

Effect of Inhaled Corticosteroids on Long-Term Growth in Pediatric Patients with Asthma and Allergic Rhinitis

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Abstract

Objective: To evaluate the effect of orally and nasally inhaled corticosteroids (ICS) on final adult height in pediatric patients with mild to moderate persistent asthma and allergic rhinitis. **Data Sources:** MEDLINE (1975–April 2013), Cochrane Library (through 2012), and International Pharmaceutical Abstracts (1975–April 2013) were searched for prospective clinical trials assessing the effects of orally or intranasally ICS use on growth in pediatric patients with asthma or allergic rhinitis using the terms inhaled/intranasal corticosteroid, linear growth, height, and asthma or allergic rhinitis. **Study Selection and Data Extraction:** Eligible articles included double-blind, randomized, placebo-controlled studies of at least 1 year with growth velocity or height as the primary outcome. **Data Synthesis:** Seven trials and 1 follow-up study analyzing the effects of orally ICSs were examined. Of these studies, 4 found a delay in growth in at least 1 subset of its participants of approximately 1 cm, 1 study found a decrease in final adult height of 1.2 cm, and 3 studies found no effect. Of the 4 studies examining nasally ICS, 1 found evidence of growth delay in a subgroup using suprathreshold dosing. There are conflicting data on whether ICS use causes long-term growth reduction in pediatric patients. The concern surrounding their long-term use including a potential delay or decrease in growth may result in underuse and potential mismanagement of persistent asthma and/or allergic rhinitis. Patients should be treated with the lowest effective corticosteroid dose to achieve symptomatic control while minimizing excessive systemic effects. Orally ICS use may cause a delay in growth, but a decrease in final adult height (1.2 cm) has been documented in only one study. This single report should not preclude daily use of inhaled corticosteroids if needed to decrease the morbidity and mortality associated with pediatric reactive airway disease. **Conclusions:** Continued studies on the systemic effects of ICS are required before truly understanding the class's effect on growth in pediatric patients with asthma and allergic rhinitis. What is understood, however, is the detriment and potential danger of mismanaged asthma care.

Keywords

inhaled corticosteroids, long-term height, linear growth

Reactive airway disease (asthma and allergic rhinitis) is a common and debilitating illness in children. Each year the estimated 9.2% of the US population from birth to age 17 years with a diagnosis of asthma require 1.75 million emergency department visits and 14.2 million missed days of school.¹ Orally and nasally inhaled corticosteroids (ICS) reduce airway inflammation and are the single most effective control medications available for pediatric reactive airway disease. ICS have consistently demonstrated reductions in asthma exacerbations, emergency department visits, and mortality and are preferred control medications for pediatric persistent asthma.^{2–5}

Despite the efficacy of ICS, many practitioners and parents are reluctant to use these drugs in children because of potential adverse effects (adrenal suppression, reduced

bone density, and especially growth retardation). As of 1998, the Food and Drug Administration (FDA) requires

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Table 1. Comparative Daily Doses of Orally Inhaled Corticosteroids.

Drug	Daily Doses ^a According to Age (years)								
	Low			Medium			High		
	0-4	5-11	≥12	0-4	5-11	≥12	0-4	5-11	≥12
Beclomethasone HFA	NA	80-160	80-240	NA	>160-320	>240-480	NA	>320	>480
Budesonide DPI	NA	180-400	180-600	NA	>400-800	>600-1,200	NA	>800	1200
Budesonide nebulization	0.25-0.5	0.5	NA	>0.5-1	1	NA	>1	2	NA
Flunisolide HFA	NA	160	320	NA	320	>320-640	NA	>640	>640
Fluticasone HFA	176	88-176	88-264	>176-352	>176-352	>264-440	>352	>352	>440
Mometasone DPI	110 ^b	110	220	NA	NA	440	NA	NA	>440
Triamcinolone CFC	NA	300-600	300-750	NA	>600-900	>750-1,500	NA	>900	>1,500
Ciclesonide HFA	NA	NA	160	NA	NA	320	NA	NA	640

CFC = chlorofluorocarbon; DPI = dry powder inhaler; HFA = hydrofluoroalkane; MDI = metered-dose inhaler; NA = not available (either not approved, no data available, or safety and efficacy not established for this age group). Adapted from National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program. Expert Panel 3: guidelines for the diagnosis and management of asthma. 2007; 314.⁴

^aDoses reported as micrograms for all drugs except budesonide nebulization, which is reported as milligrams.

^bNot indicated for children younger than 4 years.

precautionary wording for orally and nasally ICS to alert consumers of a potential reduction in growth.⁶ This warning could lead to underuse of ICS and mismanagement of pediatric reactive airway disease. The National Asthma Education and Prevention Program's Expert Panel Report 3 suggests using the lowest possible dose of corticosteroids to maintain control of symptoms.⁴ Tables 1 and 2 give the recommended pediatric doses of common oral and nasal ICS.

The controversy surrounding decreased growth and ICS use has been investigated periodically since the drugs became commonplace in pediatric asthma and allergic rhinitis therapy in the 1970s.^{3,7} Despite the array of studies surrounding this concern, there are few data regarding the long-term effect of ICS use on final adult height. Studies assessing the effect of ICS on growth most commonly include short-term trials lasting a few weeks or months to midrange studies longer than 3 months but less than a year.⁸⁻¹¹ Short-term studies often use knemometric measurements of the distance between a child's heel and knee or surrogate height markers such as hypothalamic-pituitary-adrenal axis suppression or bone and collagen turnover. Both types of measurements are useful in assessing short-term growth velocity but are limited in their use for predicting final adult height attained.^{8,9} Many short-term and midrange studies measure growth velocity (cm/year) or standard deviation score (SDS) where the difference between the patients' growth velocity and normal velocity is divided by the normal growth velocity standard deviation for individuals of the same age and sex. These studies have been well examined and most findings are consistent: ICS use delays growth and puberty but may be followed by a catch-up period during which normal adult height is obtained.^{10,11}

While a decrease in adult height may be a worrisome end point, what is more worrisome is the potential for increased emergency department visits and possible fatalities. Few

Table 2. Recommended Doses for Aqueous Intranasal Corticosteroids (Exception: Beclomethasone and Ciclesonide Aerosols).^a

Drug	Age, years	Daily Dose, µg	
		Starting	Maximum
Beclomethasone	≥6	168	336
Beclomethasone aerosol ^a	≥12	320	320
Budesonide	6-11	64	128
	≥12	64	256
Ciclesonide	≥6	200	200
Ciclesonide aerosol ^a	≥12	74	74
Flunisolide	6-14	174	232
Fluticasone propionate	≥4	100	200
Fluticasone furoate	2-11	55	110
	≥12	110	
Mometasone	2-11	100	
	≥12	200	
Triamcinolone	2-5	110	110
	6-11	110	220
	12	220	220

HFA = hydrofluoroalkane.

^aIn the U.S., beclomethasone (QNASL) and ciclesonide (Zetonna) are commercially available as a pressurized "dry" HFA-containing nasal aerosol in addition to an aqueous preparation.

studies assessed long-term effects of ICS on final adult height of pediatric patients. This article examines the long-term effects of ICS use on final adult height in pediatric patients with asthma and allergic rhinitis.

Data Sources

Relevant sources were identified through a search of MEDLINE (1975–April 2013), International Pharmaceutical Abstracts (1975–April 2013), and Cochrane Library

Table 3. Randomized Placebo-Controlled Studies Examining Long-Term Growth with Orally Inhaled Corticosteroids.

Reference	Pts., Age	Treatment, Duration	Results	Comments
Kelly (2012) ¹³	N = 943, 5-13 years	Budesonide 200 µg bid Nedocromil 8 mg bid Placebo 4-6 years	Budesonide group adult height, -1.2 cm (-1.9 to -0.5); $P = .001$	Decreased height with budesonide neither progressive nor cumulative
Bensch (2011) ¹⁵	N = 218, 4-10 years	Flunisolide 85 µg bid Placebo 1 year	No significant differences between groups	No suppression of growth at highest approved dose for age group
Skoner (2011) ¹⁸	N = 187, 4-9 years	Mometasone furoate 100 µg once daily or bid Placebo 1 year; 3-month follow-up period	Difference in bid group, -0.70 (-0.41 to -0.99); $P = .02$	200 µg/day excessive for age group
Guilbert (2011) ²⁰	N = 204, 2-3 years	Fluticasone propionate 176 µg/day Placebo 2-year treatment + 2-year follow-up period	Difference only in patients weighing <15 kg at enrollment, -1.6 cm (-2.8 to -0.4); $P = .09$	Post hoc analysis showed significantly reduced linear growth in younger and lower weight children
Skoner (2008) ¹⁶	N = 661, 5-8.5 years	Ciclesonide 40 or 160 µg Placebo 1 year	No significant differences between groups	No difference in growth
Becker (2006) ¹⁴	N = 360, 6.3-9.3 years	Beclomethasone 200 µg bid Montelukast 5 mg Placebo 56 weeks	Beclomethasone, -0.78 cm (-1.06 to -0.49) vs placebo	Growth rate decreased with beclomethasone, but dose excessive for age group
CAMP (2000) ¹²	N = 1041, 5-13 years	Budesonide 200 µg bid Nedocromil 8 mg bid Placebo 4-6 years	Mean height in budesonide group 1.1 cm less than placebo ($P = .005$)	Small, transient reduction in growth velocity; all groups had similar growth velocity at end of treatment period
Allen (1998) ¹⁷	N = 325, 4-11 years	Fluticasone propionate 50 µg once daily or 100 µg bid Placebo 1 year	No significant differences between groups	No significant difference in mean height, growth velocity, or skeletal age

(through 2012) for prospective clinical trials assessing the effects of oral ICS use on growth in pediatric patients with mild to moderate persistent asthma using the terms inhaled corticosteroid, asthma, linear growth, and height. A similar but separate search was conducted for intranasal ICS using the same parameters but substituting allergic rhinitis for asthma and including the term intranasal. The limits for both of these searches included humans younger than 18 years and English-language availability.

Data Extraction

Selection requirements included double-blind, randomized, placebo-controlled studies of at least 1 year in duration with growth velocity or height as the primary outcome. The initial Childhood Asthma Management Program (CAMP),¹² despite lacking growth velocity as a primary outcome, was included in this review because of its large sample size and because it serves as the precursor to a recent and influential study by Kelly et al. examining adult height in a majority of CAMP patients.¹³

Orally Inhaled Corticosteroids

Decreased growth. CAMP examined 1041 patients aged 5-13 years with mild to moderate persistent asthma who were

randomized to receive budesonide 200 µg dry powder inhaler (DPI), nedocromil 8 mg by metered-dose inhaler (MDI), or placebo twice daily for a mean of 4.3 years (Table 3).¹² Height was measured biannually by trained technicians using a stadiometer and adherence was assessed using patient (or parent/guardian) diaries. After 2 years, the average change in height was significant for the budesonide (22.7 cm, $P = .005$) group and nonsignificant for the nedocromil (23.7 cm, $P = .65$) group compared to placebo (23.8 cm). This small, transient reduction in growth velocity for the budesonide group was evident during the initial 2 years of treatment and did not persist thereafter according to calculations on projected final height (174.8 cm for all groups).

The follow-up study to CAMP is the only trial to date that has examined final adult height in patients administered ICS as children (Table 3).¹³ The final adult height attained in 90.6% of the original CAMP participants (N = 943) was documented in patients who were at least aged 18 years for females and 20 years for males (96.8% of group) or in younger patients whose most recent height was less than a 1-cm difference from the recorded height the previous year (3.2% of group; average age = 24.9 ± 2.7 years for all patients). A significant but slight difference in height between the budesonide group and placebo group (-1.2 cm [95% CI -1.9 to -0.5]; $P = .001$) persisted, but not in the

male subgroup (-0.8 cm [95% CI -1.8 to 0.2]; $P = .10$) or the group aged 9-13 years at study entry (-0.5 cm [95% CI -1.7 to 0.6]; $P = .37$). Significant but slight decrements in height were seen in the female (-1.8 cm [95% CI -2.9 to -0.7]; $P = .001$) subgroup and the patients aged 5-8 years at study entry (-1.9 cm [95% CI -3.2 to -0.6]; $P = .004$) subgroup when compared to placebo. The authors concluded that the initial decrease in height associated with budesonide noted in prepubertal participants during the CAMP study persisted into adulthood but did not appear to be progressive or cumulative.

Becker and colleagues compared the growth of children aged 6.4-9.4 years with asthma administered beclomethasone 200 μ g twice daily via an MDI with a spacer or montelukast 5 mg daily orally to the growth of those receiving placebo for 56 weeks (Table 3).¹⁴ Beclomethasone recipients had a 0.78 cm ($P = .001$) decrease in height compared to placebo recipients. The lack of data on long-term adult follow-up height and daily dose of beclomethasone used (400 μ g) limits the applicability of their results. Many children in this age range will receive daily doses of beclomethasone within the low-to-medium dose range ($\leq 320 \mu$ g) where such a decrease in growth may not be seen (Table 1).

No change in growth or change on post hoc analysis. A double-blind, placebo-controlled study examined flunisolide hydrofluoroalkane (HFA) 2 puffs twice daily (85 μ g/puff or 340 μ g/day) compared to placebo in 218 patients aged 4-10 years with mild persistent asthma (Table 3).¹⁵ Height was assessed by stadiometry and adherence was assessed using patient diaries. No significant difference ($P = .425$) in growth velocity between the flunisolide group (6.01 ± 1.84 cm) and the placebo group (6.19 ± 1.30 cm) occurred after 52 weeks of treatment.

A multicenter, randomized, double-blind, placebo-controlled study assessed growth velocity in 661 patients aged 5.0-8.5 years with mild persistent asthma after 1 year of ciclesonide MDI 40 or 160 μ g daily versus placebo (Table 3).¹⁶ Adherence was determined by MDI canister weight and patient diary. Compared to children receiving placebo, those receiving ciclesonide 40 and 160 μ g daily had nonsignificant growth velocity reductions of -0.02 ± 0.09 cm/year (95% CI -0.19 to 0.16) and -0.15 ± 0.09 cm/year (95% CI -0.33 to 0.03), respectively.

The growth velocities and mean change in height after 1 year in prepubescent girls (4-9 years) and boys (4-11 years) prescribed fluticasone 50 or 100 μ g DPI twice daily or placebo were not significantly different (50 μ g daily 5.91 cm/year and 5.94 cm, 100 μ g daily 5.67 cm/year and 5.73 cm, placebo 6.10 cm/year and 6.15 cm ($P = .313$ and $P = .308$, respectively) (Table 3).¹⁷ Adherence for this study was determined through counting the number of package blisters used.

Another study compared mometasone DPI 100 μ g once or twice daily to placebo in children aged 4-9 years of age with persistent asthma.¹⁸ Adherence was assessed through guardian questioning and diaries. A significant decrement in growth velocity occurred in the twice-daily mometasone group compared to the placebo group (-0.70 cm [-0.41 to -0.99]; $P = .02$). This difference may be the result of the suprathreshold dose used as the approved maximum dosing for mometasone in this age group is 110 μ g daily.¹⁹

One study found a difference in growth velocity only after post hoc analysis.²⁰ Fluticasone propionate 176 μ g daily MDI was delivered via a chamber with mask in preschool children (aged 2-3 years) with recurrent wheezing and positive modified asthma predictive index scores. No significant difference in linear growth was seen between the fluticasone and placebo groups after 2 years of treatment and 2 additional years of follow-up. However, upon post hoc analysis, the study found participants receiving fluticasone and weighing less than 15 kg at enrollment had significantly reduced linear growth (enrollment -1.6 cm [-2.8 to -0.4]; $P = .009$). It is unclear how weight plays a factor in this age group without further studies examining weight as a primary end point.

Intranasal Corticosteroids

Many children with asthma also experience allergic rhinitis (seasonal, perennial, and/or nonallergic/vasomotor) and some have nasal polyps. There are fewer studies available examining the effects of nasal compared to oral ICS on growth velocity (Table 4). There have been no intranasal studies assessing final adult height.

Decreased growth. Skoner and colleagues²¹ randomized 80 children aged 6-9 years with perennial allergic rhinitis to receive aqueous beclomethasone 336 μ g daily or placebo for 1 year (Table 4). The mean change in standing height, as determined with a stadiometer after 1 year was 5.0 cm in the beclomethasone group versus 5.9 cm in the placebo group ($P < .01$). Although children receiving beclomethasone were taller and older at baseline, a z-score analysis demonstrated that this difference in growth rate between groups was not due to preexisting group differences, but likely associated with treatment. The results of this trial were used, in part, by the FDA to require a class warning of potential growth suppressive effects for intranasal ICS.

No change in growth. The effect of budesonide nasal spray 64 μ g daily on growth in children aged 4-8 years with perennial allergic rhinitis was examined over 1 year (Table 4).²² After 1 year, no significant difference was found between budesonide and placebo in percentile for height (59% and 54% respectively, $P = .64$).

Nasal fluticasone 200 μ g daily for 1 year was studied in 150 children aged 3-9 years; no effect on growth was

Table 4. Studies Examining Long-Term Growth with Nasally Inhaled Corticosteroids.

Reference	Pts., Age	Treatment, Duration	Results	Comments
Murphy (2006) ²²	N = 229 4-8 years	Budesonide 64 µg once daily 1 year	No significant differences between groups	No suppression in growth velocity after 1 year
Allen (2002) ²³	N = 150 3.5-9 years	Fluticasone propionate 200 µg daily 1 year	No significant differences between groups	No effect on growth in prepubertal pts. with maximum dose for 1 year
Schenkel (2000) ²⁴	N = 98 3-9 years	Mometasone 100 µg daily 1 year	No significant differences between groups	No effect on prepubertal growth at 1 year
Skoner (2000) ²¹	N = 100 6-9 years	Beclomethasone 168 µg bid 1 year	-0.9 cm difference in final height after 1 year (P < 0.01)	Beclomethasone may slow growth; further studies needed, effect on final height unknown

observed (Table 4).²³ The mean height at the end of treatment was 125.5 cm in the fluticasone group and 125.4 cm in the placebo group (least-squares difference 0.12; 95% CI -0.600 to 0.352).

In 2000, Schenkel and colleagues examined the growth effects of mometasone furoate aqueous nasal spray 100 µg for 1 year in 98 children aged 3-9 years (Table 4).²⁴ There was no significant difference between the groups at baseline including the use of exogenous corticosteroids. Both the mometasone and placebo groups had similar changes in height from baseline in all weeks except weeks 8 and 52. The overall rate of growth (0.018 cm/day) was the same in both groups ($P = .80$). There was no significant difference between mometasone and placebo growth between age categories (3-5 years and 6-9 years) or sex.

Discussion

An ongoing hypothesis is that children who receive long-term ICS will experience a temporary decrease in growth velocity followed by a period of improved growth, due to increased maturation, to eventually catch up to their peers.^{25,26} When examining the evidence surrounding ICS and reduced linear growth, it is necessary to appreciate that severe and uncontrolled asthma in itself may lead to a decrease in growth velocity during childhood as well as a delay in the onset of puberty of approximately 1.3 years, but it is still unclear how final adult height is affected.^{27,28} There appears to be a variety of factors at play. A delay in puberty coincides with a delay in skeletal maturation.²⁹ The epiphyseal plate of the bone may therefore be more reflective than current age of the patient's potential height. It appears that prepubertal children may be more sensitive to the effects of ICS than adolescents who have reached maturity.³⁰ The relative severity of asthma may also play a role in decreased growth. Severe asthma may lead to increased metabolic demands due to the increased difficulty of breathing.³¹

The specific oral or intranasal ICS as well as inhaler delivery systems may also play a role on determining the effects on growth. Delivery through an MDI with or without

a spacer, DPI, or nebulizer, as well as the differing pharmacokinetic profiles of ICS medications add additional variability when comparing data.^{32,33} In sum, study results from one ICS medication and inhaler combination may not be readily related to other combinations, which makes understanding of systemic effects such as growth suppression difficult. In practice, factors such as inhaler technique and adherence play a role.³⁴ Proper use of inhalers ensures minimum systemic adverse effects by decreasing the amount swallowed. Advances in drug delivery such as HFA MDI and DPI systems may cause less inhibition of growth by allowing a greater amount of drug to reach the airway than previous designs. Inhaled delivery through the nasal passage is also a variable in determining systemic effects of ICS on growth in children with asthma. Much like orally ICS, there is much room for variability of products depending on the pharmacokinetics of the drug and the delivery device.³⁵

To avoid excessive systemic effects, pediatric patients should always be given the lowest dose of ICS as possible to adequately control their symptoms. As asthma becomes more controlled, some children may benefit from stepping down therapy including discontinuing add-on therapies and/or reducing ICS dosages. There have been some studies suggesting ICS may be used on a regular basis for short periods as an emergency medication in conjunction with albuterol as exacerbations occur.^{36,37} However, current guidelines suggest using ICS on a purely scheduled basis for at least a few weeks but ideally 3 months, so more studies will need to be performed before changing current recommendations.⁴

Summary

Orally ICS use has been linked to a reduction in growth velocity during childhood and adolescence. While this reduction may be the result of a delay in maturation, it is difficult to determine the relationship between ICS use and final adult height. Also, it is difficult to assess whether the current results, if statistically significant, are clinically relevant. To date there has been only one study that examined final adult

height after the use of an ICS. Low-dose budesonide daily for approximately 4 years in children aged 5-13 years was associated with a statistical decrement of 1.2 cm in the overall study population, but males and pubescent patient subgroups did not have significant changes in height. Further studies analyzing the role of age, sex, and maturation are required to better understand which populations, if any, are at risk. Furthermore, studies addressing the various differences in ICS, their therapeutic index, bioavailability, metabolism, and delivery methods are needed. Maintenance of efficacy while minimizing possible growth problems should be paramount in counseling and education of patients and their caregivers in an effort to promote adherence to ICS.

Intranasal ICS use and growth reduction in children with asthma and allergic rhinitis is also still questionable. Issues include how the potential for growth rate slowing may differ among the available intranasal ICS, as pharmacokinetic profiles differ and may be relevant. As well, how the risk for growth rate suppression may be increased, if at all, by the concomitant use of oral ICS remains largely unknown. Most importantly, as the effect of intranasal ICS use on final adult height is unknown, these agents should continue to be used when appropriate and there should be discussion with the patient and family prior to therapy initiation and careful monitoring throughout therapy.

The risk of growth delay or decrease in final height needs to be weighed against the risk of no asthma control. While providers and parents should exercise caution against excessive use of ICS, proper control of asthma should not be compromised because of concerns of a potential decrement of final adult height. Prevention of asthmatic exacerbations through the use of ICS prevents emergency department visits and even death. Patients should continue to use the lowest dose of ICS as possible to adequately control their symptoms as outlined by current guidelines. Extensive patient education to ensure proper technique can reduce systemic effects. Continued studies on the systemic effects of ICS are required before truly understanding the class's effect on growth in pediatric patients with asthma and allergic rhinitis. What is understood, however, is the detriment and potential danger of mismanaged asthma care.

Declaration of Conflicting Interests

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