

Growth of preschool age children receiving daily inhaled corticosteroids

Sachinkumar B. Singh, M.B.B.S.,^{1,2} Miles M. Weinberger, M.D.,¹ M. Bridget Zimmerman, Ph.D.,³ and Timothy D. Starner, M.D.¹

ABSTRACT

Data on the effects of inhaled corticosteroid (ICS) on linear growth in children <5 years old are limited with conflicting results from existing studies. This study was designed to investigate growth effects of inhaled corticosteroid use in children <5 years of age treated for asthma with ICS administered through a valved holding chamber (VHC). A retrospective cohort study was performed of 145 children in three treatment groups: (1) metered-dose inhaler (MDI) containing ultrafine beclomethasone dipropionate ($n = 62$), (2) MDI containing fluticasone propionate ($n = 32$), and (3) oral montelukast sodium ($n = 51$). Children <5 years of age between 2000 and 2009 treated for asthma with one of the three drugs were included in the study. Linear mixed model analysis was used to examine and compare growth during sustained treatment with each of the three medications. The three treatment groups did not differ significantly in their effect on growth rates ($p = 0.64$). However, female subjects had significantly slower growth than male subjects ($p = 0.017$), and the addition of intranasal corticosteroids (INS; $p = 0.013$) and the presence of atopy ($p = 0.015$) had a significant negative effect on growth. In children <5 years of age receiving maintenance therapy for chronic asthma, low-to-medium doses of ultrafine beclomethasone or fluticasone administered through a VHC were not associated with growth inhibition compared with children receiving oral montelukast. A small but statistically significant decrease in growth was seen in subjects with positive skin testing to inhalant allergens in female subjects and in subjects receiving INS.

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Asthma is one of the most common chronic diseases in children. In the United States, ~7 million children are diagnosed with asthma.¹ Over the last 10 years, hospitalization rates for asthma have been the highest among children <5 years old.¹ Treatments that improve care for this age group and that were relatively free of adverse effects would have great potential to lessen the burden of asthma. Inhaled corticosteroids (ICSs) are the most effective maintenance medications currently available for persistent asthma. They reduce airway hyperresponsiveness, block late-phase reaction to allergens, and inhibit inflammatory cell migration and activation. Long-term use of ICS in low doses is generally considered acceptably safe.²

However, there remain concerns regarding the potential of ICS to reduce growth velocity in children. Several randomized clinical trials (RCTs) have observed that ICS used in the management of mild-to-

moderate asthma in children can retard their linear growth.^{3–6} However, some other large-scale RCTs and a review article suggested that this decrease in linear growth is short term, and the magnitude of this effect is small.^{7–9} Additionally, the mean ages at entry in most of the RCTs that showed a decrease in linear growth were >5 years of age. Data on the effects of ICS on linear growth in children aged ≤ 5 years are particularly sparse and conflicting. This preschool age is characterized by relatively rapid growth rates. These rates are influenced by underlying normal inherited variations in height potential and tempo of growth.¹⁰

Studies suggest, and it has been our experience, that ICS administered through a valved holding chamber (VHC) is a convenient and effective means of controlling chronic asthma symptoms.^{11,12} The purpose of this study was to investigate growth effects of ICS use in children <5 years of age treated for persistent asthma with ICS administered through a VHC. We hypothesized that low-to-medium doses of ICS would cause growth inhibition in children <5 years of age treated for persistent asthma.

METHODS

Study Design

This study used a retrospective cohort design of 145 children in three treatment groups: (1) metered-dose inhaler (MDI) containing ultrafine beclomethasone di-

From the ¹Department of Pediatrics, University of Iowa Carver College of Medicine, Iowa City, Iowa, and Departments of ²Epidemiology and ³Biostatistics, College of Public Health, University of Iowa, Iowa City, Iowa

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Address correspondence to Timothy D. Starner, M.D., Department of Pediatrics, Division of Allergy, Immunology, and Pulmonology, University of Iowa, 200 Hawkins Drive, Iowa City, IA 52242

E-mail address: timothy-starner@uiowa.edu

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propionate (QVAR; Teva Pharmaceutical Industries, Ltd. North Wales, PA; $n = 62$), (2) MDI containing fluticasone propionate (Flovent; GlaxoSmithKline PLC, Philadelphia, PA; $n = 32$), and (3) oral montelukast sodium (Singulair; Merck & Co., Inc., Whitehouse Station, NJ; $n = 51$). We identified children <5 years of age between September 18, 2000 through April 15, 2009 treated for asthma with one of the three drugs by the Pediatric Allergy and Pulmonary Clinic at The University of Iowa. Inclusion criteria for study participation were (a) male or female subject <5 years of age on one of the three medications, (b) minimum of three measurements of height taken during routine clinic visits—each taken a minimum of 3 weeks apart, and (c) duration of medication use between the first and last height measurement for a minimum of 6 months. Exclusion criteria for study participation were (a) prior diagnosis of growth failure due to any cause, (b) simultaneous use of ICS for subjects in the montelukast group, (c) simultaneous use of multiple ICSs, and (d) presence of health conditions other than asthma that have the potential to cause growth failure (cystic fibrosis, diabetes mellitus, celiac disease, short bowel, *etc.*).

Clinic nursing personnel obtained height measurements and entered them into the medical records during each routine clinic visit. These measurements were performed with stadiometers in the recumbent position for children <2 years of age and standing for children >2 years old. Review of medication use occurred during each clinic visit. This study was approved by the University of Iowa Institutional Review Board.

Statistical Analysis

Linear mixed model analysis for fitting a random coefficient regression model was used to examine and compare growth during sustained treatment with inhaled ultrafine beclomethasone, inhaled fluticasone, and oral montelukast. Clinical height measurements were converted to z scores using the Centers for Disease Control and Prevention percentile data files with the power in the Box-Cox transformation (L), the median (M), and the generalized coefficient of variation (S) values.¹³ Length-for-age charts were used for children up to 2 years of age while stature-for-age charts were used for children >2 years of age. LMS values for the midpoint of the month were used for any age during that entire month, *e.g.*, the midpoint 2.5 months represented any age between 2.0 and 2.99 months.¹³ Height z scores were calculated from the LMS values using the formula

$$z \text{ score} = ((X/M)^L - 1)/(L \times S)$$

where X was the clinical height measurement.¹³

With height z score as the dependent variable, a model was fitted with drug, time, and the effect of drug on height z scores over time (drug * time interaction) as fixed effects. The model also included a random effect for intercept and time, with the random coefficient for time representing the random slope. From this model, an estimate of the slope was computed for each drug, which represents the change in growth rate over time. The z score slopes of linear growth were used because they normalize the changes in linear growth expected at different ages. Without taking z scores into account, directly comparing linear growth from different ages is problematic as expected rates of growth significantly change with age. A z score slope of zero corresponds to steady growth staying at the same percentile; a positive slope represents an increased growth rate with movement to a higher percentile; and a negative slope indicates a decreased growth rate to a lower percentile. The test for the effect of each drug on changes in the z score slope over time (drug * time interaction) compares the slopes among the three drugs. In addition, the effect of gender, prior ICS use (defined as documentation in the medical record of use of any ICS for any duration before enrollment), use of intranasal corticosteroids (INSs), diagnosis of aeroallergen atopy on skin testing, dose of ICS, and oral steroid courses/year on growth were examined. These covariates were included in the analysis to examine their role as potential confounders.

The dose of ICS was categorized into low, medium, and high doses for beclomethasone and fluticasone using the 2007 National Institutes of Health guidelines for diagnosis and management of asthma based on the 5- to 11-year age range because the data for <5-year age range are not well established.¹⁴ For ultrafine beclomethasone, a low dose was defined as a total daily dose of 80–160 μg and a medium dose 161–320 μg . For fluticasone, low, medium, and high doses were 88–176 μg , 177–352 μg , and >352 μg , respectively. For subjects that had aeroallergen skin testing, if their skin-prick test produced a wheal size at least 3 mm greater than the negative control with surrounding erythema or an intradermal skin test yielded a wheal size at least 5 mm greater than the negative control with surrounding erythema, the test was considered to be positive.^{15,16} Atopy was defined as having at least one positive skin test for aeroallergens.

The effect of each of the aforementioned variables (drug, gender, prior ICS use, INS use, atopy, ICS dose, and number of oral steroid courses) on height z scores was examined (variable main effect) as well as the effect of the variable over time (variable * time interaction) with the test for the variable * time interaction used to determine the effect of the variable on growth. This allows for both z score slope and intercept differences for each variable. The model was further ex-

Table 1 Demographic and clinical characteristics by drug group

Variable	Beclomethasone (n = 62)	Fluticasone (n = 32)	Montelukast (n = 51)	p Value
Gender (male)	38 (61%)	23 (72%)	38 (75%)	0.29
Age				
Median (25th–75th percentile)	3.4 (2.1–4.3)	3.4 (1.5–4.0)	3.1 (1.9–3.9)	0.57
Range	0.3–4.9	0.4–4.8	0.5–4.9	
Prior ICS	29 (47%)	10 (31%)	8 (16%)	0.002
INS#	17 (27%)	8 (25%)	15 (29%)	0.91
Atopy (positive)	40/51* (78%)	17/25* (68%)	29/44* (66%)	0.36
Drug dose				
Low	51 (82%)	22 (69%)		
Medium	11 (18%)	6 (19%)	—	0.019
High	0 (0%)	4 (13%)		
Oral steroid courses per year				
Median (25 th –75th percentile)	2.2 (0.6–4.6)	2.1 (0.2–3.5)	1.8 (0.8–3.7)	0.77
Range	0–16.5	0–6.2	0–8.2	
Months of follow-up				
Median (25 th –75th percentile)	13.1 (8.1–24.7)	13.8 (10.2–19.8)	22.0 (12.9–37.9)	0.0006
Range	6.3–66.7	6.5–30.6	6.4–86.4	

*Denominator is the number in each drug group with aeroallergen skin testing.

#Of the 40 subjects that were treated with INS across the three groups, 27 used budesonide, 9 used fluticasone, 3 used mometasone, and 1 was initially treated with fluticasone, which was later changed to mometasone.

ICS = inhaled corticosteroids; INS = intranasal corticosteroids.

panded to include a variable * drug * time interaction effect to test if the variable significantly alters the drug effect on growth (*i.e.*, does the magnitude of slope differences among the drugs differ with the level of the variable?). The variables that were found to have either a significant variable * drug * time interaction, or variable * time interaction, or variable main effect were all included in the final model that examined the effect of drug on growth. All statistical analyses were performed using SAS Version 9.2 (SAS Institute, Inc., Cary, NC). Significance was defined as values of $p < 0.05$.

RESULTS

Both the ultrafine beclomethasone and the fluticasone groups had a significantly higher proportion of subjects with prior ICS use and shorter follow-up compared with the montelukast group. The three drug groups did not differ significantly with respect to gender, age, INS use, diagnosis of atopy, and the number of oral corticosteroid courses/year (Table 1). To evaluate the distribution of age across the groups, age was categorized into three groups: “0–2 years” group had 40 subjects; “2–4 years” group had 67 subjects; and “4–5 years” group with 38 subjects. Moreover, the slopes for height z scores for most of the subjects in the three treatment groups generally appeared flat, consistent with no growth inhibition (Fig. 1).

As part of the univariate analyses, an effect of gender was observed, with z score slopes for male subjects significantly more positive, indicating more rapid growth than female subjects. INS also had a significant negative effect on z score slopes, consistent with a small but significant decrement of growth for those on INS. Likewise, those positive for atopy had more negative z score slopes, indicating poorer growth compared with those with no diagnosis of atopy (Table 2). To make z score slopes more comprehensible, these slopes can be converted to change in height in centimeters, *e.g.*, a z score slope of $-0.25/\text{yr}$ in a male subject with an age of 3.4 years (median age in the two ICS groups) at the 50th percentile for height at baseline corresponds to a change in height of -1.0 cm over 1 year. Gender, INS use, atopy and the effects of each of these on z score slopes over time (gender * time, INS * time, and atopy * time) were included as fixed effects in the model that tested for the effect of drug on z score slopes. Results from this fitted model are the primary findings of this study and showed no significant differences among the three drugs on their effect on growth rates (Table 3; $p = 0.64$). Effect of covariates on the slope showed a small but statistically significantly slower rate of growth in female subjects compared with male subjects, with INS and positive atopy also having a significant negative effect on growth (Table 3). Because data on atopy were not available for 25

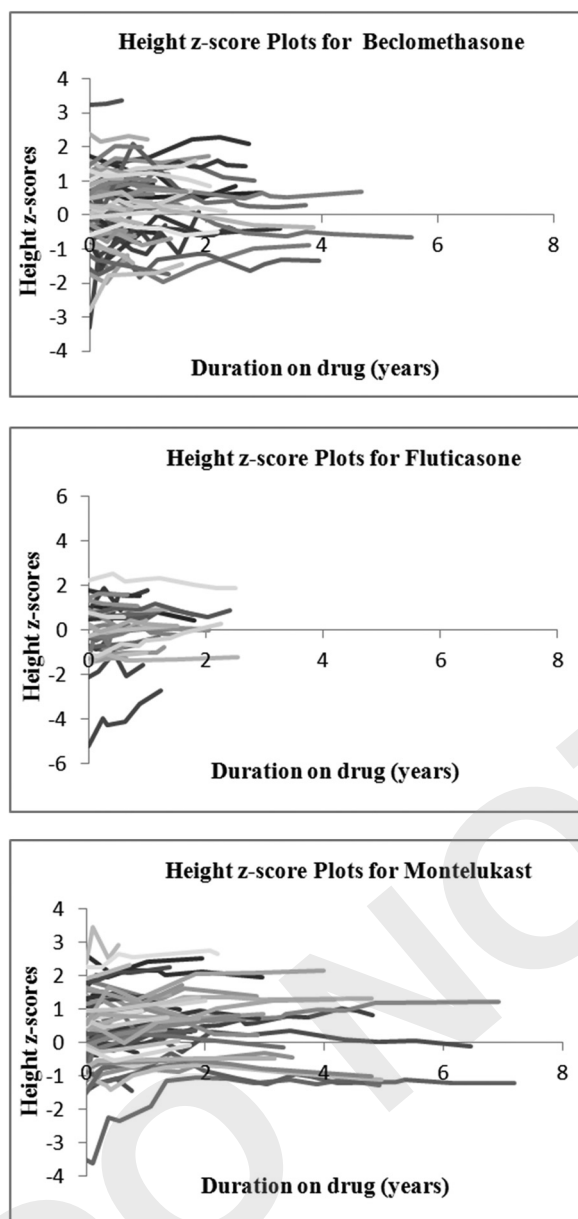


Figure 1. Height z score plots of individual patients for the three study drugs. The overall tendency toward the horizontal with a slope of zero was consistent with no growth inhibition.

subjects, a second model was fitted that did not include atopy (Table 3). Even after excluding atopy from the model, no significant differences in z score slopes were noted between the three drug groups ($p = 0.147$).

From our fitted model that included the fixed effects of the drug, gender, and INS use on z score slopes over time (drug * time, gender * time, and INS * time), a z score slope estimate for each drug/gender/INS combination was obtained. Examination of these z score slopes showed steady or increased growth rates for most of these groups with the exception of a slight decrease in growth among female subjects on INS. To graphically illustrate the growth patterns of these

group combinations, estimates of the height z score means were computed at baseline (time = 0), 1 year, and 2 years using the fitted model. These height z score means were then converted to their corresponding standard normal distribution percentiles and plotted over time (Fig. 2). In terms of height percentiles, the decreased growth in female subjects on INS corresponded to a change in mean percentile over 1 year of -0.5% for fluticasone, -4.4% for montelukast, and -5.9% for beclomethasone. In contrast, the 1-year change in mean percentile for female subjects not on INS was $+7.0\%$ for fluticasone, $+6.9\%$ for montelukast, and $+0.5\%$ for beclomethasone. For male subjects, the 1-year change in mean percentile was between -0.4% and $+13.7\%$ (data not shown).

DISCUSSION

Our retrospective study in children <5 years of age with persistent asthma found no significant effects of ICS on linear growth after controlling for important confounding factors. Counter to our hypothesis, the data support the absence of growth suppression in this age range at low-to-medium doses of ICS delivered through a VHC.

The results of our study are consistent with previous studies of ICS that included but were not limited to preschool children with asthma.^{17,18} However, our results differed from those of a trial conducted by Guilbert *et al.*, which found an initial reduction in linear growth in preschool children treated with ICS for the purpose of assessing subsequent development of persistent asthma.⁸ In contrast, patients in our study received ICSs because of a clinical course already consistent with persistent asthma, and many had already been receiving ICS before entering our study. Therefore, the small initial decrement in growth may have been missed in our patients. Additionally, the Guilbert *et al.* trial excluded patients already having severe asthma and likely included some patients who were at risk but never subsequently developed persistent asthma.¹⁹ Therefore, children in that trial would not be expected to manifest the potential growth benefit from controlling severe asthma and could only experience potential growth suppressive effects from ICS use.

Our study also showed an effect of INS use and atopy on growth in younger children. Children on INS had small but significantly lower rates of linear growth compared with children not receiving INS (Table 3; $p = 0.013$). These results are consistent with a previous study by Skoner *et al.*, which found significant reduction in the growth rate in prepubescent children receiving treatment with intranasal aqueous beclomethasone dipropionate for a period of 12 months.²⁰ Furthermore, exclusion of data on diagnosis of atopy in our study made this effect more significant (Table 3; $p = 0.004$),

Table 2 Effect of study demographic and clinical variables on slope (variable * time interaction) and as modifier of drug effect on slope (variable * drug * time interaction)

Variable	Variable * Time Interaction		Variable * Drug * Time Interaction	
	<i>p</i> Value	Slope Difference (SE)	<i>p</i> Value	Slope Difference (SE)
Gender	0.010	Male–female: 0.174 (0.066)	0.692	For female subjects BECL–MONT: 0.028 (0.0120) FLUT–MONT: 0.088 (0.0164) For male subjects BECL–MONT: –0.066 (0.086) FLUT–MONT: 0.140 (0.100)
Prior ICS	0.950	Yes–no: 0.005 (0.076)	—	
INS	0.004	Yes–no: –0.202 (0.068)	0.813	For INS = yes BECL–MONT: –0.025 (0.130) FLUT–MONT: 0.080 (0.153) For INS = no BECL–MONT: –0.070 (0.084) FLUT–MONT: 0.157 (0.105)
Atopy	0.022	Positive–negative: –0.189 (0.081)	0.626	For atopy = positive BECL–MONT: –0.107 (0.092) FLUT–MONT: 0.074 (0.118) For atopy = negative BECL–MONT: 0.070 (0.165) FLUT–MONT: 0.092 (0.175)
Oral steroid courses per year	0.193	Per +1 dose/yr: 0.018 (0.014)	—	

BECL = beclomethasone; FLUT = fluticasone; ICS = inhaled corticosteroids; INS = intranasal corticosteroids; MONT = montelukast.

leading us to conclude that INS use in this study may in part be a proxy for atopy in young children. We further hypothesize that increased absorption of INS through inflamed nasal mucosa over a prolonged duration could additionally have contributed to this INS-related decrease in linear growth velocity. However, it should be noted that growth for those not on INS for both male and female subjects was greater than expected, perhaps because of improved control of their persistent asthma (positive *z* score slopes; see Fig. 2). The lower rates of linear growth found for those on INS mainly approach expected growth rates with a *z* score slope near zero rather than becoming significantly negative. Although statistically significant, the magnitudes of the differences associated with INS were sufficiently small that they likely have little clinical importance.

Although we did not collect data on the incidence of atopic dermatitis in our study population, it may be reasonable to assume that a substantial proportion of patients diagnosed with atopy (positive skin-prick test)

also had atopic dermatitis, which may explain the effect of atopy on growth. Studies performed in children with atopic dermatitis have observed associated linear growth changes. Of note, Patel *et al.* conducted a study in prepubertal children with atopic dermatitis and observed delays in bone age and slowing down of height and height velocity with age in these children.²¹ Moreover, they also noted that these changes were not affected by history of asthma, body surface area of involvement, and use of topical steroids.

Because our study had missing data on atopy for 25 subjects, we performed a sensitivity analysis excluding atopy from the final model. This analysis did not yield significant differences in height *z* score slopes between the three treatment groups. We could not conduct a subgroup analysis with hypothesis testing for the combinations of various covariates because of insufficient power. However, as an alternative, mean height *z* scores (with 95% confidence intervals) were computed from the fitted model and converted to standard normal percentiles, which were plotted to observe for

Table 3 Results of linear mixed model multivariate analysis testing the effect of drug on growth

Variable	Effect of Drug on Growth with Gender, INS, and Atopy as Covariates*		Effect of Drug on Growth with Gender and INS as Covariates	
	p Value	Difference in Slope + SE (95% CI) .	p Value	Difference in Slope + SE (95% CI) .
Drug	0.640	BECL-MONT: -0.024 ± 0.074 ($-0.173, 0.124$) $p = 0.745$ FLUT-MONT: 0.065 ± 0.090 ($-0.115, 0.244$) $p = 0.475$ BECL-FLUT: -0.089 ± 0.094 ($-0.277, 0.099$) $p = 0.349$	0.147	BECL-MONT: -0.029 ± 0.067 ($-0.163, 0.104$) $p = 0.661$ FLUT-MONT: 0.133 ± 0.082 ($-0.030, 0.297$) $p = 0.109$ BECL-FLUT: -0.163 ± 0.084 ($-0.329, 0.004$) $p = 0.056$
Gender	0.017	Male-female: 0.179 ± 0.073 ($0.033, 0.324$)	0.011	Male-female: 0.167 ± 0.064 ($0.039, 0.295$)
INS	0.013	Yes-no: -0.182 ± 0.035 ($-0.324, -0.040$)	0.004	Yes-no: -0.192 ± 0.065 ($-0.322, -0.063$)
Atopy	0.015	Positive-negative: -0.189 ± 0.075 ($-0.339, -0.038$)	—	—

*Twenty-five subjects with missing data for atopy were not included in the analysis.

BECL = beclomethasone; CI = confidence interval; FLUT = fluticasone; INS = intranasal corticosteroids; MONT = montelukast.

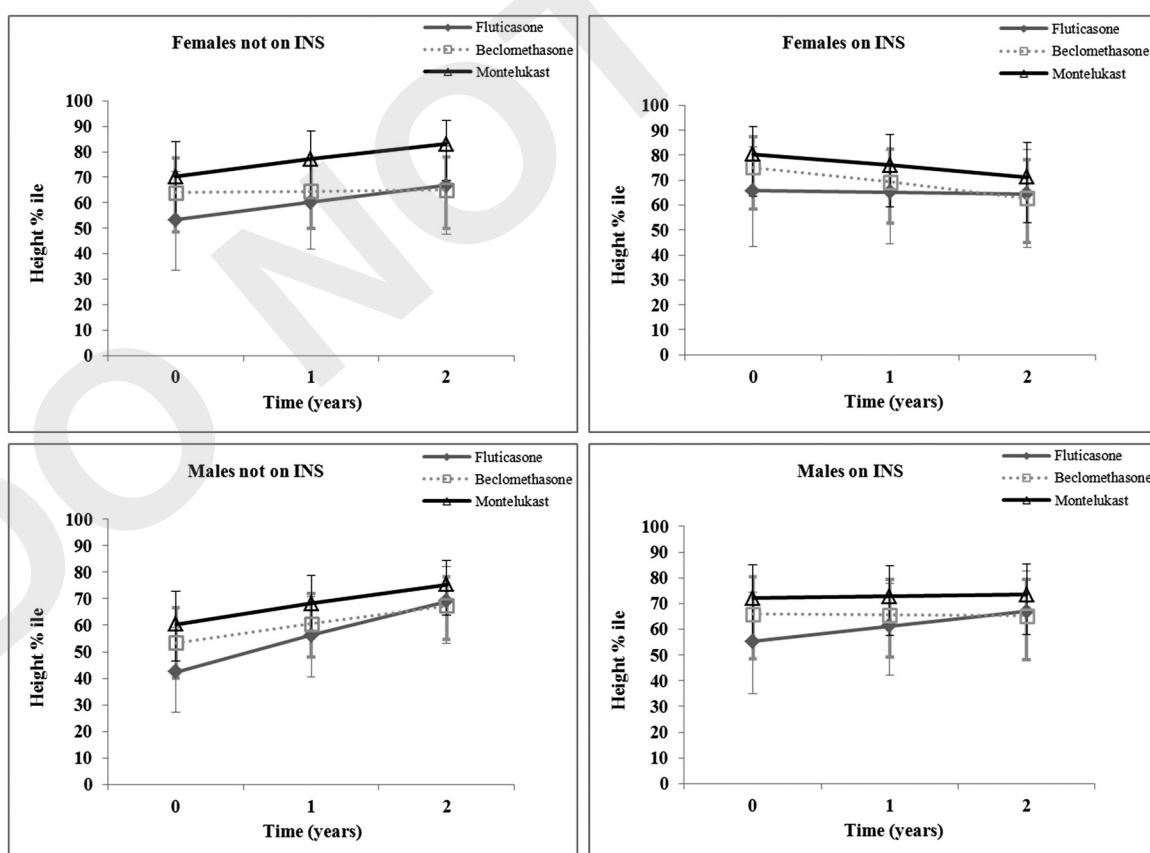


Figure 2. Mean change in height percentile over time for male and female subjects in relation to the use of intranasal corticosteroids (INSs).

meaningful trends. This enabled us to evaluate growth across different combinations of gender, use of INS, and treatment received.

Our study has several key strengths. Using the Centers for Disease Control and Prevention growth charts, we expressed the clinical height measurements as

height z scores. This in turn enabled longitudinal tracking of changes in expected linear growth velocity over time. This study also controlled for a number of important factors that could potentially confound the association between ICS use and change in linear growth velocity, thereby providing a more accurate estimation of this association. Data collection from a single clinical center with a relatively uniform approach to managing asthma and rhinitis minimized variations in clinical assessment. Our study used a cohort design and tracked the subjects on any of the three drug treatments over time to look for growth effects.

This study has several important limitations. The retrospective design of this study did not allow us to ascertain objective data related to medication adherence. Although medication administration was routinely reviewed at each clinic visit, true adherence to medications is frequently reported to be lower than that obtained by history.²² However, this is unlikely to explain the observed lack of association between ICS use and reduced linear growth, because our study was sensitive enough to find a small but statistically significant effect of INS on growth, thereby supporting the overall conclusion.

Another limitation of this study is that data on linear growth were obtained from clinical height measurements performed during routine clinic visits. Although the medical assistants and nursing personnel that recorded the vital signs used in this retrospective study did have regular in-service training for obtaining these measurements, the standards of routine clinical practice and training for measuring these data are certainly less rigorous than is the standard for prospective clinical trials. When suspected erroneous height measurements were encountered (*e.g.*, height recorded in inches rather than centimeters, height measurement on a successive visit lower than the previous height measurement by >0.1 cm), all study-relevant data from that visit were excluded from the analysis. A total of 1.37% of clinic visits were excluded because of such erroneous height measurements.

A final limitation of this study is that although the median period of follow-up in the two ICS groups was ~13 months, many subjects had a follow-up duration of <1 year and a longer period of time would have been more optimal. However, even the minimum 6-month duration of therapy included in the study may be adequate for the primary outcome of this study because growth inhibition generally has its peak effect in early months after its initiation. For example, a previous study by Guilbert *et al.*, conducted in preschool children at risk of asthma, observed that the decrease in growth velocity was only significant during the first 8 months of treatment with ICS, suggesting that the most significant effects on growth suppression occurred during that period.⁸

We recognize that our study design is inconsistent with the recommendations made by the Food and Drug Administration (FDA) in its guidance for industry-sponsored trials for evaluating growth effects in children using ICS and INS.²³ That guidance recommended use of controlled phase 3 or 4, randomized, double-blind, and parallel group clinical trials for evaluating growth effects. Furthermore, the guidance suggests that the study period be divided into a baseline period of at least 16 weeks, a treatment period of at least 48 weeks, and a follow-up period of at least 8 weeks. The FDA guidelines also recommended not enrolling children <3 years of age to minimize the confounding effects of nonlinear growth rates. However, the guidance clearly stated that these recommendations are “not intended to reproduce actual clinical practice.” In contrast with these recommendations for controlled clinical trials, our study was a retrospective observational study in actual clinical practice with a median period of follow-up of ~13 months in both the ICS groups and was performed in a real-world clinical use setting. Moreover, the key aim of this study was to evaluate the effect of ICS on growth in preschool children (<5 years of age), an age group for which no clear design recommendations are listed in the FDA guidance. Additionally, the use of height z scores in place of the raw clinical height measurements in our study may have reduced the likelihood of confounding due to nonlinear growth rates in this <5-year age group.

In summary, low-to-medium doses of ultrafine beclomethasone or fluticasone administered through a VHC in children <5 years of age with persistent asthma did not appear to cause growth inhibition. Although gender, INS, and diagnosis of atopy had significant effects on linear growth, the magnitudes of these effects were small and are unlikely to be clinically important.

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