

Assessing the effect of intranasal steroids on growth

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Several studies have evaluated the effects of childhood use of corticosteroids on growth. In short-term studies, the budesonide (BUD) metered dose inhaler and methylprednisolone (injection) had significant effects on lower-leg growth, whereas terfenadine did not. When two doses of BUD (nasal inhaler, 200 or 400 µg once daily) were compared with placebo, only the 400-µg dose had a significant effect on short-term growth. Intranasal mometasone furoate (MF) (100 and 200 µg) had no significant effect on short-term lower-leg growth. In intermediate studies of 1-year duration, intranasal beclomethasone dipropionate (84 µg twice daily) significantly affected growth rate, whereas in a separate study, 100 µg intranasal MF once daily did not. Long-term growth data come from retrospective studies of children with asthma. In these studies, no significant effect on growth has been demonstrated in children taking inhaled beclomethasone dipropionate or BUD. The reason for the discrepancy between intermediate and long-term studies is unclear and warrants further study. Variables in childhood growth including seasonal variations may make growth difficult to assess. However, because growth suppression has been reported in children receiving inhaled or intranasal corticosteroids, the lowest effective dose of drug with a low systemic absorption ratio should always be used. Overall, there appears to be no growth suppression with 100 µg intranasal MF used once daily in children. (*J Allergy Clin Immunol* 2001;108:S40-4.)

Key words: Beclomethasone, dipropionate, budesonide, intranasal corticosteroids, mometasone furoate

Corticosteroids are known to be potent inhibitors of nearly every component of the growth axis. It is therefore essential that the effects of intranasal corticosteroids on growth are assessed carefully. When the effects of steroids on growth and maturation in children are reviewed, it is important to appreciate that growth may be divided into 3 distinct age-related phases.¹ There is a period of rapidly decelerating growth during the first 2 to 3 years of life. This phase is probably controlled by the same factors that are important for fetal growth, the main one being nutrition. Then there is a childhood growth phase occurring from approximately age 3 to 11 years. This phase is governed by the action of the endocrine system, particularly growth hormone. The final phase is

Abbreviations used

BDP: Beclomethasone dipropionate
BUD: Budesonide
MDI: Metered-dose inhaler
MF: Mometasone furoate

pubertal growth, which relies on a combination of growth hormone and sex steroids.

The relative importance of the various factors that affect growth differs among these three phases; therefore, conclusions from studies performed on one age group cannot be generalized to the other age groups. To assess the potential impact of an intranasal corticosteroid on growth, studies should be performed on children during each phase of growth.²

EFFECTS OF EXOGENOUS STEROIDS

Studies that evaluate the effect of exogenous corticosteroids on growth can be divided into 4 categories: (1) growth marker studies, which measure steroid-induced changes in various serum markers that are thought to reflect bone and collagen formation/degradation or growth; (2) short-term studies, which assess growth over a period of 6 months or less; knemometry is a particularly sensitive measure of short-term growth (of the lower leg) over a period of weeks; (3) intermediate-term studies, which evaluate growth during periods longer than 6 months but do not include an assessment of final adult height; and (4) long-term studies, which assess growth over many years and include final adult height in relation to predicted adult height.

Clinically, the most important outcome measure of human growth is the final height in relation to expected final height, allowing for sex and midparental height differences. When the results from growth studies are evaluated, it is important to realize that an effect on growth found in short- or intermediate-term studies (Table I) is not necessarily equivalent to an effect on final adult height.³

Several studies have demonstrated weak correlations between short-term height velocity and annual height velocity and between steroid-induced changes in short-term lower-leg growth rate and statural growth during the subsequent year.⁴⁻⁸ One-month lower-leg length velocity does not adequately predict the variation in annual statural height velocity. In addition, the correlation between two consecutive annual height velocity values for normal prepubertal children is also very small. A low gain in 1 year is not necessarily followed by a low gain

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TABLE I. Comparison of short-term and intermediate-term growth with inhaled BDP versus no treatment

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the next year and vice versa.⁷ Height velocity computed over a period of 3 or 4 years in childhood only accounts for between 34% and 38% of the variation in final height; only a partial correlation exists between 1-, 2-, 3-, and 4-year values for height velocity.⁷

Growth marker studies

During recent years, the blood levels of various biochemical markers, such as growth hormone, somatomedin-1 (also known as insulin-like growth factor I), insulin-like growth factor binding protein-3, carboxyterminal propeptide of type-1 procollagen, and the aminoterminal propeptide of type III procollagen, have been found to correlate to some extent with growth rate. However, the predictive value of drug-induced changes in the levels of these markers is not known. Because changes in growth markers are not an adequate predictor of effects on growth, studies on growth markers will not be summarized.

Short-term studies

Knemometry measures changes in short-term linear growth of the lower leg over a period of weeks and may offer a valuable adjunct/alternative to traditional growth studies because knemometry allows very controlled designs. However, the clinical implication of knemometry findings still needs further study. This is because 1-month lower-leg growth velocity and steroid-induced changes in short-term lower-leg growth rate do not account for the variation in annual statural height velocity.^{7,8} Furthermore, daily treatment with 2.5 mg or 5 mg prednisolone totally stopped lower-leg growth.⁹ This indicates that knemometry is too sensitive and probably amplifies or exaggerates the growth-stunting effects of exogenous steroids. On the other hand, if an exogenous steroid has no adverse effect on lower-leg growth in a properly performed knemometry study, it is most unlikely that such treatment will be associated with any growth suppression during long-term treatment.

At present, the effects of intranasal steroids on lower-leg growth have been measured in knemometry studies with the use of intranasal budesonide (BUD) and mometasone furoate (MF).

BUD powder metered-dose inhaler (MDI) (200 µg twice daily) was compared with terfenadine and a single intramuscular injection of 60 mg methylprednisolone acetate in 44 children with allergic rhinitis to grass pollen in a randomized, double-blind, parallel-group study.¹⁰

An open 4-week run-in period was followed by a 6-week treatment period. Compared with run-in treatment, both methylprednisolone acetate and BUD significantly reduced lower-leg growth rates by 0.28 mm/wk ($P < .01$; 95% confidence interval, 0.09 to 0.47) and 0.54 mm/wk ($P < .001$; 95% confidence interval, 0.34 to 0.72), respectively. Terfenadine did not adversely affect lower-leg growth rate as compared with run-in.

BUD dry powder nasal inhaler (Turbuhaler; Astra Zeneca, London, UK) (200 µg and 400 µg once daily) was compared with placebo in 38 children with allergic rhinitis to grass pollen in a randomized, double-blind, parallel-group study¹¹ in a similar study design. In the 400 µg BUD group, mean growth velocity was reduced by 0.18 mm compared with run-in; however, this difference was not statistically significant. In the two other groups, the mean growth velocities were almost identical during run-in and treatment.

MF intranasal aqueous suspension (100 µg and 200 µg once daily), BUD intranasal aqueous suspension (400 µg once daily), and placebo were compared in 22 children with seasonal or perennial allergic rhinitis in a randomized, double-blind, double-dummy, cross-over study.¹² Each treatment period was of 2 weeks' duration, and all treatment periods were separated by 2-week wash-out periods. There was no significant difference between lower-leg growth rate during placebo treatment (0.35 mm/wk), treatment with 200 µg MF once daily (0.48 mm/wk), or treatment with 400 µg BUD once daily (0.37 mm/wk). Lower-leg growth rate during treatment with 100 µg MF once daily (0.58 mm/wk) was significantly higher than the growth rate with placebo ($P = .024$) and BUD ($P = .033$). Figure 1 illustrates lower-leg growth rate with MF, BUD, and placebo.

It should be noted that various intranasal steroids have different pharmacokinetic properties including systemic absorption and activity after administration.^{13,14} Therefore, each drug-device combination should be studied separately and conclusions from one drug or formulation should not be transferred to other drugs or devices. This is especially important with regard to steroid inhalers that are used in the treatment of asthma.

Intermediate-term studies

Two recent studies have evaluated the effect of intranasal steroids on statural growth over a period of 1 year.

One year's treatment with 168 µg beclomethasone dipropionate (BDP) was compared with placebo in 100

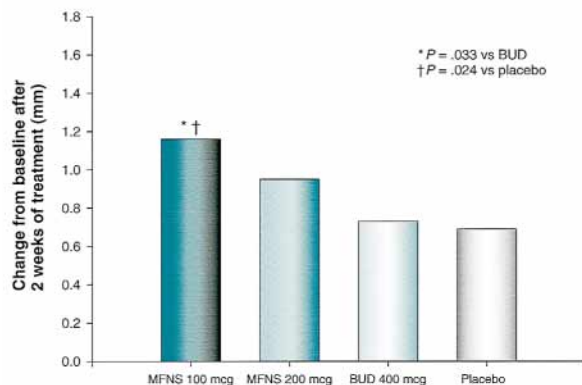


FIG 1. Knemometric measurement of short-term lower-leg growth.

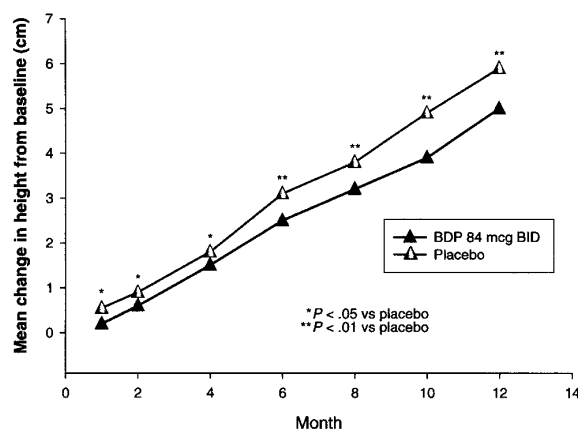


FIG 2. Statural growth during 1 year of treatment with BDP or placebo.

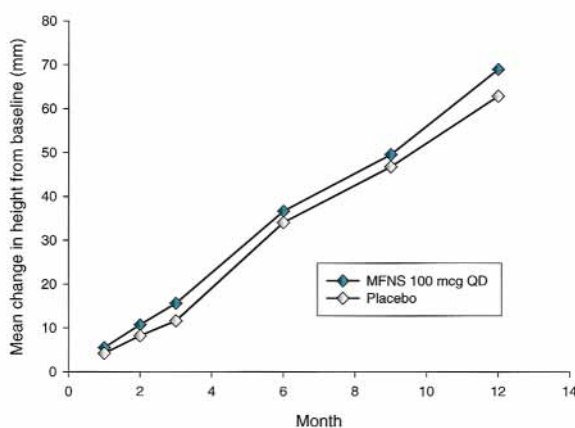


FIG 3. Statural growth during 1 year of treatment with mometasone furoate nasal spray or placebo.

children (ages 6 to 9.5 years) with perennial rhinitis in a randomized, double-blind, parallel-group study.¹⁵ Stadiometric height measurements were obtained at baseline and at 1, 2, 4, 6, 8, 10, and 12 months. The two groups were comparable at baseline for all demographic parameters except that the BDP group was significantly ($P = .04$)

older (7.5 vs 7.1 years) and taller (127.7 vs 125.1 cm) than the placebo group. After adjusting for these differences, the rate of growth was found to be significantly lower in the BDP group than in the placebo group (0.013 vs 0.017 cm/d, $P < .01$). By 12 months, the BDP group had grown 5 cm and the placebo group 5.9 cm ($P < .01$). Data are illustrated in Figure 2. Similar results were obtained when the data were analyzed by sex, age, concomitant or previous steroid use, and concurrent illnesses.

MF (100 µg once daily) was compared with placebo in a 1-year study with an almost identical design in 98 children (ages 3 to 9 years) with perennial rhinitis.¹⁶ Statural height was measured at baseline and at 4, 8, 12, 26, 39, and 52 weeks. The two groups were comparable at baseline for all demographic parameters except statural height, which was 120.2 cm in the MF group and 120.9 cm in the placebo group. At 8 and 52 weeks, the mean increase in height was significantly greater in the MF group than in the placebo group, mean increase at week 52 being 69.5 mm (MF) and 63.5 mm (placebo) ($P = .02$); 12-month data are illustrated in Figure 3. Adjustment for the baseline difference in statural height did not affect this result. However, the slope (rate of change in height) was not significantly different between the two groups. MF did not retard growth in either sex or any age subgroup of patients.

Long-term studies and final height

At present no prospective, long-term studies have assessed the impact of long-term treatment with intranasal steroids on final height. The only data on final height come from studies on asthma treatment. Balfour-Lynn^{17,18} followed 66 children for an average of 13.1 years. No difference was found in overall growth rate between children who received BDP and those who did not. Final heights were reported to be within the predicted range in the children treated with beclomethasone dipropionate. No data on predicted height estimated from parental height were given.^{17,18} Similar results were reported in a controlled prospective study in children treated for 3 to 13 years with inhaled BUD at a mean daily dose of 412 µg.¹⁹ Normal adult height was obtained by children with asthma who received long-term treatment with inhaled BUD. Similar findings have been reported in retrospective studies.²⁰

A meta-analysis of 21 studies representing 810 patients corroborated the findings in the above-mentioned studies. The analysis compared attained height with predicted height of children with asthma treated with inhaled or oral steroids.²¹ A significant but small growth impairment was found in children receiving oral steroids, whereas children treated with inhaled steroids attained normal height. Furthermore, there was no statistical evidence of inhaled steroid therapy being associated with impaired growth at higher doses or during extended therapy. Although firm conclusions about the effect of inhaled corticosteroids on final height should be made with caution, the results of the studies addressing this question have consistently indicated that children with asthma who are treated with inhaled steroids will usually attain normal final height.

The reason for the apparent discrepancy among the findings of some intermediate-term studies with inhaled corticosteroids and the conclusions of final height studies is unclear. Several studies with 400 µg BDP once daily have found a growth retardation of 1.5 cm per year. This would result in a 15-cm height reduction after 10 years of treatment. Such marked effects would be difficult to miss in clinical practice or in long-term prospective studies. Some possible explanations for the discrepancy include the possibility of tachyphylaxis, the possibility that steroids only retard rather than reduce growth, varying sensitivity to exogenous steroids in different age groups (the BDP studies have mainly been in prepubertal children), the use of spacers for the administration and titration of the dose in the "real life" situation, differences in disease severity between the various studies, and a lower compliance in the everyday clinical situation. More prospective studies are needed to assess the relative importance of these possibilities.

GROWTH ASSESSMENT FOR PATIENTS WITH ASTHMA

Asthma, which frequently coexists with rhinitis, is often associated with a prepubertal deceleration of growth velocity, which resembles growth retardation.^{17,18,22-27} This reduced growth rate continues into the mid-teens and is associated with a delay in the onset of puberty. The delay in pubertal maturation is also associated with a delay in skeletal maturation, so that the bone age of the child corresponds to the height; ultimately, there is no decreased final height, although it is reached at a later-than-normal age.^{17,18,22-27}

This difference in growth patterns appears to be unrelated to the use of inhaled corticosteroids, but it appears to be more pronounced in the children with the most severe asthma. Therefore, it is important that growth studies correct for variation in asthma severity. Moreover, poor socioeconomic conditions may have an effect on growth that is more pronounced than the effect of high-dose inhaled corticosteroids.²⁸ This should also be considered in the analysis of steroid effects on growth.

INDIVIDUAL SENSITIVITY TO STEROIDS?

Case reports sometimes suggest that growth inhibition may be observed in individual children with asthma.²⁹ It must be remembered that when such reports are evaluated, growth is a very complex process that may be affected by a host of factors including disease severity, psychologic factors, growth factors, receptor affinity, nutrition, body composition, age, puberty, genetic factors, and treatment.

Children often show spontaneous fluctuations in growth velocity with seasonal variations, with most children growing faster in the summer when compared with the winter.⁴ More recently, it has also become clear that in some children, fluctuations are not purely seasonal but represent cycles of growth that may span 2 years or

more.⁵ This leads to a very small correlation between the growth velocity in 1 year and that in the next year.⁶ These variations, in combination with a standard error of the height measurement (which for trained observers is approximately 0.2 cm to 0.3 cm) and the abnormal growth pattern seen in many asthmatic children unrelated to the use of inhaled steroids, mean that case reports of apparently reduced growth in association with an asthma treatment should be interpreted with caution. No firm conclusions about cause-and-effect relations should be made without the support of further controlled studies.

CONCLUSIONS

Childhood growth is influenced by a number of factors such as phase of growth, socioeconomic conditions, the presence of disease, and seasonal variations in growth pattern, which complicate its assessment. In addition, the studies themselves, be they short-, intermediate-, or long-term, have inherent limitations.

Overall, the data indicate that in children, treatment with 100 and 200 µg intranasal MF once daily or 200 µg BUD powdered MDI once daily is highly unlikely to adversely affect growth. This is in contrast with 200 µg BUD powdered MDI twice daily, which has been shown to reduce lower-leg growth rate, and 168 µg BDP aqueous spray, which reduced statural growth over 1 year. However, final height was not affected by long-term treatment with these same drugs at doses that caused growth retardation in short-term trials. Therefore, it is important to note that the results of short-term studies do not appear to predict intermediate- or long-term growth. Similarly, results from intermediate-term studies are poor predictors of final statural height. The reason for these discrepancies is unclear and warrants further study.

The possibility of increased sensitivity to the growth-retarding effect of inhaled steroids within certain individuals is complex. Some data suggest that an increased sensitivity exists within a population at an unknown frequency. However, normal fluctuations in growth rates complicate the interpretation of individual growth data. Because the occurrence of measurable systemic effects and the risk of clinical side effects increase with dose, the lowest dose able to control the disease should always be used. Furthermore, inhaler-steroid combinations with low systemic absorption ratio should be used.

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