger performed a prospective, observational study to examine the relationship between the side of nasal bleeding and the hand used in administering an INS.⁴ Of 559 consecutive patients using an intranasal steroid for >3 months, 28 patients (5%) reported epistaxis within the prior 2 months. Of the 32 reported sides of bleeding (unilateral and bilateral combined), 25 episodes (78%) were on the same side as the hand used to apply the spray. A strong correlation was found between the side of bleeding

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Table 1 Potential side effects of intranasal corticosteroids

Local	Systemic
Dryness	HPA axis suppression
Burning	Growth issues in children
Epistaxis	Ocular changes—increased intraocular pressure, glaucoma, and cataracts
Nasal septal perforation	

HPA = hypothalamic–pituitary–adrenal.

and both the hand used ($p < 0.001$) and the handedness of the patient ($p < 0.002$). Therefore, a high degree of the epistaxis seen in use of INSs does not appear to be caused by the formulation but caused by trauma by the patient. Thus, proper patient education on correct technique may reduce the incidence of epistaxis.

In addition, in the Chervinsky *et al.* study on safety of CIC there were measures of systemic activity.² These were assessed by 24-hour urinary free cortisol and morning plasma cortisol comparing CIC with placebo in patients with perennial allergic rhinitis who were ≥ 12 years of age. There were no clinically relevant changes from baseline or differences between the CIC and placebo treatment groups for both measures at 24, 48, and 52 weeks. In evaluating possible ocular complications, unrefracted and if appropriate refracted visual acuity by a Snellen chart, slit lamp eye examination, and tonometry were performed. Lens opacification was performed using the lens opacification system III method. There was no evidence of treatment-related differences in unrefracted or refracted visual acuity over the study period. No clinically meaningful difference between the CIC and placebo treatment groups was observed in intraocular pressure. Furthermore, no clinically meaningful differences were observed between the two treatment groups in any of the lens opacification system III parameters (nuclear color, nuclear opalescence, cortical cataract, and posterior subcapsular cataract). Shorter-term studies have also failed to show any meaningful topical or systemic adverse events with CIC for allergic rhinitis in children, adolescents, and adults.^{5–7}

Berger *et al.* evaluated safety in children 6–11 years with CIC in perennial allergic rhinitis.⁸ In evaluating urinary cortisol over a 6-week period, there was a numerical decrease with CIC at 25, 100, and 200 $\mu\text{g}/\text{day}$ compared with placebo but this was not judged to be clinically relevant. There were no significant changes from baseline or differences between treatment groups in morning plasma cortisol. In another study, CIC safety was evaluated in children with perennial allergic rhinitis between 2 and 5 years of age.⁹ In this pediatric study, subjects were randomized to either CIC at 25, 100, and

Table 2 Intranasal corticosteroid: Systemic bioavailability

Ciclesonide	$\leq 0.1\%$
Mometasone furoate	$\leq 0.1\%$
Fluticasone furoate	0.55%
Fluticasone propionate	1–2%
Budesonide	30–40%
Beclomethasone	40–50%
Triamcinolone acetonide	40–50%
Flunisolide	50%

Modified from Ref. 10

200 $\mu\text{g}/\text{day}$, or placebo for 6 weeks. CIC and its active metabolite, desisobutyl CIC, were undetected in the majority of the serum samples analyzed. At the end of the study, changes from baseline in 24-hour urinary free cortisol in the CIC at 200 $\mu\text{g}/\text{day}$ and placebo were not appreciably different although there was a trend toward larger decreases in 24-hour urinary free cortisol in the other two treatment doses, which suggests a non-dose-dependent effect. There was no appreciable difference between the three CIC doses and placebo in morning plasma cortisol after 6 weeks. Also, these same patients were evaluated for change in intraocular pressure at the end of 6 weeks. There was no significant difference in change in intraocular pressure with the three different doses of CIC compared with placebo. In a 12-week study with CIC at 200 $\mu\text{g}/\text{day}$ versus placebo in 2- to 5-year old children with perennial allergic rhinitis there was no significant difference in morning plasma cortisol at end point.⁹

An important aspect in looking at safety of INSs is systemic bioavailability, especially because there appears to be no difference in clinical efficacy between the different compounds. Table 2 shows the newer moieties such as CIC, fluticasone furoate (FF), mometasone furoate (MF), and fluticasone propionate (FP) have negligible systemic absorption compared with older agents such as beclomethasone dipropionate (BDP), budesonide (BUD), and triamcinolone acetonide (TAA) and therefore less potential risk for systemic activity.¹⁰

So far, no growth studies have been published measuring the effect of CIC intranasally in the pediatric population. A study did evaluate growth in children with mild persistent asthma using to two different doses of inhaled CIC, 40 and 160 $\mu\text{g}/\text{day}$, over a 1-year period.¹¹ There was no detectable effect on childhood growth velocity with either dose.

Coexisting asthma and allergic rhinitis are often treated with both INSs and inhaled corticosteroids. This could have the potential to increase adverse systemic events. Ratner *et al.* evaluated whether intranasal CIC at 200 $\mu\text{g}/\text{day}$ has any additional effect on cortisol suppression

added to inhaled BDP hydrofluoroalkane (HFA) at 320 μg twice daily for 43 days by measuring the effect on plasma cortisol area under the curve from time 0 to 24 hours after dosing ($\text{AUC}_{0-24\text{hr}}$).¹² During the 10-day run-in period, the BDP HFA group showed a significant decrease in plasma cortisol $\text{AUC}_{0-24\text{hr}}$ compared with placebo. When intranasal CIC was added, the change in mean plasma cortisol $\text{AUC}_{0-24\text{hr}}$ was similar for CIC and placebo with no significant difference suggesting no added systemic effect from intranasal CIC. To ensure that cortisol suppression was not exhausted by response to BDP HFA as the reason for no difference in plasma cortisol $\text{AUC}_{0-24\text{hr}}$ between the addition of intranasal CIC or placebo, at the end of the study a single 2-mg dose of dexamethasone was administered. There was a significant decrease in mean plasma cortisol ($p < 0.001$) in both the CIC and the placebo group showing that additional hypothalamic-pituitary-adrenal (HPA) axis suppression was possible. Therefore, it was confirmed that there was no additive inhibitory effect of intranasal CIC when added to inhaled BDP HFA. In a similar study design as the Ratner study mentioned previously, Kim *et al.* coadministered intranasal CIC at 200 $\mu\text{g}/\text{day}$ with FP/salmeterol at 500/50 μg twice daily for 43 days and assessed cortisol suppression compared with placebo nasal spray.¹³ There was no significant change in mean plasma cortisol $\text{AUC}_{0-24\text{hr}}$ between intranasal CIC and placebo when added to FP/salmeterol. Again, the single 2-mg dose of dexamethasone was administered at the end of the study and showed that significant HPA axis suppression was still possible and not maxed out with FP/salmeterol only.

Studies are proceeding for approval of an aerosol CIC in HFA for treatment of allergic rhinitis. A phase 1 study using two different doses of CIC at 282 and 148 $\mu\text{g}/\text{day}$ for 14 days showed low systemic exposure and no effect on systemic cortisol levels compared with placebo.¹⁴ A phase 3 study evaluated the efficacy and safety of CIC HFA at 80 and 160 $\mu\text{g}/\text{day}$ in seasonal allergic rhinitis for 2 weeks.¹⁵ Treatment-emergent adverse events were mild to moderate in intensity with the most common being epistaxis, nasal discomfort, and nonulcerative lesions of the nonseptal mucosa. The incidence of nasal erosions was no different between the two doses of CIC and did not lead to discontinuation from the study. No nasal septal perforations were reported.

FLUTICASONE FUROATE

FF was approved by the Food and Drug Administration for seasonal and perennial allergic rhinitis in 2007. It has a low bioavailability at 0.55%. To assess HPA axis function in adults with perennial allergic rhinitis, FF at 110 $\mu\text{g}/\text{day}$ was compared with placebo and an active-controlled prednisone over 6-week period.¹⁶ FF was noninferior to placebo in change from

baseline in 24-hour serum cortisol weighted mean and 24-hour urinary free cortisol excretion, total 24-hour urinary free cortisol excretion, and 6- β -hydroxycortisol excretion. The plasma concentration of FF was undetectable after 6 weeks of treatment. In a pediatric study of children with perennial allergic rhinitis between 2 and 11 years of age, FF at 110 $\mu\text{g}/\text{day}$ was compared with placebo on HPA axis effect.¹⁷ FF was noninferior to placebo with respect to change from baseline (expressed as a ratio) in 24-hour serum cortisol weighted mean. Urinary cortisol excretion over 24 hours at baseline and end of treatment was similar between treatment groups; no patients had 24-hour excretion levels below normal range after 6 weeks of treatment. Plasma concentrations of FF were generally nonquantifiable ($<10 \text{ pg/mL}$).

A 1-year study was performed to assess safety in adults and adolescents with perennial allergic rhinitis comparing FF at 110 $\mu\text{g}/\text{day}$ (448 subjects) to placebo (144 subjects).¹⁸ Epistaxis was seen in 8% of placebo patients in contrast to 20% on active drug. In measuring 24-hour urine cortisol excretion, there was no significant difference between FF and placebo at 12, 24, and 52 weeks. Over the 12-month period mean change in intraocular pressure from baseline was similar in the FF group compared with placebo. There was high variability in intraocular pressure (both increases and decreases) during the study. Twelve patients in the FF group and no patients in the placebo group had an intraocular pressure value $\geq 21 \text{ mmHg}$. No patient had a value of $\geq 21 \text{ mmHg}$ on more than one reading and there was no associated increase in fundusoscopic cup to disk percentage or visual field disturbance as seen with glaucoma. Posterior subcapsular cataracts that were not seen at baseline occurred in two patients on FF (0.33%) and one patient on placebo (0.50%).

Growth in prepubertal children with perennial allergic rhinitis using FF was assessed in a short-term (2 week) lower-leg growth rate by knemometry.¹⁹ The adjusted mean lower-leg growth rate was 0.40 and 0.42 mm/week with FF and placebo, respectively. The difference in adjusted mean lower-leg growth rate between FF and placebo was -0.016 mm/week (95% CI, -0.13 – 0.10). FF was noninferior to placebo, because the lower boundary of the 95% CI was above the prespecified noninferiority margin of -0.20 mm/week . Therefore, in this study no evidence of a growth effect was found with FF. So far, no 1-year growth study has been published evaluating FF in children with allergic rhinitis.

MOMETASONE FUROATE

Extensive studies have been published before 2006 showing the overall safety of MF. Schenkel *et al.* showed no growth effect with MF in prepubertal chil-

dren between 3 and 9 years of age with perennial allergic rhinitis.²⁰ Recent review articles on MF have looked at pharmacokinetic/pharmacodynamics profile and safety of this agent.²¹ Hochhaus *et al.* showed data that MF is stable in nasal tissues and efficiently metabolized in the liver.²² Its systemic bioavailability is one of the lowest among currently available INSs, comparable with CIC and FF. Bioactive glucocorticoid metabolites have not been observed in humans. Ratner *et al.* performed a multicenter, active-controlled, evaluator-blind, 12-month study of 255 children aged 6–11 years with a ≥ 1 -year history of perennial allergic rhinitis.²³ The subjects were randomized to receive once-daily MF at 100 $\mu\text{g}/\text{day}$ ($n = 166$) or the active comparator BDP at 168 $\mu\text{g}/\text{day}$ ($n = 85$). Cosyntropin stimulation testing, as well as tonometry and slit lamp procedures, were performed in this study. It was found in this 1-year study that response to cosyntropin was normal and no posterior subcapsular cataracts were observed in either group. Although no significant changes in intraocular pressure were observed with MF nasal spray, one subject receiving BDP presented with this effect. Zitt *et al.* reviewed clinical studies with ~ 4500 patients and found no evidence of HPA axis suppression in children and adults in the clinically relevant doses of MF for treatment of allergic rhinitis. The most common treatment adverse events were epistaxis, headache, and pharyngitis in adults and adolescents.

TRIAMCINOLONE ACETONIDE

TAA is one of the older corticosteroid molecules used in the treatment of allergic rhinitis in children and adults. Over the last few years, new research has been published in the pediatric population assessing safety with the use of TAA for allergic rhinitis. In children between 2 and 5 years of age, a 4-week double-blind placebo-controlled efficacy and safety study was performed with TAA at 110 $\mu\text{g}/\text{day}$ followed by a 6-month, open-label phase.²⁴ Treatment-emergent adverse events that were the most commonly seen greater than placebo in double-blind phase were cough, pyrexia, and headache. Epistaxis occurred in 5.1% of the TAA group compared with 5% in the placebo arm. HPA axis function was assessed with low-dose cosyntropin test. There was no significant difference in the mean cortisol levels after cosyntropin stimulation between the TAA and placebo groups after the 4 weeks of the double-blind treatment. The authors did note that in six cases (four with TAA and two placebo), the serum cortisol level after cosyntropin stimulation was low after the double-blind arm but became normal in the open-label phase. The authors comment that TAA at 110 $\mu\text{g}/\text{day}$ in children between 2 and 5 years of age seems unlikely to cause HPA axis suppression from their data, but as with all INSs, an effect with TAA can

not be ruled out. Skoner *et al.* evaluated 1- and 2-year growth results for children with allergic rhinitis treated with TAA at 110–220 $\mu\text{g}/\text{day}$ aqueous nasal spray.²⁵ There were 39 children treated for 1 year and a subset of 30 for a 2nd year of treatment in an open-label, nonrandomized single-site study. For each child, statural heights at baseline and at the 1- and 2-year (where available) visits, together with growth rates, were measured and were compared with predicted values. There was no significant effect on statural growth detected in this study.

FLUTICASONE PROPIONATE

Because of the number of years that FP has been on the market and now is available in a generic version, there have been few recent safety studies. Vaidyanathan *et al.* looked at comparative safety and efficacy of two formulations of FP nasal spray at 200 $\mu\text{g}/\text{day}$ —one generic and the original product.²⁶ Subjects were treated for 4 weeks and 10-hour overnight urinary cortisol/creatinine (OUCC) ratio was used to assess the HPA axis. With either formulation, there was no significant suppression of the OUCC ratio compared with baseline. The measurement of OUCC excretion has been shown to be as sensitive as an integrated 24-hour plasma or urinary free cortisol collection and is more sensitive than a spot measurement of 8:00 A.M. plasma cortisol levels.

BUDESONIDE

BUD, the only INS with category B for pregnancy in the United States, has been available for years in the United States first as a chlorofluorocarbon aerosol and now in aqueous form. Like FP, BUD has had few studies on safety since 2006. Murphy *et al.* measured growth velocity for 1 year in prepubertal children with perennial allergic rhinitis with BUD at 64 $\mu\text{g}/\text{day}$ in the aqueous form.²⁷ The change from baseline in growth velocity, height after treatment, and the percentage of patients whose percentile for height decreased from baseline to the end of treatment were evaluated. Treatment with BUD aqueous nasal spray for 1 year did not have any significant effect on mean growth velocity, mean height, or other growth parameters in prepubertal children with perennial allergic rhinitis when compared with placebo treatment. The authors also assessed mean 24-hour urinary cortisol/creatinine ratio and it was similar for the two treatment groups at baseline, end of treatment, and follow-up. The mean 24-hour urinary cortisol/creatinine ratio at the end of double-blind treatment decreased from the baseline value for both the BUD and the placebo groups but there was no significant difference, suggesting no HPA axis suppression effect.

A Turkish study looked at ocular side effects with intermittent use of intranasal BUD in children for >2 years.²⁸ There were 150 subjects between the ages of 8 and 15 years who used a mean BUD dose of 93.3 $\mu\text{g}/\text{day}$ with a mean total of 42.2 g of BUD during the observation period. The results were compared with a control group of 90 subjects. There was no significant difference between the BUD group and controls in visual acuity, intraocular pressure, central corneal thickness, Schirmer I test, tear breakup time, and corneal topography. Cataract formation, corneal ectasia, ocular hypertension, and dry eye were not observed in any of the patients.

BECLOMETHASONE DIPROPIONATE

In 2000, a 1-year safety study in children 6–9 years age detected growth suppression with aqueous BDP at 168 μg twice daily compared with placebo.²⁹ The same study failed to show any effect on HPA axis by assessing measurements of 8:00 A.M. basal cortisol concentrations and response to 25 μg cosyntropin stimulation. Since 2006, there have been no articles published on this agent looking at safety in the treatment of allergic rhinitis. Presently, in development is BDP in an HFA aerosol for allergic rhinitis. Results from studies evaluating efficacy and safety of BDP HFA aerosol should be available in the near future.

CONCLUSIONS

INSs are the gold standard for treatment of seasonal and perennial allergic rhinitis in the adult and pediatric population. The latest Practice Parameters on the Diagnosis and Management of Rhinitis by the major U.S. allergy organizations states INSs are the most effective medication class for allergic rhinitis.³⁰ In the Practice Parameter management algorithm, INSs can be used as a first-line therapy for all severities of allergic rhinitis. A worry with the use of these agents, especially on a long-term basis, is the possibility of topical and systemic adverse events. This concern led to the position paper opposing their possible move to OTC status in the United States. Since that paper, there have been a few new corticosteroid moieties released that have published safety data and further safety studies have been performed on some of the older agents. As a class, INSs have indicated a good safety profile over 15 years of clinical experience. The data is reassuring, especially with agents with very low systemic bioavailability. No evidence of damaging topical events to the nasal mucosa has been seen in studies up to 1 year. In general, there is no evidence of HPA axis suppression in 1-year studies. Most of these agents do not have a growth effect in children. There is no clear association of glaucoma or cataract development with INS use. Whether these agents can now be considered for OTC status is

not clear. Presently, they are available without a prescription in numerous countries, including England and Australia. It is very important to emphasize that there are no data on overuse of these agents, which could seriously impact their safety profile. Presently, there are no studies longer than 1 year. Another concern is the use of these medications for conditions other than allergic rhinitis by the general public. Although there are arguments that can be made on both sides of the question, it appears to be prudent that medical supervision should continue with INSs.

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