Inhaled and intranasal corticosteroids (ICS and INS) are guideline-recommended, first-line therapies for asthma and allergic rhinitis, respectively.(1, 2) There are significant risks in adults and children as well, summarized in a previous position statement of the Joint Task Force of the American Academy of Allergy, Asthma & Immunology and American College of Allergy, Asthma & Immunology.(3) Since its publication in 2006, additional new 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 evidence of dose-relatedness 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 IV studies with growth as the primary outcome. Most of those early Phase IV trials were poorly designed and flawed, but many produced positive results (growth suppression of about 1 cm/year). Much evidence for growth suppression accrued, prompting the FDA to conduct a meeting in 1998 to review all growth data collected in trials of ICS and INS. The result was a class-labeling change for all ICS and INS stating they all can affect growth; summarized; it states the potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the availability of safe and effective non-corticosteroid treatment alternatives, a recommendation for monitoring of growth routinely using stadiometry, and the publication of a guidance on the proper conduct of future growth studies. (6) In order to eliminate design flaws present in earlier studies, the guidance issued specific

recommendations about the study population (age, disease severity), study design (baseline period, 52-week blinded 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 ICS used for asthma. In contrast, there was evidence of growth suppression for only one INS, beclomethasone,(4) and not for FP, MF and BUD.(7-9) Subsequently, there were three ICS studies (10-12) and two INS studies conducted fully or largely in accordance with the FDA guidance. Two of the three ICS studies were negative (no growth effect). However, rather than concluding that one of the ICS (ciclesonide) had no growth effect (10) the FDA concluded that conclusions could not be drawn from this study because compliance could not be assured.(13) Compliance in this trial was assessed using standard methods (diary and canister weights) and was similar to that in previously-published growth studies. Of the two INS studies, both yielded a positive result .(TAA and FF) (14) (15) Collectively, these results suggest that all INS, which previously produced 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.

Prior to the availability of the results of the TAA and FF INS studies, INS were assumed to have no effect on growth based on the use of an excessive dose in the positive BDP study, high oral bioavailability of BDP relative to other INS, (16) and negative studies for the INS FP, MF and BUD. However, based on the position FDA took on the negative ciclesonide ICS study, conclusions should not be drawn from these three negative INS studies because compliance could not be assured. 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, since evidence of “catch-up” growth after ICS discontinuation was observed in some of the studies. (17) This was supported by an earlier study that suggested that there was no effect of long-term ICS treatment in children on final adult height.

(18) In contrast, in a study with better study design, long-term follow-up of a large number of 5-12 year old children treated for 4-6 years with low-dose ICS in the Childhood Asthma Management Program showed a small, but significant effect on final adult height. (5)

On a clinical basis, INS and ICS must be used in a supervised, controlled environment. It is essential that nasal steroids are prescribed by a clinicians, so that they may continually engage in discussions of potential benefits and risks, and assure the parents that he/she will make every effort to use the lowest ICS dose possible long-term. In addition, clinicians can work closely with parents to ensure that risks are miminized through monitoring, and develop a partnership for long-term, routine monitoring of growth using stadiometry.(19)

What about children with asthma, who are already using ICS, and whose parents place them on OTC INS for allergic rhinitis symptoms? To date, no studies have adequately evaluated the effect of combined INS and ICS treatment on growth. However, effects possibly larger than those seen in INS or ICS studies would be expected.

If INS are made available OTC, long-term and appropriate monitoring of dose and height by a trained professional will not be possible and will undoubtedly and unnecessarily cause growth suppression in a large number of children.

Analyzing data from INS and ICS, we learn that some adults and children are more sensitive to the adverse effects. Therefore analyses of mean data cannot be reassuring. One must consider the consequences of over-the-counter use of steroids when extrapolated to the general population. Many allergic individuals have concomitant asthma and atopic dermatitis; thus, they may be exposed to cumulative dosages of inhaled, intranasal, and dermatological steroids. 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 INS has excessive risk.

Ocular side effects are concerning as 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 (OR 2.5, 95% 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 elders who underwent cataract removal compared with 21,868 randomly-matched controls.(21) The use of ICS 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 for those receiving intranasal steroids with insufficient power to detect differences between the types of steroids used. These larger, population-based studies demonstrate that topical corticosteroids can be a risk factor for posterior subcapsular cataracts.

Use of INS 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 INS on bone health. (24) The review noted that several of the larger studies showed that inhaled corticosteroids cause a dose-related reduction in bone mineral density. In addition, three-cross sectional studies found a dose-related increase in fractures in people taking an inhaled corticosteroid 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 inhaled corticosteroids found a reduction of osteocalcin, a marker of bone formation that correlates with a lower growth hormone peak response. (25) Due to the paucity of data of intranasal corticosteroids on bone and ocular complications, we cannot state this route of administration is safe in an unmonitored setting.

The adverse local effects of INS are well-known and could present particular concern to patients and families. These include epistaxis, nasal irritation, changes in taste and smell, Candida infection, contact dermatitis, and septal perforation. (3) A medical professional is necessary to perform nasal examinations to evaluate if damage is occurring. Also, a Healthcare Provider is best positioned to advise their patients properly on appropriate usage techniques and treatment of these known and expected complications.

The correct monitoring and management of local and systemic adverse effects can only be done in a healthcare setting. With these considerations, we recommend that INS NOT be approved for over-the-counter usage.

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