Inhaled Corticosteroids and Growth: Still an Issue after All These Years

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"Growing up with asthma, vivid childhood memories include the rancid taste of daily potassium iodide expectorant, buzz of ephedrine inhalers and aminophylline, and emergency epinephrine injections administered by my pediatrician father. The issue about inhaled corticosteroids and growth, in some ways, comes down to this: Would I have traded all of that for more effective treatment that I knew might slow my growth and cost me 1 or 2 cm in eventual height?"

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Inhaled corticosteroids (ICSs) are the most effective treatment for persistent asthma. ICSs currently approved for children with asthma include beclomethasone dipropionate, budesonide, fluticasone propionate, mometasone furoate, and ciclesonide. Previous case reports[1] and prospective trials[2-6] have led to the following conventional, but imperfect, wisdom that moderate-dose continuous ICS treatment: (1) can cause dose-dependent slowing of growth in prepubertal children; (2) does not slow normally rapid early life and adolescent growth; (3) does not diminish adult height attainment; and (4) will less frequently slow growth as ICSs with oral bioavailability are phased out.

The issue of ICSs and growth is not of concern because the general risks-vs-benefit analysis of ICSs has changed. Rather, drug formulations, delivery devices, characteristics of patients receiving ICS, and data on the effects of ICS on growth during early life[7] and adolescence[8] and on adult height[9] have changed, so that asthma therapy counseling based on previous observations may include misperceptions and warrants reexamination. A case presentation of a child referred for evaluation of slow growth (**Figure 1**) illustrates how factors not addressed in previous ICS growth studies influence an individual's risk for ICS-mediated growth suppression in clinical practice. Awareness of these newer factors will aid proper prescribing, monitoring, and anticipatory guidance, balancing the magnitude of growth suppression risk against the importance of asthma control.

Concern regarding the effects of ICS on growth is warranted because glucocorticoids inhibit linear growth in multiple ways (**Figure 2**).[10] Mechanisms by which glucocorticoids inhibit growth include blunting of pulsatile growth hormone release through augmentation of hypothalamic somatostatin tone, down-regulation of hepatic and growth plate growth hormone receptor expression, inhibition of insulin-like growth factor 1 bioactivity and osteoblast activity, acceleration of chondrocyte apoptosis, and suppression of collagen synthesis and adrenal androgen production. Furthermore, ICS compounds are extraordinarily potent glucocorticoids, considered to have 8-23 times the potency of dexamethasone, according to glucocorticoid receptor binding affinity.[11] Relative topical potencies are mometasone > fluticasone propionate > ciclesonide > beclomethasone monoproprionate (active form of beclomethasone diproprionate) > budesonide.[12,13] As a result, small amounts of systemically absorbed ICS can produce a significant glucocorticoid effect capable of suppressing childhood growth.

Misperception: The Risk of Growth Inhibition by ICS Is Reduced by Formulation/Device Changes that Increase the Efficiency of ICS Delivery to Small Airways.

Observation: Increased Delivery of ICS to Small Airways Increases ICS Delivery to Systemic Circulation and, Unless Doses Are Titrated Downward Proportionately, Increases Growth-Suppressing Effects.

The systemic ICS burden represents the sum of (essentially complete) absorption of drug delivered to the lung (therapeutic fraction) plus the intestinal absorption of swallowed drug (nontherapeutic fraction) that escapes hepatic first-pass inactivation (**Figure 3**) and is distinct for each ICS drug/device. Importantly, however, for all available ICSs, the most efficient path to the systemic circulation is via the lungs, so that a change in the formulation or delivery device for an ICS that improves drug delivery to the lungs also increases systemic bioavailability and the risk of systemic effects unless commensurate dosage reductions are made.

Growth studies leading to the conventional wisdom described above were conducted with ICS dosages defined as "moderate" at the time (eg, ~400 μg/day of beclomethasone,[3,4] 200-400 μg/day of budesonide,[6,14] ~200 μg/day of fluticasone propionate[5]) and delivered via either a chlorofluorocarbon (CFC)-propelled metered dose inhaler or a dry powder inhaler. In response to the 2010 prohibition of CFC propellants by the US Food and Drug Administration (FDA) owing to environmental concerns, manufacturers turned to hydrofluoroalkane (HFA) propellants, which, because of greater solubility, allow the formulation of

ADHD	Attention deficit hyperactivity disorder
CFC	Chlorofluorocarbon
FDA	Food and Drug Administration
HFA	Hydrofluoroalkane
ICS	Inhaled corticosteroid
SSRI	Selective serotonin reuptake inhibitor

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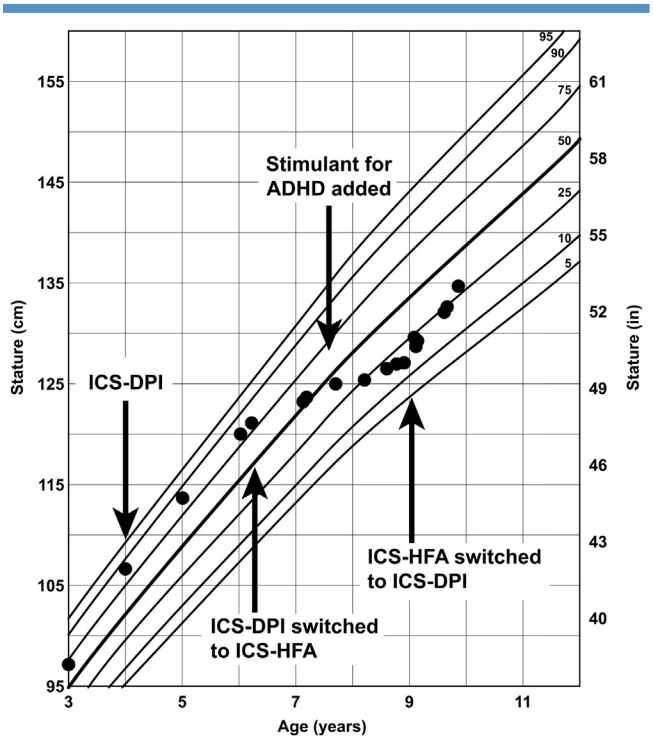

Figure 1. Growth curve for a boy referred for evaluation of growth failure at age 8.8 years. At age 4 years asthma was diagnosed and treated with twice-daily dry powder ICS plus a long-acting beta agonist. At age 6.3 years ICS treatment was changed to twice-daily equal dosages of ICS delivered via an HFA inhaler, which growth rate slowed from 6.5 to ~3 cm/year. At age 7.5 years, stimulant medication for treatment of ADHD was added and growth rate declined to ~2 cm/year during the ensuing 18 months of combined ICS-HFA plus stimulant treatment. Transition of ICS treatment back to equal dosages of dry powder ICS plus a long-acting beta agonist was accompanied by an increase in growth rate. *DPI*, dry powder inhaler.

compounds as a solution (not a suspension, like CFCs) with smaller and more consistent particle size, key attributes that enable some HFA-propelled devices to deliver drugs more efficiently and evenly to large, intermediate, and small airways at the same nominal dosage.[15] (**Figure 3**) For fluticasone propionate, the transition from a CFC to an HFA propellant device does not involve a change in particle size and thus does not significantly alter lung or systemic circulation delivery.[16] In contrast, a beclomethasone HFA metered dose inhaler delivers >50% of a dispensed dose to the lung using a solution with extrafine particles, compared with only 4%-8% delivered by a CFC metered dose inhaler.[17,18] Accordingly, studies have shown that delivery of beclomethasone via an HFA inhaler not only produces a clinically equivalent therapeutic response at 35%-50% of the dose delivered via a CFC inhaler,[19] but also leads to ~70% higher serum beclomethasone levels at doses equal to those delivered via a CFC inhaler.[20] Thus, it is not surprising that 1-year growth in children is slowed by a mean of 1.1 cm during continuous treatment with a very low dose of 40 μg HFA beclomethasone twice daily (ie, approximately 20% of the nominal dose used in previous CFC beclomethasone growth studies) compared with placebo.[21]

The phase-out of CFC propellants also accelerated the development of multidose dry powder inhalers, which vary markedly in their ability to generate fine ICS particles (<5 μm) capable of small airway deposition. For instance, dry powder budesonide inhaled from a Turbuhaler (AstraZeneca, Lund, Sweden) shows 30% deposition,[22] compared with just 8% for dry powder fluticasone propionate inhaled from a Diskus (GlaxoSmithKline, London, United Kingdom). Accordingly, despite budesonide's much lower glucocorticoid receptor binding affinity compared with fluticasone propionate,[13] budesonide treatment is more suppressive of overnight hourly cortisol concentrations than fluticasone propionate on a microgram-for-microgram prescribed dose when each drug is delivered by a dry powder inhaler.[23] Furthermore, because lung deposition of fluticasone propionate delivered by HFA metered dose inhalation is at least twice that delivered by dry powder inhalation (~16% vs ~8%), a dose of dry powder fluticasone propionate that has minimal systemic effects could have growth suppressive effects when administered by HFA metered dose inhalation (**Figure 1**).[24] In summary, enhanced small particle ICS lung delivery resulting from a change in either drug formulation (eg, beclomethasone) or delivery device (eg, fluticasone propionate dry powder inhaler to metered dose inhaler) should alert prescribers to possible growth suppression effects at dosages historically deemed "low" and "safe" (eg, beclomethasone 40-80 μg twice daily) or when the equivalent nominal dosage of an ICS is prescribed using a different device (eg, fluticasone propionate 100 μg twice daily delivered by dry powder inhaler vs HFA inhaler) (**Figure 3**).

Misperception: Occurrences of ICS-Mediated Growth Suppression Would Diminish with Avoidance of ICSs with Significant Bioavailability of Swallowed Drug.

Observation: Prescriptions Are Increasing for ICSs with Effects on Growth Augmented by Bioavailability of the Swallowed Drug.

Assuming titration to the lowest effective dose for asthma control, very low oral bioavailability reduces the risk for systemic adverse effects by limiting the access of ICSs to the systemic circulation solely through the target organ (lung), with no additional drug absorption through a nontherapeutic (intestinal) route. This is important because percentages of swallowed ICSs absorbed into systemic circulation vary widely: beclomethasone, 25%-40%[25,26]; budesonide, 10%[22]; and fluticasone propionate, mometasone, and ciclesonide, ≤1%.[16] These differences help explain the variations in first-year growth suppression observed during treatment with dosages of various ICSs estimated as clinically equivalent at controlling asthma: −1.5 cm/year for beclomethasone 400 μg/day,[2,3]