

Factors influencing growth effects of inhaled corticosteroids in children

Peter M. Wolfgram, MD,^a and David B. Allen, MD^b *Milwaukee and Madison, Wis*

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Activity Objectives

1. To understand growth-suppressing actions of glucocorticoids.
2. To understand factors affecting growth during inhaled corticosteroid (ICS) treatment, including age, drug choice, dosing frequency, and adherence.
3. To identify steps to decrease the risk of growth attenuation from ICS therapy.

Recognition of Commercial Support: This CME activity has not received external commercial support.

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The authors declare that they have no relevant conflicts of interest. J. T. Li has consulted for Abbott.

Key words: Growth suppression, asthma, methylphenidate, inhaled corticosteroids, children

CLINICAL VIGNETTE

A 9-year, 10-month-old boy treated with inhaled corticosteroids (ICSs) for asthma returned to the endocrine clinic for follow-up of linear growth. He began taking Advair Diskus

(100/50; GlaxoSmithKline, Research Triangle Park, NC), 1 inhalation twice daily, when he was 4 years old. During treatment with Advair Diskus, he grew steadily along his previous height trajectory at between the 75th and 90th percentiles (Fig 1). Around 6 years of age, treatment was changed to Advair hydrofluoroalkane (HFA; 45/21), 2 inhalations twice daily. Repeat measurement 12 months later revealed that his height percentile had fallen to the 50th percentile. At that time, methylphenidate was started for treatment of

From ^athe Department of Pediatrics, Medical College of Wisconsin, Milwaukee, and ^bthe Department of Pediatrics, University of Wisconsin School of Medicine & Public Health, Madison.

Received for publication July 17, 2015; revised September 8, 2015; accepted for publication September 17, 2015.

Corresponding author: David B. Allen, MD, Department of Pediatrics, University of Wisconsin, H4/448 Clinical Science Center, 600 Highland Ave, Madison, WI 53792-4108. E-mail: dallen@wisc.edu.

0091-6749/\$36.00

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<http://dx.doi.org/10.1016/j.jaci.2015.09.039>

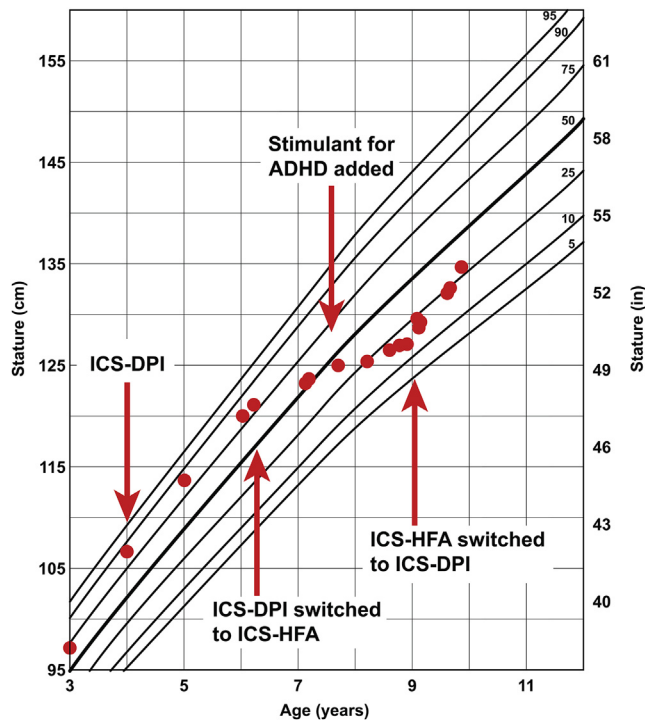


FIG 1. Growth history of the clinical vignette's subject reflects ICS delivery device adjustments and addition of a stimulant for ADHD.

attention-deficit disorder. During the subsequent 2 years, while receiving methylphenidate and Advair HFA, his asthma was well controlled, but his height percentile continued to decrease to the 15th to 25th percentile. After treatment was switched back to Advair Diskus (100/50), 1 inhalation twice daily, his growth velocity promptly improved, and he began trending toward his previous height percentile (Fig 1).

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REVIEW

ICS therapy helps children with asthma to live healthier and more active lives; however, the potential growth-suppressing effects of ICSs continue to concern prescribers and families and to spur research efforts to develop drug device options that more completely separate therapeutic effects from unwanted systemic effects. Nevertheless, with regular reassessment of asthma control and growth rate coupled with consistent efforts toward dose reduction to the lowest effective dose, ICSs offer the provider the best available option for tailoring asthma therapy to optimize disease control and patient outcomes.

Glucocorticoids suppress the growth axis at multiple levels

Glucocorticoids in excess of normal physiologic production (eg, systemically absorbed ICSs) can suppress linear growth through interruption of the growth hormone (GH) axis. Centrally, glucocorticoids facilitate pituitary synthesis of GH but diminish pulsatile GH secretion. Peripherally, ICSs reduce GH receptor expression in growth plates and liver and reduce the production and bioactivity of its secondary messenger, insulin-like growth factor 1. Without a normal GH/insulin-like growth factor 1 effect, growth plate proliferation of chondrocytes, cartilage matrix production, and osteoblast activity are all diminished, and chondrocyte apoptosis is increased.^{E1} Use of stimulant medications for attention-deficit hyperactivity disorder (ADHD), selective serotonin reuptake inhibitors (SSRIs) for mood disorders, and poor patient health increase the potential for growth attenuation. Additionally, before peaking in the pubertal years, GH secretion is low in the late prepubertal years, and children predisposed to later puberty can be more sensitive to the inhibitory effects of ICSs.

Drug delivery device characteristics affect systemic ICS exposure

ICS potency, as assessed by glucocorticoid receptor affinity, greatly exceeds that of cortisol and varies with the ICS agent. Other important pharmacodynamic and pharmacokinetic aspects that affect ICS bioactivity include percentage of drug delivery to the lungs, activity of the portion absorbed into the systemic circulation through the lungs, oral bioavailability of swallowed ICSs, efficiency of systemic clearance, and lipophilicity (which influences ICS volume of distribution, clearance, and half-life). Clinically, linear growth functions as a very sensitive indicator of the systemic effects of ICSs, although suppression of basal cortisol production provides even more sensitive evidence of the presence of circulating ICSs. Growth studies demonstrating the dose-dependent effect of ICSs on growth have generally focused on children during late prepubescent years; however, recent studies indicate that growth effects of similar magnitude can be seen in much younger children when drug device treatments that enhance ICS delivery are used.^{E2}

Reduction in ICS particle size is a relatively recent and key medication modification with important ramifications for lung delivery and systemic absorption and therefore potential systemic effects. Specifically, ICS formulations with smaller mass median aerodynamic diameters (MMADs), as is the case with smaller HFA drug particles relative to larger chlorofluorocarbon (CFC) drug particles, show improved therapeutic effects caused by more efficient delivery to the small airways; however, enhanced lung delivery also leads to increased systemic bioavailability and with it potential for growth suppression and other adverse effects. When

comparing metered-dose inhaler (MDI) preparations, HFA-based beclomethasone dipropionate (BDP) led to plasma BDP metabolite concentrations approximately 3-fold greater than those with CFC-based BDP therapy at lower or similar nominal doses.^{E3} It is important for providers to consider the potential clinical significance of HFA formulations versus previous CFC formulations because even at the lowest labeled dose of 40 µg of HFA-based BDP twice daily, growth rates were 1.1 cm lower (compared with placebo) over 44 weeks in 5- to 18-year-olds with mild persistent asthma. However, importantly, the rate of exacerbations in the daily BDP therapy was half that of the placebo group.^{E4} These data illustrate that, in the midst of optimizing asthma treatment, careful surveillance is key to detect early and avoid prolonged adverse growth effects caused by delivery device changes and drug reformulations.

With even larger MMADs than CFC-based particles and less efficient device delivery than MDIs, dry powder inhalers (DPI) exhibit lower systemic bioactivity. For example, DPI-administered fluticasone propionate, 100 µg twice daily, given to prepubertal children had a minimal effect on growth velocity; however, 2- to 3-year-old toddlers receiving only 88 µg of fluticasone propionate twice daily through CFC-based MDIs showed growth attenuation, which was greatest in the smallest and youngest participants.^{E2,E5} The toddler study suggests the need to continually reassess patients' therapeutic ICS requirements, with particular attention to smaller patients with more efficient modes of ICS delivery, such as MDIs. The findings in growth attenuation are complemented by evidence that greater suppression of cortisol occurs with fluticasone delivered through an MDI compared with that delivered through a DPI.^{E6}

Theoretically, a prime example of an ICS agent designed to avoid systemic bioactivity is ciclesonide, a prodrug with a lower MMAD, and conversion in the lung to the active metabolite (des-ciclesonide) focuses the ICS effect to the lungs and facilitates once daily dosing. Furthermore, in contrast to another prodrug, BDP, des-ciclesonide undergoes greater than 99% hepatic clearance, thus minimizing steroid absorption of a nontherapeutic glucocorticoid that lacks therapeutic benefit. Although these characteristics would predict a more favorable growth safety profile, a recent Cochrane review evaluating ciclesonide, budesonide, and fluticasone research data cautioned that further longer-term studies and studies of superiority are required to verify the benefits and risks before ciclesonide is recommended as standard clinical practice.^{E7}

ICS dosing frequency and adherence influence risk for growth suppression

For a number of reasons, the timing and frequency of ICS dosing would appear to be important factors for potential growth effects. The growth axis exhibits a diurnal pattern, with the greatest frequency and amplitude of 4 to 6 GH pulses beginning after the onset of sleep and ending in the early morning hours. This pattern is a near mirror image of cortisol dynamics, which are highest in the early morning and lowest at bedtime, highlighting the interplay of the natural "antagonism" of these 2 hormone systems. Thus the presence of exogenous glucocorticoid effects from nocturnal ICS administration likely exerts a more potent suppressive effect on nocturnal growth axis activity than first-morning dosing. However, once-daily morning budesonide dosing of 200 µg administered through a DPI slowed growth by 1 cm over 1 year compared with growth seen in prepubertal peers receiving montelukast, suggesting even once-daily morning dosing can impose growth suppression.^{E8}

Judicious use of ICS rescue therapy in children with mild persistent asthma can minimize exacerbations while allowing normal growth, even with an HFA formulation of beclomethasone.^{E4} However, regardless of daily or rescue use of ICS therapy, the potential for increased frequency of oral steroids and worsened asthma-related morbidities must be weighed as a patient is titrated to the lowest effective ICS dose.

One attribute common to virtually all children experiencing unwanted systemic effects from ICS treatment is high adherence to the prescribed treatment regimen. In the authors' experience virtually all children demonstrating growth suppression with moderate-dose ICS treatment exhibit notably high degrees of compliance, regardless of the child's clinical status. Studies have shown documented adherence to twice-daily ICS administration typically decreased to 50% to 60% during the first year of treatment and varied markedly from patient reports.^{E9} As a result, typically prescribed dosages might exceed those needed to control asthma in a child of an extraordinarily compliant family and lead to growth suppression and other systemic effects. The expected waning in treatment adherence with time contributes to the observation that growth attenuation effects are generally inversely related to study durations.^{E1,E10}

Cotreatment with other growth-suppressing medications can increase susceptibility to the ICS growth effect

Simultaneous ICS treatment for asthma and stimulant treatment for ADHD are becoming increasingly commonplace, making it important to consider possible growth-inhibiting influences through distinct pathways with additive or synergistic effects. Studies of growth during continuous treatment with methylphenidate show a mean reduction in first-year growth rate of 1.25 cm/y (approximately 20% reduction in growth rate for a prepubertal child),^{E11} with persistence of the effect creating mean differences in height gain compared with control children of between 2 and 3 cm after 2 to 3 years.^{E12} Decreased GH secretion and slow growth, even during puberty, have been reported with stimulant and SSRI treatment.^{E13} Although often attributed to simultaneous poor weight gain, significant changes in height SD scores in methylphenidate-treated versus control children have been reported in the absence of any change in weight and body mass index values. Although precise mechanisms remain uncertain, increased dopamine and noradrenaline levels associated with stimulant treatment can inhibit secretion of GH, prolactin, thyroid hormones, sex hormones, and insulin. Decreased GH secretion and slow growth, even during puberty, have also been reported with commonly prescribed SSRIs.^{E1}

Thus far, limited analysis of long-term height attainment in treated and control children with ADHD has not shown diminished adult height^{E14}; however, growth slowing as a potential adverse effect during the first years of stimulant treatment appears well established. Thus, as illustrated by the case presented, when confronted by the increasingly common situation of a child receiving multiple drug therapy, especially involving glucocorticoids, stimulants, and perhaps SSRIs, anticipation of and prudent monitoring for possible enhanced adverse medication effects on growth are advised.

Potential for decreased adult height with daily ICS therapy

Results suggest lasting adult height loss rather than just prolonged or retarded growth can occur with long-term daily ICS use. Taking

the example of budesonide, 2 large studies demonstrated decreased growth velocity during the initial 2 years of therapy, whereas a more recent study concluded the mean adult height was 1.2 cm shorter for children treated with 400 µg/d budesonide (CFC) for 4 to 6 years than for the control placebo group.^{E15} Furthermore, larger daily budesonide doses during the first 2 years of therapy were associated with shorter adult height, but it is important to consider mean adult height was only a ½-inch lower in ICS-treated than untreated children, and the quality of life enjoyed by these children with better controlled asthma might exceed the potential benefit of being ½ inch taller without ICS therapy.^{E15}

THE CASE REVISITED

Given poor growth leading up to the visit at 9 years of age, the patient was switched back to Advair Diskus (100/50), 1 inhalation twice daily, and 10 months later, his height percentile was greater than the 25th percentile, suggesting less growth suppression by ICS therapy. Control of his asthma was adequate with DPI therapy, it is reasoned that the lower systemic ICS exposure allowed the prepubescent boy's growth axis to rebound; however, similar results might have been realized with a lower MDI dose.

REFERENCES

- E1. Allen DB. Inhaled corticosteroids and growth: still an issue after all these years. *J Pediatr* 2015;166:463-9.
- E2. Guilbert TW, Mauger DT, Allen DB, Guilbert TW, Mauger DT, Allen DB, et al. Growth of preschool children at high risk for asthma 2 years after discontinuation of fluticasone, et al. Growth of preschool children at high risk for asthma 2 years after discontinuation of fluticasone. *J Allergy Clin Immunol* 2011;128:956-63.e1-7.
- E3. Agertoft L, Laulund LW, Harrison LI, Pedersen S. Influence of particle size on lung deposition and pharmacokinetics of beclomethasone dipropionate in children. *Pediatr Pulmonol* 2003;35:192-9.
- E4. Martinez FD, Chinchilli VM, Morgan WJ, Boehmer SJ, Lemanske RF Jr, Mauger DT, et al. Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): a randomised, double-blind, placebo-controlled trial. *Lancet* 2011;377:650-7.
- E5. Bisgaard H, Allen D, Milanowski J, Kalev I, Willits L, Davies P. Twelve-month safety and efficacy of inhaled fluticasone propionate in children aged 1 to 3 years with recurrent wheezing. *Pediatrics* 2004;113:e87-94.
- E6. Martin RJ, Szefer SJ, Chinchilli VM, Martin RJ, Szefer SJ, Chinchilli VM, et al. Systemic effect comparisons of six inhaled corticosteroid preparations, et al. Systemic effect comparisons of six inhaled corticosteroid preparations. *Am J Respir Crit Care Med* 2002;165:1377-83.
- E7. Kramer S, Rottier BL, Scholten RJ, Boluyt N. Ciclesonide versus other inhaled corticosteroids for chronic asthma in children. *Cochrane Database Syst Rev* 2013;2:CD010352.
- E8. Gradman J, Wolthers OD. A randomized trial of lower leg and height growth in children with asthma treated with inhaled budesonide from a new dry powder inhaler. *Pediatr Allergy Immunol* 2010;21:e206-12.
- E9. Milgrom H, Bender B, Ackerson L, Bowry P, Smith B, Rand C. Noncompliance and treatment failure in children with asthma. *J Allergy Clin Immunol* 1996;98:1051-7.
- E10. Wolthers OD, Allen DB. Inhaled corticosteroids, growth, and compliance. *N Engl J Med* 2002;347:1210-1.
- E11. Methylphenidate: growth retardation. *Prescribe Int* 2011;20:238-9.
- E12. Dura-Trave T, Yoldi-Petri ME, Gallinas-Victoriano F, Zardoya-Santos P. Effects of osmotic-release methylphenidate on height and weight in children with attention-deficit hyperactivity disorder (ADHD) following up to four years of treatment. *J Child Neurol* 2012;27:604-9.
- E13. Weintrob N, Cohen D, Klipper-Aurbach Y, Zadik Z, Dickerman Z. Decreased growth during therapy with selective serotonin reuptake inhibitors. *Arch Pediatr Adolesc Med* 2002;156:696-701.
- E14. Biederman J, Spencer TJ, Monuteaux MC, Faraone SV. A naturalistic 10-year prospective study of height and weight in children with attention-deficit hyperactivity disorder grown up: sex and treatment effects. *J Pediatr* 2010;157:635-40.e1.
- E15. Kelly HW, Sternberg AL, Lescher R, Fuhlbrigge AL, Williams P, Zeiger RS, et al. Effect of inhaled glucocorticoids in childhood on adult height. *N Engl J Med* 2012;367:904-12.