



Risk of Adverse Effects, Misdiagnosis, and Suboptimal Patient Care With the Use of Over-the-Counter Triamcinolone

Samuel L. Friedlander, MD^{*}; Wellington S. Tichenor, MD[†]; and David P. Skoner, MD[‡]

^{*} Case Western Reserve University/University Hospitals of Cleveland, Cleveland, Ohio

[†] Department of Medicine, New York Medical College, New York, New York

[‡] Department of Medicine, Allegheny General Hospital, Temple University School of Medicine, Philadelphia, Pennsylvania

ARTICLE INFO

Article history:

Received for publication May 31, 2013.

Received in revised form August 28, 2013.

Accepted for publication August 28, 2013.

The Food and Drug Administration's (FDA's) Nonprescription Drug Advisory Committee (NDAC) convened a meeting July 31, 2013, to discuss whether to recommend over-the-counter (OTC) access to triamcinolone acetonide nasal spray (Nasacort AQ; Sanofi-Aventis, Bridgewater, New Jersey) in adults and children 2 years or older. Organizations opposing this proposed change included the Allergy & Asthma Network Mothers of Asthmatics, American Academy of Allergy, Asthma, and Immunology (AAAAI), American College of Allergy, Asthma, and Immunology (ACAAI), American Academy of Otolaryngic Allergy, American Academy of Otolaryngology–Head and Neck Surgery, and American Academy of Pediatrics. Despite opposition from these lay and medical organizations, the NDAC voted to recommend that the FDA allow the switch from prescription to OTC nasal triamcinolone. However, as of the time of this writing, the final decision by the FDA has not been made. The FDA is not required to follow the recommendations of its advisory panels but usually does. Opponents of the OTC switch recognized the benefits of patient access to OTC medications. However, they expressed concern that the potential for misdiagnosis, inappropriate medication use, the lack of medical supervision, and inherent adverse effects when nasal corticosteroids are not monitored by appropriately trained medical professionals would make the risks of OTC use greater than the benefits.

Inhaled corticosteroids (ICSs) and intranasal corticosteroids (INSs) are guideline-recommended, first-line therapies for asthma and allergic rhinitis, respectively.^{1,2} However, their use confers significant risks in adults and children as listed in Table 1. The risks

are reviewed in a previous position statement of the Joint Task Force of the AAAAI and ACAAI.³ Since its publication in 2006, additional evidence has emerged from studies in children that further strengthen the arguments put forth in the position paper.

Via a combination of absorption from the respiratory and gastrointestinal tracts, corticosteroids can be detected in the blood after ICS and INS use and have been clearly linked to growth suppression in children.^{4,5} There is also evidence of dose dependency and variation in sensitivity and risk across individuals.

Most of the earlier studies were designed primarily to detect efficacy, with growth as a secondary outcome. However, the FDA also required manufacturers to conduct phase 4 studies with growth as the primary outcome. Most of those early phase 4 trials were poorly designed and flawed, but many revealed growth suppression of approximately 1 cm per year. Much evidence of growth suppression accrued, prompting the FDA to conduct a meeting in 1998 to review all growth data collected in trials of ICSs and INSs. The result was a class-labeling change for all ICSs and INSs, stating that they all can affect growth. Summarized, it states that the potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the availability of safe and effective noncorticosteroid treatment alternatives; it also recommends monitoring growth routinely using stadiometry and publishing recommendations on the proper conduct of future growth studies.⁶ To eliminate design flaws present in earlier studies, the guidance issued specific criteria regarding the study population (age and disease severity), study design (baseline period, 52-week masked treatment period, and a follow-period), and analysis.

In studies not designed according to the FDA guidance, there was evidence of a growth effect of all ICSs used for asthma. In contrast, there was evidence of growth suppression for only one INS, beclomethasone,⁴ and not for fluticasone propionate, mometasone furoate, or budesonide.^{7–9}

Subsequently, 3 ICS studies^{10–12} and 2 INS studies^{13,14} were conducted fully or largely in accordance with the FDA guidance.

Reprints: Samuel L. Friedlander, MD, Case Western Reserve University/University Hospitals of Cleveland, 34055 Solon Road, Suite 104, Solon, OH 44139; E-mail: Samuel.Friedlander@uhhospitals.org.

Disclosures: Dr. Friedlander has served as a speaker and on the advisory board of Teva and as a speaker for Sunovion. Dr. Tichenor has served on the advisory board of Sinucare. Dr. Skoner has received grants and research support from Novartis, Merck, GlaxoSmithKline, Teva, and Sunovion. He has served as a consultant for Merck and Sunovion, and has also served on the Speaker's Bureau for Merck, Novartis, and Sunovion.

Table 1

Association between inhaled and intranasal corticosteroids and adverse effects on growth, the ocular system, and local anatomical effects in children and adults

Study	No. of study participants	Medication	Duration	Adverse effect
Effects on Growth				
Skoner et al, ⁴ 2000	100	Beclomethasone INS, 168 µg twice daily	1 Year	Mean change in standing height of 5.0 cm (beclomethasone) vs 5.9 cm (placebo) ($P < .01$); growth suppressive effects across age and sex in 6- to 9-year-old prepubertal children
Kelly et al, ⁵ 2012	943	Budesonide ICS, 200 µg twice daily	4.3 Years, mean follow-up	Mean adult height decrease persisted as 1.2 cm lower in former 5- to 12-year-old children treated 4–6 years in CAMP ($P = .001$); adult height obtained in 90.6% of participants at mean age of 24.9 years
Allen et al, ⁷ 2002	150	Fluticasone INS, 200 µg daily	1 Year	No effects on growth velocity in prepubertal children ages 3.5–9 years; not designed according to the FDA guidance ⁶
Schenkel et al, ⁸ 2000	98	Mometasone furoate INS, 100 µg daily	1 Year	No suppression of growth in children ages 3–9 years; not designed according to the FDA guidance ⁶
Murphy et al, ⁹ 2006	229	Budesonide INS, 64 µg daily	1 Year	No suppression of growth velocity in children ages 4–8 years; not designed according to the FDA guidance ⁶
Skoner et al, ¹⁰ 2008	661	Ciclesonide ICS, 40 or 160 µg daily	1 Year	No suppression of growth velocity in children ages 5–8.5 years
Becker et al, 2006 ¹¹	360	Beclomethasone ICS twice daily	56 Weeks	Linear growth velocity 0.78 cm less than placebo ($P < .001$) in prepubertal children ages 6–9 years
Bensch et al, ¹² 2011	218	Flunisolide ICS, 180 µg twice daily	1 Year	No suppression in growth velocity in prepubertal children ages 4–10 years
GlaxoSmithKline ¹³	474	Fluticasone furoate INS, 110 µg daily	1 Year	Decreased growth velocity –0.27 cm per year (95% CI, –0.48 to –0.06); phase 4 long-term growth study in prepubertal children, mean age, 6.63 years
Sanofi-Aventis ¹⁴	299	Triamcinolone INS, 110 µg daily	1 Year	Decreased growth velocity –0.45 cm per year (95% CI, –0.78 to –0.11); phase 4 long-term growth study in prepubertal children ages 3–9 years
Ocular Effects				
Mitchell et al, ²⁰ 1999	3,654	ICS	Cross-sectional	Association between ICS and elevated intraocular pressure or glaucoma in 49- to 97-year-olds with family history of glaucoma
Garbe et al, 1998 ²¹	3,677 Cases and 21,868 controls	ICS	Case-control	OR for cataract extraction was 3.06 in ICS users >3 years in elders ≥70 years old
Smeeth et al, ²² 2003	15,479 Cases and 15,479 controls	INS	Case-control	Higher doses and longer duration of INS therapy was associated with risk of cataract
Adverse Local Effects				
Dosen and Haye, ²⁸ 2007	197	INS	Open, prospective	Nasal steroid and decongestant sprays were the cause of septal perforation in 28.4%, particularly in females
Cervin and Andersson, ²⁹ 1998	32	INS	Case report	Most common risk factor in septal perforation cases were due to INSs (11 of 32 cases; 10 were in females); concluded septal perforations were underreported

Abbreviations: CAMP, Childhood Asthma Management Program; CI, confidence interval; FDA, Food and Drug Administration; ICS, inhaled corticosteroid; INS, intranasal corticosteroid; OR, odds ratio.

Two of the 3 ICS studies had negative results (no growth effect). However, rather than concluding that the third ICS (ciclesonide) had no growth effect,¹⁰ the FDA stated that conclusions could not be drawn from this study because adherence could not be ensured.¹⁵ Adherence in this trial was assessed using standard methods (diary and canister weights) and was similar to that in previously published growth studies. Of the 2 INS studies, both reported growth suppression (fluticasone furoate and triamcinolone).^{13,14} Collectively, these results suggest that all INSs, which previously suggested no growth effect in less optimally designed studies, should be required to undergo testing for growth effects using the same rigorous design recommended in the FDA guidance.¹⁶

Before the availability of the results of the triamcinolone and fluticasone furoate INS studies, INSs were assumed to have no effect on growth based on the use of an excessive dose in the positive beclomethasone study, high oral bioavailability of beclomethasone relative to other INSs,¹⁷ and negative studies for the INSs fluticasone, mometasone, and budesonide. However, on the basis of the position the FDA took on the negative ciclesonide ICS study results, conclusions should not be drawn from these 3 INS studies with negative results because adherence could not be ensured. It has become clear that when better science is applied in studies designed with growth as a primary outcome, growth suppression can be detected. Even this effect was deemed insignificant until recently because evidence

of catch-up growth after discontinuation of ICS therapy was observed in some of the studies.¹⁸ This finding was supported by a previous study that suggested that there was no effect of long-term ICS treatment in children on final adult height.¹⁹ In contrast, in a study with better design, long-term follow-up of a large number of 5- to 12-year-old children treated for 4 to 6 years with low-dose ICSs in the Childhood Asthma Management Program revealed a small but significant effect on final adult height.⁵ If INSs are made available OTC, long-term and appropriate monitoring of dose and height by a trained professional will not be likely and could potentially result in growth suppression in a large number of children.

Analyzing data from INSs and ICSs, investigators have found that some adults and children are more sensitive than others to the adverse effects. Therefore, mean data analyses cannot be reassuring. One must consider the consequences of OTC use of steroids when extrapolated to the general population. What about individuals with asthma or atopic dermatitis who are already using corticosteroids and then add an OTC INS for allergic rhinitis symptoms? To date, no studies have adequately evaluated the effect of cumulative dosages of inhaled, intranasal, and dermatologic steroids on growth. However, effects larger than those seen in INS or ICS studies may be expected. Further, the adverse effects of corticosteroids, including on bone resorption and growth, may not present themselves for years. Although short-term data may be

reassuring, there is a paucity of long-term data. Unmonitored and potentially greater use of INSSs has excessive risk.

Ocular adverse effects are concerning because topical corticosteroids may elevate intraocular pressure and be associated with cataract formation. In the cross-sectional, population-based Blue Mountain Eye Study, there was an association between ICS use and glaucoma or elevated intraocular pressure in people with a family history of glaucoma (odds ratio, 2.5; 95% confidence interval [CI], 1.2–5.8).²⁰ Older individuals may be at particular risk of cataract development. The Quebec Universal Health Insurance Program for the Elderly evaluated 3,677 elderly patients who underwent cataract removal compared with 21,868 randomly matched controls.²¹ The use of ICSs for 3 or more years was associated with a 3.06-fold increase of cataract extraction (95% CI, 1.53–6.13).

Similar findings occurred in the General Practice Research Database in the United Kingdom when studying intranasal steroids.²² There was a dose-dependent relationship with both larger corticosteroid doses and increased numbers of prescriptions increasing the risk of cataract. The odds ratio was 1.33 (95% CI, 1.21–1.45) for those receiving intranasal steroids with insufficient power to detect differences among the individual brands of steroids used. These larger, population-based studies demonstrate that topical corticosteroids can be a risk factor for posterior subcapsular cataracts.

Use of INSSs can also increase the risk of osteoporosis. According to a World Health Organization review paper, “all considered inhaled corticosteroids...appear to affect bone metabolism in adults and, as a consequence, markers of bone mineral density...Triamcinolone acetonide led to the most deleterious effect.”²³ A review of studies published between 1966 and January 2004 was conducted to evaluate the effects of INSSs on bone health.²⁴ The review noted that several of the larger studies found that ICSs caused a dose-related reduction in bone mineral density. In addition, 3 cross-sectional studies found a dose-related increase in fractures in people taking an ICS compared with controls. The review concluded that “it is not clear whether there is a threshold dose for adverse events...Strategies are needed to reduce the systemic effects of inhaled corticosteroids.”²⁴

In adults, nasal steroids could adversely affect bone metabolism. Studies of adults taking ICSs found a reduction of osteocalcin, a marker of bone formation that correlates with a lower growth hormone peak response.²⁵ Because of the paucity of data of INSSs on bone and ocular complications, it is not known whether this route of administration is safe in an unmonitored setting.

Drug interactions are also a concern, particularly if medications are dispensed without physician or pharmacist guidance. Although less commonly seen because of current oversight of triamcinolone, drug-drug interactions can occur. According to Micromedex, caution is required when mixing triamcinolone with various medications. With interactions listed in parentheses, this includes the following: the antiviral ritonavir (increased corticosteroid levels), antibacterials including fluoroquinolones (increased risk of tendon rupture), the antifungal itraconazole (increased corticosteroid levels), the dermatologic medicine tretinoin (decreased tretinoin efficacy), herbal medications such as *Echinacea* and ma huang (both with decreased corticosteroid effectiveness) and even licorice (increased corticosteroid levels).²⁶

Patients often misuse OTC topical nasal decongestants. Should the FDA extend the OTC market to INSSs, there is a potential for a significant increase in complications as a result of abuse of INSSs. This can occur because of patient misperception that OTC medications are safer than prescription ones because they are readily available even in young children. Because individuals may be familiar with the immediate relief from topical decongestants, many patients may unrealistically expect nasal sprays to work immediately. This could potentially lead to patients using many times the

expected therapeutic dose of INSSs and the potential consequences, including septal perforations²⁷ and overdosing dangers.

The adverse local effects of INSSs are well known and could present particular concern to patients and families. These effects include epistaxis, nasal irritation, changes in taste and smell, *Candida* infection, contact dermatitis, and septal perforation.^{3,28,29} A medical professional is necessary to perform nasal examinations to evaluate whether damage is occurring. Also, a health care professional is best positioned to advise their patients properly on appropriate use of techniques and treatment of these known and expected complications.

The FDA proposes that the risks identified above can be modified sufficiently by package labeling that informs the consumer. However, risk cannot be eliminated or sufficiently mitigated by labeling alone. Multiple studies have documented significant risks to children from a parent who does not read or comprehend a package label because of lack of time or health literacy, respectively.^{30,31}

On a clinical basis, INSSs and ICSs must be used in a supervised, controlled environment. Both medical professional societies and patient advocacy groups agree it is essential that nasal steroids are prescribed by a clinician. In doing so, medical professionals may continually engage in discussions of potential benefits and risks and assure patients and parents that they will make every effort to use the lowest possible ICS dose in the long term. The potential for misdiagnosis or misuse by laypersons could potentially delay treatment of other conditions. In addition, clinicians can work closely with patients to ensure that risks are minimized through monitoring. They can develop a partnership for long-term, routine monitoring of growth using stadiometry, particularly in children.³² The correct monitoring and management of local and systemic adverse effects can only be performed in a health care setting. With these considerations, we are concerned that the OTC availability of INSSs could result in inappropriate and potentially unsafe use and lead to adverse effects, misdiagnosis, and suboptimal patient care outcomes.

Acknowledgments

We gratefully acknowledge writing assistance and guidance from Linda Cox, MD, and Stanley Fineman, MD, MBA.

References

- [1] Expert Panel Report 3 (EPR-3). Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. *J Allergy Clin Immunol*. 2007;120:S94–S138.
- [2] Wallace D, Dykewicz M, Bernstein D, et al. The diagnosis and management of rhinitis: an updated practice parameter. *J Allergy Clin Immunol*. 2008;122:S1–S84.
- [3] 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*. 2006;96:514–525.
- [4] Skoner DP, Rachelefsky GS, Meltzer EO, et al. Detection of growth suppression in children during treatment with intranasal beclomethasone dipropionate. *Pediatrics*. 2000;105:E23.
- [5] Kelly HW, Sternberg AL, Lescher R, et al. Effect of inhaled glucocorticoids in childhood on adult height. *N Engl J Med*. 2012;367:904–912.
- [6] Food and Drug Administration. Orally inhaled and intranasal corticosteroids: evaluation of the effects on growth in children. 2007 [cited 2010 April 14]. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071968.pdf. Accessed July 24, 2013.
- [7] Allen DB, Meltzer EO, Lemanske RF Jr, et al. No growth suppression in children treated with the maximum recommended dose of fluticasone propionate aqueous nasal spray for one year. *Allergy Asthma Proc*. 2002;23:407–413.
- [8] Schenkel EJ, Skoner DP, Bronsky EA, et al. Absence of growth retardation in children with perennial allergic rhinitis after one year of treatment with mometasone furoate aqueous nasal spray. *Pediatrics*. 2000;105:E22.
- [9] Murphy K, Uryniak T, Simpson B, O'Dowd L. Growth velocity in children with perennial allergic rhinitis treated with budesonide aqueous nasal spray. *Ann Allergy Asthma Immunol*. 2006;96:723–730.
- [10] Skoner DP, Maspero J, Banerji D. Ciclesonide Pediatric Growth Study Group. Assessment of the long-term safety of inhaled ciclesonide on growth in children with asthma. *Pediatrics*. 2008;121:e1–e14.

- [11] Becker AB, Kuznetsova O, Vermeulen J, et al. Linear growth in prepubertal asthmatic children treated with montelukast, beclomethasone, or placebo: a 56-week randomized double-blind study. *Ann Allergy Asthma Immunol*. 2006;96:800–807.
- [12] Bensch GW, Greos LS, Gawchik S, Kpamegan E, Newman KB. Linear growth and bone maturation are unaffected by 1 year of therapy with inhaled fluticasone hydrofluoroalkane in prepubescent children with mild persistent asthma: a randomized, double-blind, placebo-controlled trial. *Annals Allergy Asthma Immunol*. 2011;107:323–329.
- [13] ClinicalTrials.gov Website, U.S. National Institutes of Health. Phase 4 Fluticasone Furoate Nasal Spray (VERAMYST) Long Term Pediatric Growth Study. Updated May 16, 2013. <http://clinicaltrials.gov/ct2/show/results/NCT00570492?term=allergic+rhinitis&intr=fluticasone&rank=24§=X36015>. Accessed August 26, 2013.
- [14] Clinical Trials.gov Website, U.S. National Institutes of Health. Study of Triamcinolone Acetonide on the Growth Velocity of Children, Ages 3 to 9, With Perennial Allergic Rhinitis (PAR). Updated August 7, 2012. <http://clinicaltrials.gov/ct2/show/results/NCT00449072?term=phase+4+triamcinolone+growth&rank=1§=X6015#outcome1>. Accessed August 26, 2013.
- [15] Malozowski S. Assessment of the long-term safety of inhaled ciclesonide on growth in children with asthma. *Pediatrics*. 2008;122:213.
- [16] Bartholow A, Deshaies D, Skoner J, Skoner D. A critical review of the effects of inhaled corticosteroids on growth. *Allergy Asthma Proc*. 2013;34:391–407.
- [17] Daley-Yates PT, Price AC, Sisson JR, Pereira A, Dallow N. Beclomethasone dipropionate: absolute bioavailability, pharmacokinetics and metabolism following intravenous, oral, intranasal and inhaled administration in man. *Br J Clin Pharmacol*. 2001;51:400–409.
- [18] Guilbert TW, Morgan WJ, Zeiger RS, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med*. 2006;354:1985–1997.
- [19] Agertoft L, Pedersen S. Effect of long-term treatment with inhaled budesonide on adult height in children with asthma. *N Engl J Med*. 2000;343:1064–1069.
- [20] Mitchell P, Cumming RG, Mackey DA. Inhaled corticosteroids, family history, and risk of glaucoma. *Ophthalmology*. 1999;106:2301–2306.
- [21] Garbe E, Suissa S, LeLorier J. Association of inhaled corticosteroid use with cataract extraction in elderly patients. *JAMA*. 1998;280:539–543.
- [22] Smeeth L, Boullis M, Hubbard R, Fletcher AE. A population based case-control study of cataract and inhaled corticosteroids. *Br J Ophthalmol*. 2003;87:1247–1251.
- [23] Richy F, Bousquet J, Ehrlich GE, et al. Inhaled corticosteroids effects on bone in asthmatic and COPD patients: a quantitative systematic review. *Osteoporos Int*. 2003;14:179–190.
- [24] Mortimer KJ, Harrison TW, Tattersfield AE. Effects of inhaled corticosteroids on bone. *Ann Allergy Asthma Immunol*. 2005;94:15–21.
- [25] Malerba M, Bossoni S, Radaeli A, et al. Growth hormone response to growth hormone-releasing hormone is reduced in adult asthmatic patients receiving long-term inhaled corticosteroid treatment. *Chest*. 2005;127:515–521.
- [26] Triamcinolone. In: DrugPoints® System [Internet database]. Greenwood Village, CO: Thomson Healthcare. Updated periodically.
- [27] Lanier B, Kai G, Marple B, Wall GM. Pathophysiology and progression of nasal septal perforation. *Ann Allergy Asthma Immunol*. 2007;99:473–479.
- [28] Dosen LK, Haye R. Nasal septal perforation 1981–2005: changes in etiology, gender and size. *BMC Ear Nose Throat Disord*. 2007;7:1.
- [29] Cervin A, Andersson M. Intranasal steroids and septum perforation—an overlooked complication? a description of the course of events and a discussion of the causes. *Rhinology*. 1998;36:128–132.
- [30] Lazarus SG, Lanski SL, Smith AS, Simon HK. Cold preparation use in young children after FDA warnings: do concerns still exist? *Clin Pediatr (Phila)*. 2013; 52:534–539.
- [31] Yin HS, Mendelsohn AL, Nagin P, van Schaick L, Cerra ME, Dreyer BP. Use of active ingredient information for low socioeconomic status parents' decision-making regarding cough and cold medications: role of health literacy. *Acad Pediatr*. 2013;13:229–235.
- [32] Skoner DP. Balancing safety and efficacy in pediatric asthma management. *Pediatrics*. 2002;109:381–392.