Inhaled Corticosteroid Therapy for Asthma in Preschool Children: Growth Issues

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ABSTRACT. Although inhaled corticosteroids (ICS) have emerged as the preventive treatment of choice for persistent asthma in children, few studies have been conducted in infants and very young children that assess the benefits and risks of ICS therapy, particularly with regard to growth. Oral glucocorticoids inhibit growth at multiple levels by blunting pulsatile growth hormone (GH) secretion, decreasing insulin-like growth factor-1 bioactivity, and directly inhibiting new collagen synthesis. Normal childhood growth can be divided conceptually into 3 phases according to primary growth-supporting factors: nutrition-dependent growth of infancy, GH-dependent childhood growth, and sex steroid/GH stimulation of pubertal growth. Susceptibility to glucocorticoid-induced growth suppression appears to increase during periods of transition from one phase to another, particularly in the immediate prepubertal years. Studies using ICS at varying dosages demonstrate the possibility of short-term growth suppression, but long-term studies suggest a negligible effect, if any, on final adult height or bone mineral density. Although certain speculations regarding the safety of ICS use in infants and very young children can be made based on these data, age-specific studies are needed to account for effects of differences in oral versus airway deposition and growth axis resiliency, which may occur in these patients. Pediatrics 2002;109:373–380; ICS therapy, growth assessment, glucocorticoids, ICS-induced growth suppression, bone metabolism.

ABBREVIATIONS. ICS, inhaled corticosteroid; GH, growth hormone; IGF-1, insulin-like growth factor-1; MDI, metered-dose inhaler; MFNS, mometasone furoate nasal spray; Ht-SD, height standard deviation; TBMC, total bone mineral content.

Although inhaled corticosteroid (ICS) therapy has emerged as the treatment of choice for persistent asthma in children,1 few studies have been conducted in the very young that assess the benefits and risks of these agents.2–4 Of particular concern is the potential for growth retardation in those children who receive long-term corticosteroid therapy.5 Integral to addressing concerns regarding this potential adverse effect of ICS therapy is an understanding of the mechanisms by which glucocorticoids affect growth and the reasons for variable susceptibility to such growth suppression during childhood. This article reviews normal early childhood growth physiology, including confounding variations in normal growth, mechanisms of glucocorticoid-induced growth suppression, data concerning growth effects of ICS in general, and important differences (particularly systemic bioavailability of the swallowed drug) that affect the ratio of therapeutic-to-systemic effects of individual ICS preparations. From this information and the small amount of data available regarding ICS effects in infants and very young children, predictions regarding risk of ICS therapy on growth in children of preschool-age and challenges for future investigations are offered.

NORMAL EARLY CHILDHOOD GROWTH PATTERNS

Normal childhood growth can be divided conceptually into 3 phases (Fig 1).6 Although these phases are not distinct and frequently overlap, they provide information for predictions of varying susceptibility to growth inhibition during a child’s life. The first phase, the nutrition-dependent growth of intrauterine development and infancy, generally extends to 12 months or slightly into the second year of life. This phase is characterized by both the most rapid growth velocity and most rapidly decreasing growth velocity experienced during an individual’s growing lifetime. The second phase of growth, the growth hormone (GH)-dependent phase, becomes predominant between 12 to 24 months of age and extends up to the pubertal growth phase. During this time, which is characterized by a long period of decelerating growth velocity, the body appears almost exclusively dependent on GH-mediated stimulation of linear growth. During the 2 to 3 years before puberty (particularly when puberty is delayed), spontaneous GH secretion may wane substantially, and susceptibility to growth suppression from a variety of exogenous influences increases. The onset of the third pubertal growth phase is variable and reflects a still poorly defined signal of body maturity (usually well-correlated with bone age maturation) rather than chronological age. Sex hormones (predominantly estrogen in both males and females) markedly stimulate the secretion of GH during this phase. The pubertal growth phase concludes when epiphyseal maturation is complete.

Several factors further confound the already complicated task of growth assessment during infancy. First, a child’s growth generally channels toward the genetic endowment during the first year of life. For
example, in a relatively small infant born to tall parents, the growth velocity will channel upward. Conversely, the velocity will decrease in a large infant born to parents of short stature. Such growth channeling is typically accomplished by 12 to 15 months. Second, some children experience additional downward crossing of percentiles on the growth curve between age 12 and 30 months. These children, many of whom have a family history of delayed growth and puberty, are experiencing growth deceleration during the transition from nutrition-driven growth to GH-dependent growth. This normal variant growth pattern, constitutional growth delay, is a common normal variation of growth, and whereas the child’s growth lags behind the normal percentile lines for some time, normal growth velocity typically resumes. Because the slowed tempo of growth results in delayed bone maturation, delayed onset of puberty can be predicted.

A confounding factor in evaluating normal early childhood growth is the difficulty in obtaining an accurate measurement. Growth curves for children from birth to 3 years of age reflect length, not height. Because a substantial difference between a child’s length and height may occur—as much as a 1- to 1.5-centimeter variance—it is critical to plot only length measurements on the growth curve covering birth to 3 years of age. Thus, several intricacies of normal early childhood growth complicate the evaluation of the benefits versus risks of ICS therapy in preschool-aged children, particularly the risk for growth suppression.

**GLUCOCORTICOID-INDUCED GROWTH SUPPRESSION**

Glucocorticoid excess causes growth suppression through several pathways (Fig 2). One major mechanism of glucocorticoid-induced growth suppression is direct and indirect inhibition of GH secretion. Glucocorticoids appear to augment hypothalamic somatostatin secretion, which exerts an inhibitory effect on pituitary pulsatile GH secretion. Directly, glucocorticoids regulate the expression and binding of the GH receptor downward. Furthermore, exogenous glucocorticoids appear to interfere with the bioactivity of insulin-like growth factor-1 (IGF-1), the primary second messenger of GH, probably by altering protein binding of IGF-1 to limit circulation of free IGF-1. Glucocorticoids also have a direct inhibitory effect on the synthesis of new connective tissue and, at certain ages, diminish androgen production by the adrenal gland, normally a critical stimulator of growth during the early phase of the pubertal growth spurt.

Although specific mechanisms of oral glucocorticoids on growth suppression can be defined and discussed, explanations for inhibitory effects on growth of consistent moderate-dose ICS exposure remain obscure, nevertheless. For instance, GH secretion is not predictably reduced in poorly-growing children with asthma who are treated with ICS. The extrapolation of studies performed in older children to preschool-aged children is also problematic. During this period, the growth rate is simultaneously more rapid and more rapidly decreasing than during late childhood. A transition from nutrition-dependent growth occurs concurrently with an increasing dependence on GH, the primary site of glucocorticoid-induced growth suppression. Depending on the relative contributions of nutrition- and GH-dependent processes to a child’s normal growth, sensitivity to ICS-induced growth suppression might be decreased or increased, respectively. The normal variations in growth during the first 3 years further complicate analysis.

**FACTORS AFFECTING THE RISK OF ICS-INDUCED GROWTH SUPPRESSION**

Certain factors are likely to affect the risk of ICS-induced growth suppression in preschool-aged children. In addition to specific patient characteristics already discussed (genetic stature, pattern of constitutional growth delay, and ages of susceptibility to growth suppression), the time of administration of
ICS therapy and systemic drug bioavailability may also be important.

In the prepubertal child, GH secretion is generally confined to nighttime, usually beginning after sleep onset, which coincides with the normal nadir in blood cortisol levels. The risk for adverse effects of ICS therapy is increased either when systemic exposure exceeds normal endogenous cortisol production or when the pattern of cortisol effect is sufficiently abnormal to disrupt other normal hormone secretion. Thus, the time of ICS dosing may influence their effect on growth suppression (Fig 3). For example, bedtime ICS dosing could create a nonphysiologic increase in cortisol effect, which might have a disproportional effect on the normally active nocturnal growth axis compared with a dose given at times of the day when cortisol levels are higher and normal GH secretion lower. Findings from a study using once-daily intranasal budesonide versus a twice-daily regimen appear to support this hypothesis.

Fig 2. Mechanisms of glucocorticoid-induced growth suppression. The growth suppression effects of exogenous glucocorticoids include inhibition of pulsatile GH secretion, IGF-1 bioactivity, GH receptor expression, collagen synthesis, and adrenal and androgen production. Adapted from Allen.

Fig 3. Potential interaction between growth axis and nocturnal administration of an ICS. The timing of ICS dosing may influence their effect on growth suppression. Bedtime dosing would create a nonphysiologic cortisol effect (dotted line), which might have a disproportional effect on the growth axis (dashed line), compared with a dose given at other times of the day when the cortisol levels are much higher (ie, 6 AM to 12 noon). Adapted from Allen.
**SYSTEMIC DRUG AVAILABILITY**

Systemic bioavailability of each ICS preparation represents the combined fractions of inhaled drug absorbed across the airway mucosa and swallowed drug that is absorbed through the gastrointestinal tract and escapes hepatic inactivation (Fig 4).7,13 In general, ICS drug that reaches the terminal airway is virtually completely absorbed into the circulation. Thus, the most important distinguishing factor among ICS in terms of the balance between targeted and desired therapeutic effects in the lung versus unwanted systemic effects is the bioavailability of swallowed drug. This factor may be especially important in younger children because of the greater proportion of drug they might swallow.

Important differences exist among ICS, which include relative binding affinity for the glucocorticoid receptor and lipophilicity.7 Theoretically, these factors are proportionate to potency and could be balanced by titrating down to an appropriate lowest effective dose. Additionally, exposure to relatively nontherapeutic swallowed ICS absorption can be minimized by selecting ICS with essentially complete first-pass hepatic inactivation.

**EFFECTS OF ICS ON GROWTH OF PREPUBERTAL CHILDREN**

During the past decade, it has been demonstrated convincingly that uninterrupted treatment with beclomethasone at a dose of 400 μg/day is capable of reducing growth rates of prepubertal children. For example, in an efficacy study comparing beclomethasone with salmeterol in 241 children with stable asthma (mean age: 9.3 ± 2.4 years),14 the children were assigned to 1 of 3 study groups: beclomethasone (200 μg twice daily; N = 81), salmeterol (50 μg twice daily; N = 80), or placebo (N = 80). Beclomethasone was significantly more effective in decreasing airway hyperresponsiveness than either salmeterol or placebo (P < .003 and P < .001, respectively) and in decreasing the need for albuterol rescue therapy (P < .001). Linear growth in the children who received beclomethasone, however, was significantly less than in the children who received either placebo or salmeterol (3.96 cm, 5.04 cm, and 5.40 cm, respectively). Three other studies3,15,16 have confirmed this reduction of ~1.5 cm/year in growth of prepubertal children treated with 400 μg/day of beclomethasone.

Consistent administration of sufficient doses of intranasal beclomethasone also appears to have a detectable effect on growth. A double-blind, randomized, parallel-group study17 in 100 prepubertal children with perennial allergic rhinitis treated with intranasal beclomethasone 168 μg twice daily, (N = 51) or placebo (N = 49) for 1 year showed a significant difference in mean change in standing height of 5.0 cm, compared with 5.9 cm in the placebo patients. This difference was apparent as early as the 1-month treatment visit and was primarily attributable to therapy and no other confounding variable. This study emphasizes the need for clinicians to consider systemic effects of combined (eg, intranasal and inhaled) sources of glucocorticoid medications.

These studies raise 2 important questions. First, can the effect of beclomethasone (or other ICS) on growth be persistent and thereby reduce final height attainment? Available data suggest that significant long-term growth suppression does not occur. Studies of adults who received long-term beclomethasone treatment during childhood18,19 revealed final height measurements within the range of genetic expectations. More recently, studies of long-term treatment with budesonide revealed the resumption of normal growth rates after an initial deceleration of ~1 cm/year in children20 and the eventual attainment of adult heights equal to genetic predicted heights.21 Second, the relatively high bioavailability of swallowed beclomethasone raised the question whether growth effects would be reduced with the use of

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Fig 4. Distribution of ICS. Systemic bioavailability of each drug, the result of the oral (swallowed fraction) and lung fraction, is the most important distinguishing factor among ICS in terms of their therapeutic versus systemic effects. A significant portion of drug that reaches the terminal airway is absorbed into the circulation; yet, the swallowed fraction comprises 70% to 90% of drug, and this percentage may be higher in younger children because of the greater proportion of drug they might swallow. Selecting a drug with low bioavailability from the nontargeted organ (intestine) can minimize nontherapeutic drug exposures. Adapted from Barnes.35
clinically equivalent doses of ICS with improved first-pass hepatic inactivation (eg, fluticasone or mometasone). In a double-blind, randomized, parallel-group, multicenter study,22 268 prepubescent children (4.0–11.9 years of age) with persistent asthma were given fluticasone propionate (50 µg twice daily or 100 µg twice daily using a breath-actuated dry powder inhaler) or placebo for 1 year. More placebo patients did not complete the study, primarily because of inadequate asthma control. There were no statistically significant differences among the groups in mean height, mean growth velocity, or mean skeletal age at any time during the study. An overall difference of 0.42 cm/year in mean change from baseline in height between patients in the fluticasone (100 µg BID) group and the placebo group did emerge, however, indicating that a small effect of the drug on linear growth could not be ruled out. Numerically, the effect of fluticasone at clinically equivalent dosages appeared to be about one fourth that observed with beclomethasone.

It is important to recall that drug delivery to the lung (and hence systemic bioavailability) is significantly affected by delivery systems, technique, and other factors. Thus, results derived from studies using a dry powder delivery system for fluticasone (Diskhaler) may not necessarily apply to equal doses delivered by the metered-dose inhaler (MDI) device. On the other hand, in a randomized, prospective, controlled study of 23 prepubertal children 5 to 10 years old treated with fluticasone (200 µg/day delivered by MDI) or clinically equivalent dosages of beclomethasone (400 µg/day), fluticasone-treated children showed no detectable effect on linear growth or markers of bone metabolism over a period of 20 months. In contrast, beclomethasone-treated children showed significant slowing of linear growth and reductions in morning fasting plasma cortisol, supporting a differential therapeutic-to-systemic effect of the 2 ICS preparations give via MDI.23

In another study24 evaluating the systemic effects of once-daily mometasone furoate nasal spray (MFNS) in 82 children 3 to 9 years of age with perennial allergic rhinitis, the patients received either MFNS (N = 42) or placebo (N = 40) for 1 year. After 1 year of therapy, no significant difference in growth suppression was observed between the 2 groups, (+6.95 cm in patients receiving MFNS and +6.35 cm in patients receiving placebo). The investigators concluded that MFNS demonstrated an absence of systemic effects. Importantly, the MFNS study used a once-daily dosing regimen compared with the beclomethasone study’s twice-daily regimen. Nonetheless, these studies strongly suggest that the reduced total systemic bioavailability of fluticasone and MFNS compared with clinically equivalent doses of beclomethasone (a difference largely related to differences in first-pass hepatic inactivation of swallowed drug) improve the ratio of therapeutic to systemic effects of these airway corticosteroid preparations.

Only 2 studies have examined the effects of nebulized budesonide on linear growth. In an open, prospective study25 among 40 children with severe asthma who were younger than 3 years of age at study onset, investigators evaluated the effect of the study drug (1–4 mg/day, adjusted as needed) on linear growth. In this study, height was expressed as a height standard deviation (Ht-SD), calculated by subtracting the mean height for age from the measured height and dividing by the Ht-SD for the specific age. The mean baseline Ht-SD was −0.46, which improved to −0.17 at the posttreatment evaluation. The investigators pointed out that nebulized budesonide therapy for at least 6 months in very young children resulted in a minimal, albeit not statistically significant, improvement in linear growth.

In a more recent trial,26 the effect of nebulized budesonide therapy on change in Ht-SD was compared with that of conventional asthma treatment in children aged 6 months to 8 years over 52 weeks. The study design was complex in that it included 3 groups, 1 of which did not receive ICS as part of the conventional asthma therapy. Only in this group was there a small statistically significant improvement in Ht-SD (P = .003) in patients who received conventional asthma treatment compared with nebulized budesonide. In the other 2 groups, both of which included ICS therapy in the conventional asthma treatment regimen, no significant difference was observed in Ht-SD. Although data remain limited, it appears that the systemic bioavailability of nebulized budesonide lies between that of fluticasone and beclomethasone.

ICS THERAPY AND BONE METABOLISM

Concern has also grown concerning the effect of long-term ICS therapy on bone metabolism.27 Bone marrow accretion follows a triphasic pattern mirroring that of growth velocity. Increase in bone mineral density is rapid during the first 3 years of life, slows during childhood, and rapidly increases again during puberty, during which there is a 50% accumulation of adult bone mineral density. Several factors influence bone metabolism, including absorption of dietary calcium, which is critically important in preschool-aged children. Glucocorticoids may adversely affect bone metabolism by way of several pathways including directly on bone formation and indirectly through interference with calcium absorption (Fig. 5). Consequently, glucocorticoid excess related to ICS therapy during early childhood or adolescence could conceivably have detrimental effects on bone mineralization.

Thus far, however, studies of children treated with moderate-dose ICS have not reported any significant effects on bone mass or density. In children 4 to 17 years of age with asthma treated with inhaled beclomethasone (300–800 µg/day for a mean of 25 months),28 bone mineral density did not significantly differ from that of age- and sex-matched controls measured by radiographic absorptiometry and bone mineral content measured by single-photon absorptiometry and dual-energy x-ray absorptiometry. Furthermore, serum levels of calcium, magnesium, zinc, total alkaline phosphatase, bone specific alkaline phosphatase, parathyroid hormone, 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin D were also not
different from that of controls. Cortical and trabecular (lumbar spine) bone mass (measured by dual-photon absorptiometry) and volumetric bone density in prepubertal asthmatic children receiving beclomethasone (mean duration: 6.7 months; mean dose: 319.3 μg/day) did not differ from those in children treated with cromolyn sodium or from normative data for matched nonasthmatic children.30

A 6-month longitudinal study found that the change in vertebral bone mineral density in asthmatic children (2.3% increase) receiving inhaled beclomethasone 300 to 400 μg/day did not differ significantly from nonasthmatic controls (4% increase).31 Another 6-month longitudinal study32 reported a mean change in bone mineral density among children treated with beclomethasone (mean dose, 400 μg/day) of 1.8%, which was nonsignificantly lower ($P = .16$) than the 6.1% increase among the control patients. A significant increase in serum osteocalcin (a marker for bone formation) occurred in the beclomethasone group from 66.8 ng/mL to 81.6 ng/mL ($P < .005$). Among 157 children treated with budesonide (mean daily dose: 504 μg) for 3 to 6 years (mean: 4.5 years), bone mineral density, bone mineral capacity, and total bone calcium did not differ from that of age-matched asthmatic children who had never been treated with exogenous corticosteroids for more than 14 days.33

A recently completed study27 assessed the effects of relatively high-dose ICS therapy (beclomethasone or budesonide) on total bone mineral content (TBMC) in 48 prepubertal children (mean age: 7.8 years) with asthma. Nine children (mean age: 8.4 years) who did not receive ICS therapy served as controls. Dual energy x-ray absorptiometry was used to measure the TBMC.

The mean change in TBMC over a 12-month period in children receiving ICS therapy (average dosage: 0.67 mg/m²/day) was 264 g ($±68$ g) compared with 330 g ($±84$ g) in the control children ($P < .025$). Changes in TBMC were not different in children receiving budesonide compared with those who received beclomethasone. The change in TBMC in the ICS therapy group was related inversely to the dose of the inhaled drug ($P = .016$) after the investigators adjusted for such confounding factors as age, height, and weight. Of note, the average dosage in this study was high, and half of the children required at least 1 short course of oral corticosteroid therapy. A key question not addressed in this study is whether such an effect would occur in the setting of lower systemic bioavailability.

Overall, direct measurements of bone and of bone metabolism markers do not indicate that moderate doses of ICS affect bone density. More long-term studies of high-dose therapy and comparisons of different drugs are needed, however. This is especially true for studies of the effects of ICS during the toddler years and adolescence, for which no information is currently available.

EFFECTS OF ICS THERAPY IN PRESCHOOL-AGED CHILDREN: SPECULATIONS

Although few studies have been performed in very young children and data regarding the mechanisms of ICS and their effects in this patient population are lacking, certain speculations can be made. First, it is probable that a decreased fraction of drug will be delivered to the lungs and an increased fraction will be delivered to the gut in these children. This would increase systemic drug activity for those drugs with incomplete inactivation of swallowed drug and the likelihood of adverse effects on linear growth. Second, the susceptibility of the growth axis to ICS-induced suppression appears highest during late childhood; whether children showing decreasing growth velocity during the preschool-age period are equally susceptible is not known. It is likely, though, that preschool and late prepubertal children are more at risk for ICS-induced effects than are adolescents. It might be possible to identify preschool-aged children at higher risk for adverse effects of ICS.
therapy, such as children with a family history of constitutional growth delay or delayed puberty. Judicious selection of medication and closer monitoring of growth may be more important in these at-risk children.

EVALUATING GROWTH EFFECTS OF ASTHMA TREATMENT IN PRESCHOOL-AGED CHILDREN: CHALLENGES

Several challenges remain to be addressed regarding the use of ICS therapy in very young children. The preschool age is characterized by both relatively rapid and rapidly decreasing growth rates that are influenced by underlying normal inherited variations in height potential and tempo of growth. These variables need to be kept in mind when designing studies to evaluate the safety of medications in this special population. Further complicating study design is the fact that although the age differences are narrow, there are, from a growth standpoint, 3 separate groups of children who must be considered: infants, toddlers, and preschoolers. Ethical and technical issues are important challenges as well. Investigators must decide whether to include observation or placebo groups in clinical studies. Keeping in mind the difference between length and height, accurate measurements are more difficult to obtain in very young children. Finally, investigators must decide whether a study drug protocol that allows for titration to the lowest effective dose and a real life approach to the treatment of asthma will be applied.

CONCLUSION

For children of all ages with persistent asthma, ICS treatment is currently recommended. Although ICS therapy has improved the control of asthma markedly while diminishing the risk of corticosteroid adverse effects, a fear of potential adverse systemic effects continues to accompany the use of ICS. Unfortunately, these fears result in some children being deprived of appropriate and effective treatment, or even exposed to a greater risk of periodic oral corticosteroid treatment. Nevertheless, because these agents may be used for long periods of time in a large number of children, safety issues are paramount.

Several conclusions appear well-supported by studies of ICS in school-aged prepubertal children. First, ICS used in small dosages present no significant risk for systemic adverse effects. When ICS are used at higher dosages and continuously for long periods of time, important differences in drug characteristics, particularly the efficiency of inactivation of swallowed drug (which does not exert a therapeutic effect before gaining access to the systemic circulation) affect the ratio of therapeutic to systemic effects of individual ICS. From a practical viewpoint, the long-term clinical history of ICS therapy is informative. Detectable suppression of childhood growth can occur when ICS with relatively poor first-pass inactivation are administered at doses of 400 μg/day or greater. This effect on 1-year growth is reduced when clinically equivalent doses of ICS with improved first-pass inactivation of swallowed drug are used. Administration of ICS alone has not been associated with any detectable effects on final adult height, however. Harmful effects of ICS on bone metabolism, although not yet adequately studied, would not be expected with the use of an ICS dosage that does not suppress basal hypothalamic-pituitary adrenal axis function or childhood growth. An important caveat to these conclusions is that they refer to ICS used alone and in recommended doses, not in combination with intranasal or other topical corticosteroids.

Extension of ICS treatment to younger children may be important in reducing or preventing long-term consequences of poorly treated lung inflammation. At the same time, while ICS safety is supported by studies of older children, careful investigations of ICS safety in children of preschool age are needed. Differences in safety profiles among the available ICS exist, but there have been few direct comparative studies attempting to establish rank in benefit-to-risk ratios. Importantly, the safety profile of all ICS preparations, which focus on the antiinflammatory effects on the lung, is markedly better than oral glucocorticoids. The risk of adverse effects can be minimized by using the lowest effective dosage, by limiting systemic availability of the drug through careful selection of the inhalation device and proper technique, by the adjunct use of alternative antiinflammatory agents, and, when higher doses are required, by choice of ICS medication. Monitoring of growth in children is a sensitive method of detecting significant ICS systemic effects and can enhance a family’s confidence in the safety of the medication.

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*Pediatrics* 2002;109;373

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