State of the Art

Do Inhaled Corticosteroids Inhibit Growth in Children?

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Contents

Introduction
General Considerations
  Pharmacodynamics of Inhaled Corticosteroids
  Pharmacokinetics of Inhaled Corticosteroids
  Systemic Effects and Clinically Important Adverse Effects
  Dosing Regimen
Growth
  Growth in Healthy Children
  Influence of Disease
Effects of Exogenous Corticosteroids on Growth
  Mechanisms of Corticosteroid-induced Growth Inhibition
Design and Analysis of Growth Studies
  Assessment of Measurable Systemic Effects of Inhaled Corticosteroids
  Assessment of Clinically Relevant Effects
  Markers of Bone Formation and Resorption
  Short-term Growth Studies
  Intermediate-term Studies
  Studies in Preschool Children
  Comparison of Different Inhaled Corticosteroids
  Conclusions from Short- and Intermediate-term Growth Studies
  Long-term Studies and Studies of Final Adult Height
  Discrepancies between Intermediate- and Long-term Growth Studies
  Problems in Growth Assessment: Individual Sensitivity to Corticosteroids
Discussion and Summary

Twenty years ago, most children with asthma were treated only intermittently for exacerbations of the disease. Some patients with severe disease were also given daily or alternate-day prednisolone or inhaled corticosteroids. Treatment has since evolved to include the maintenance use of theophylline, long-acting β_2-agonists, or sodium cromoglycate in children with persistent asthma.

During the last decade, inhaled corticosteroids have been started earlier in the treatment plan and have also been used in patients with mild, persistent disease. Although this change in therapy is supported by both pathophysiologic findings and efficacy data, its safety is often questioned. Many pediatricians are still concerned about the potential adverse effects of long-term treatment with inhaled corticosteroids, particularly on growth. As a result, this class of medication remains underused in children in many countries (1). In the USA, only 9% of all inhaled corticosteroid prescriptions written for asthma were for children younger than 12 yr of age, despite the fact that children make up nearly one third of the total asthmatic population of 14 to 15 million.

In 1998, the US Food and Drug Administration (FDA) convened a panel of experts to review the available published and unpublished evidence with respect to the effects of inhaled corticosteroids on growth in children with asthma. As a result of this review, a precautionary wording for the entire class of medications was implemented. The summary states that inhaled corticosteroids, along with other factors, may cause a reduction in short-term growth velocity, from 0.3 to 1.8 cm/yr in pediatric patients. This report was intended to inform physicians about possible risks and to encourage them to monitor growth during treatment. Although the report was not intended to dissuade physicians from using inhaled corticosteroids, it undoubtedly increased the concerns of many patients and prescribing physicians. After the review was published, heated debates about the clinical importance and consequences of the reported findings have been common at scientific meetings. Some believe that inhaled corticosteroids should be less widely used in children, whereas others consider the findings to be clinically unimportant, and they point out that patients may die from asthma but not from short stature.

The aim of this State of the Art is to try to put the facts and fears about growth, asthma, and inhaled corticosteroids into perspective. The influence on growth of asthma itself and of the use of inhaled corticosteroids will be discussed in some detail. In addition, some of the factors that are important in assessing the clinical relevance and general applicability of the findings of the various growth studies will be briefly summarized.

GENERAL CONSIDERATIONS

Pharmacodynamics of Inhaled Corticosteroids

The risk of adverse effects of a treatment should always be related to the doses required to control the disease. As for other drugs, the clinical effects of inhaled corticosteroids are best evaluated in dose-response trials. The findings of such studies are important to establish the clinically relevant doses of inhaled corticosteroid for use in various patient groups and in trials in which possible effects on growth are studied.

Over the last 5 yr, a number of well-conducted dose-response or dose-titration studies have been carried out in children, mainly in groups with moderate and severe asthma (2 to 7). The findings of these studies have been consistent and in good agreement with the findings of dose-response studies in adults (8). All studies have demonstrated marked and rapid clinical improvement and changes in symptoms and lung function at very low daily doses of about 100 μg. Additional improvement in these parameters with increasing doses is rather small, often requiring an additional fourfold increase in dose to produce a further statistically significant (but clinically very small) effect. In patients with mild disease, low doses have also been found

(*Received in original form January 11, 2001 and in revised form May 8, 2001*)

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Am J Respir Crit Care Med Vol 164. pp 521–535, 2001
Internet address: www.atsjournals.org

to normalize exhaled nitric oxide (eNO) and to offer full protection against exercise-induced asthma (7, 9), whereas children with more severe asthma may require 4 wk of treatment with budesonide, 400 μg/d, via a pressurized metered-dose inhaler (pMDI) plus spacer, to achieve maximal protection (3). *Low doses are so effective clinically that even very large, well-conducted studies normally fail to show any statistically significant or clinically relevant additional effect on symptoms and lung function when the dose is increased above 100 μg/d* (8). The marked effect of low doses may be even more pronounced in children with mild disease, but, at present, no studies have used doses below 100 μg/d.

In addition, a large number of studies have found that, in children, the beneficial effects of low doses of inhaled corticosteroid (200 μg/d) are normally more pronounced than for any other antiasthma drug with which they have been compared. (9–22). These findings are important when interpreting the clinical relevance of growth studies.

Pharmacokinetics of Inhaled Corticosteroids

The pharmacokinetics of the various inhaled corticosteroids available for the treatment of asthma differ markedly and, together with differences in the inhalation systems used with the various products, may lead to important differences in both clinical and systemic effects. The *topical effects* of an inhaled corticosteroid depend on the glucocorticosteroid activity of the molecule and probably also the local pharmacokinetics in the target tissue and cells. The *systemic effects* are related to the glucocorticosteroid activity of the molecule, the total amount of corticosteroid that is absorbed (becomes systemically bioavailable) and the rate of clearance of the corticosteroid from the body. The systemic bioavailability is the sum of the amount of the drug that becomes systemically available after absorption from the lung, and after gastrointestinal absorption and first-pass metabolism of the swallowed fraction of the dose (Figure 1). The oral bioavailability of most of the more recently developed inhaled corticosteroids (e.g., mometasone furoate, fluticasone propionate, budesonide) is low and therefore most of the systemically available corticosteroid comes from the inhaled fraction that enters the systemic circulation after absorption from the lung (23–38). This is not the case for inhaled corticosteroids such as beclomethasone dipropionate (BDP), triamcinolone acetonide and flunisolide, which have a low first-pass metabolism (50 to 70%) of the swallowed dose (39). Thus, the swallowed fraction of these corticosteroids may contribute markedly to the amount of drug systemically available after an inhalation.

It is obvious from Figure 1 that a clinically very effective inhaler, which deposits a high proportion of drug in the intrapulmonary airways, will be expected to have a greater systemic effect than a clinically less effective inhaler with low intrapulmonary drug deposition. On the other hand, if the systemic bioavailability after oral dosing is not zero, the contribution of the orally deposited and swallowed drug to the systemic effect will increase with increasing oral drug deposition and decreasing first-pass metabolism. These considerations may be clinically important because differences in inhaler and drug characteristics may result in a threefold difference in the therapeutic index of some inhaled corticosteroids. This may be of even greater clinical importance in children who, because of their smaller airway diameter, have a much higher proportion of the inhaled dose deposited in the oropharynx and a lower proportion deposited in the intrapulmonary airways than do adults (40–42).

Thus, for inhaled corticosteroids with a high gastrointestinal availability of drug, the risk of unwanted systemic effects can be reduced without loss of clinical effect by choosing an inhaler-drug combination with a high therapeutic index and tailoring the dose to the severity of the disease, as is done routinely in day-to-day management in most clinics. *At present, no placebo-controlled growth trials have employed such measures.* All studies that found that longitudinal statural growth was retarded in children treated with BDP, 400 μg/d, (11, 14, 21, 43) used a fixed dose (no tailoring) for 1 yr. Moreover, in all the studies, a pMDI or dry powder inhaler was used for delivery. These devices deposit more than 85% of the dose into the oropharynx in children, and this fraction of drug is extensively absorbed systemically because of the low first-pass metabolism of BDP (44–46). The therapeutic index of the treatment in these trials would have been markedly better if a spacer device, which reduces oropharyngeal deposition of drug, had been used for delivery (44).

Because the delivery characteristics of inhalers influence the therapeutic index and the risk of clinically important systemic side effects, it is important to recognize that conclusions drawn from studies of one inhaler/drug combination may not be appli-

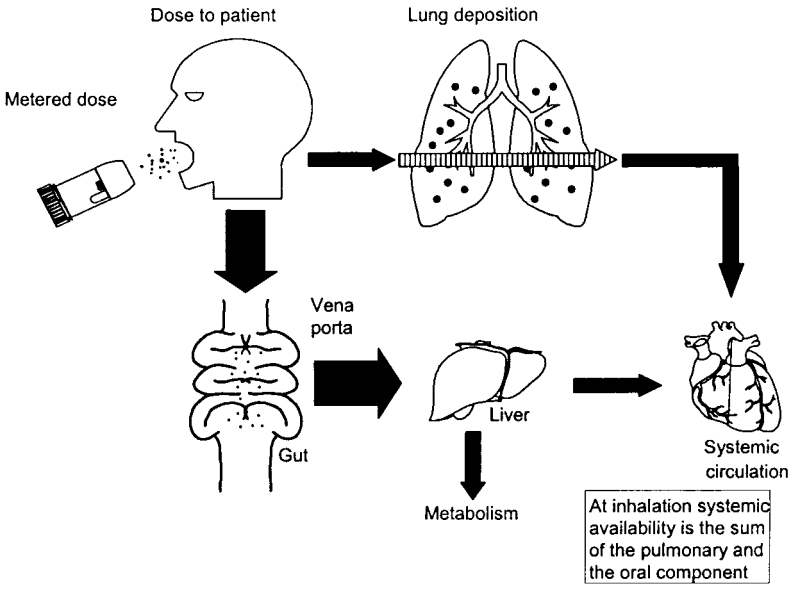

Figure 1. The fate of inhaled corticosteroids. The amount of an inhaled corticosteroid reaching the systemic circulation is the sum of the pulmonary and orally bioavailable fractions. The fraction deposited in the mouth will be swallowed, and the systemic availability will be determined by absorption from the gastrointestinal tract and degree of first-pass metabolism. The fraction deposited in the intrapulmonary airways is likely to be more or less completely absorbed in active form to the systemic circulation, as there is no evidence for metabolic inactivation of any currently available inhaled corticosteroid in airway tissue. The systemic concentration will be reduced by continuous recirculation and inactivation of the drug by the liver.

cable to other drug/inhaler combinations—even where the drug is the same (8, 47).

Systemic Effects and Clinically Important Adverse Effects

Often no distinction is made between a measurable systemic effect and a clinically relevant adverse effect of an inhaled corticosteroid. This may lead to unwarranted and unnecessary fear among physicians and patients.

All inhaled corticosteroids are absorbed systemically to some extent. Whether the absorbed drug leads to a measurable systemic effect depends on the amount of drug that is absorbed, the potency and pharmacokinetics of the drug, and the sensitivity of the method used for measuring the systemic effect. Thus, for a given drug or inhaler, there will always be a dose below which no systemic effect can be detected, no matter which method is used. As the dose increases, there will be a dose range within which systemic effects are measurable in one or more systemic effect models. More often than not, however, these measurable effects merely reflect small changes within the normal range of the normal biologic feedback system; even if they do not they may have no clinical relevance.

With regard to growth, the clinical relevance of detectable systemic effects must sometimes be questioned. This does not just apply to the effects of inhaled corticosteroid therapy. For example, sodium cromoglycate treatment has been found to have a significant effect on urinary excretion of growth hormone (GH) (48) and markers of bone metabolism (49), and treatment with inhaled β_2-agonists has been found to adversely affect the secretion of GH (50, 51). Although statistically significant, these findings are probably not clinically relevant though, as yet, there have been no thorough clinical studies to assess this.

Another problem with studies to assess measurable systemic effects is that they are often short-term, single-dose, standardized, or crossover in design and are carried out on healthy volunteers or patients with very mild disease, who will tolerate treatment with placebo for a certain period. The clinical relevance of the findings from such studies to patients with more severe asthma is not known. Recent studies have suggested that the systemic effects of an inhaled corticosteroid may be markedly higher in healthy volunteers than in patients (52, 53). Similar differences may be seen between patients with mild disease and those with more severe disease (54–56). Finally, little is known about how long a measurable effect will persist. There are some indications that the effect is more pronounced at the start of treatment, after which it may be attenuated to some extent (21, 57–60).

The dose levels at which measurable systemic effects of inhaled corticosteroids are seen has been investigated in short-term controlled studies in healthy volunteers and patients with mild disease. Though the clinical relevance of such findings may be questioned, it can probably be assumed that doses of inhaled corticosteroid that are not associated with any measurable systemic effects in sensitive laboratory test systems are also clinically safe.

Clinically relevant adverse effects should be studied in controlled, long-term clinical trials, using clinically relevant doses, in groups of patients with a disease severity and age similar to that of the patients for whom the drugs would normally be prescribed. Such studies require large numbers of patients and are difficult to conduct.

Dosing Regimen

Once-daily dosing of inhaled corticosteroids is becoming more widely used in patients with mild asthma. Although more studies are needed, preliminary evidence suggests that once-daily administration may have less effect on short-term lower leg growth rate and markers of collagen and bone turnover than twice-daily dosing with the same total dose (61–63). Little is known about the effect of once-daily dosing on the therapeutic index of the various inhaled corticosteroids.

GROWTH

Growth in Healthy Children

When assessing the effects of corticosteroids on growth in children, it is important to appreciate that growth may be divided into three distinct stages (64).

1. Growth during the first 2 to 3 yr of life is both rapid and rapidly decelerating. This phase is probably controlled by the same factors that are important for fetal growth, the main one being nutrition.
2. Childhood growth occurs from approximately 3 to 11 yr of age. This phase is mainly influenced by the endocrine system, particularly growth hormone.
3. Pubertal growth largely depends on a combination of growth hormone and sex corticosteroids.

The importance of the various factors affecting growth seems to differ between these three phases. Two recent studies found that the growth-retarding effect of an inhaled corticosteroid administered for 1 yr was more marked in prepubertal than in pubertal schoolchildren (11, 59), and was statistically significant only in prepubertal children. The FDA normally recommends that growth studies are conducted in prepubertal children 6 to 9 yr of age. This increases the likelihood of detecting possible unwanted effects, because this age group seems to be most sensitive to the adverse effects of inhaled corticosteroids (59). However, the general applicability of these results is questionable, because of the possibility of a lower sensitivity in other age groups (11, 59).

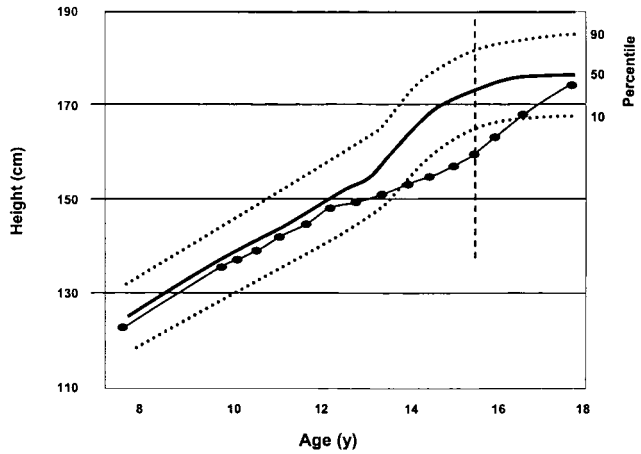

Figure 2. The most commonly observed influence of asthma on growth is a reduction in growth rate, which is most often seen towards the end of the first decade of life. The reduced growth rate continues into the midteens and is associated with a delay in the onset of puberty. This prepubertal deceleration of growth velocity resembles growth retardation. However, the delay in growth is also associated with a delay in skeletal maturation so that the bone age of the child corresponds to the height, and there is no reduction in final height, which is reached at a later than normal age. This difference in growth pattern seems to be unrelated to the use of inhaled corticosteroids, but to be more pronounced in children with the most severe asthma.

Influence of Disease

Asthma may influence the growth of a child in two ways.

(*1*) *Direct effects of disease severity*. Asthma and its level of control may directly affect growth in the same way as most chronic diseases of childhood. The most commonly observed effect of asthma on growth is a reduction in growth rate, usually towards the end of the first decade of life (Figure 2) (65–71). This reduced growth rate continues into the mid-teens and is associated with a delay in the onset of puberty. The prepubertal deceleration of growth velocity resembles growth retardation. The delay in pubertal growth is, however, also associated with a delay in skeletal maturation so that the bone age of the child corresponds to the height. Ultimately, there is no decrease in attained adult height, though it is reached at a later age than normal (65–71). This difference in growth pattern seems to be unrelated to the use of inhaled corticosteroids and is more pronounced in those children with the most severe asthma. The deviant growth pattern seen in many children with asthma complicates the interpretation of results from cross-sectional studies comparing the heights of asthmatic children treated with inhaled corticosteroids with those of normal children or children with asthma who are not treated with inhaled corticosteroids.

Recent studies have confirmed that poorly controlled asthma may itself adversely affect growth. Thus, height standard deviation scores before treatment with inhaled corticosteroids were found to correlate significantly with lung function (17, 59) and degree of asthma control (72, 73); the poorer lung function or asthma control are, the lower the height standard deviation score will be. Furthermore, a retrospective study of a cohort of children with different degrees of asthma suggested that severe asthma adversely affects final height (74) and a large population-based study of more than 3,000 children with asthma also suggested that severe asthma adversely affects growth (75). The exact mechanisms by which severe or poorly controlled asthma adversely affects growth are unclear, but there may be similarities with the factors operating in poor socioeconomic conditions, which have been shown to have an equivalent adverse effect on growth to high-dose inhaled corticosteroids (75). These observations are important and must be considered when assessing the general applicability of the findings of various controlled growth studies.

(*2*) *Effects of disease severity on systemic availability of inhaled drugs*. The level of lung function in asthma may affect the systemic availability of inhaled corticosteroids. Several studies have suggested that the systemic bioavailability and effects of an inhaled drug are more pronounced in patients with mild asthma than in patients with more severe disease (52–56). This is probably due to differences in deposition pattern caused by a smaller airway diameter in patients with more severe disease. Thus, children with mild disease are more likely to experience adverse growth effects from a given dose of inhaled corticosteroid than are children with more severe disease. The clinical relevance of the findings of studies using inhaled corticosteroid, 400 μg/d or more, in patients with mild asthma should, therefore, be questioned because such doses are rarely needed by patients with disease of this severity. These doses would normally be used in children with moderate or severe asthma, in whom the systemic absorption of drug would be less and who would also be at greater risk of growth retardation caused by uncontrolled asthma.

EFFECTS OF EXOGENOUS CORTICOSTEROIDS ON GROWTH

Mechanisms of Corticosteroid-induced Growth Inhibition

It is well known that long-term treatment with oral corticosteroids adversely affects growth (Figure 3). The pathogenesis of this growth suppression is complex and not well understood. Systemic corticosteroids may inhibit GH secretion, insulinlike growth factor-1 (IGF-1) activity (increasing IGF-1 binding protein-3), collagen synthesis, and adrenal androgen production (76, 77). Furthermore, systemic corticosteroids may reduce GH receptor expression and uncouple the receptors from their signal transduction mechanisms (78). Finally, corticosteroids may also exert a direct growth-suppressing effect on the growth plates at quite low concentrations (76, 79). In contrast, no consistent association between *inhaled* corticosteroids and alterations in the GH axis have been shown, either with respect to change in GH production (48, 51, 79–82) or to changes in IGF concentration or activity, though some studies have suggested that significant changes in IGF-1 or its binding globulin may be seen during short-term treatment with high doses (83). A study designed to evaluate the possible mechanisms of growth inhibition by inhaled corticosteroid found no differences in GH secretion, serum cortisol, osteocalcin, and IGF-1 levels or bone mineral density between a group of children with suspected corticosteroid-induced growth retardation and

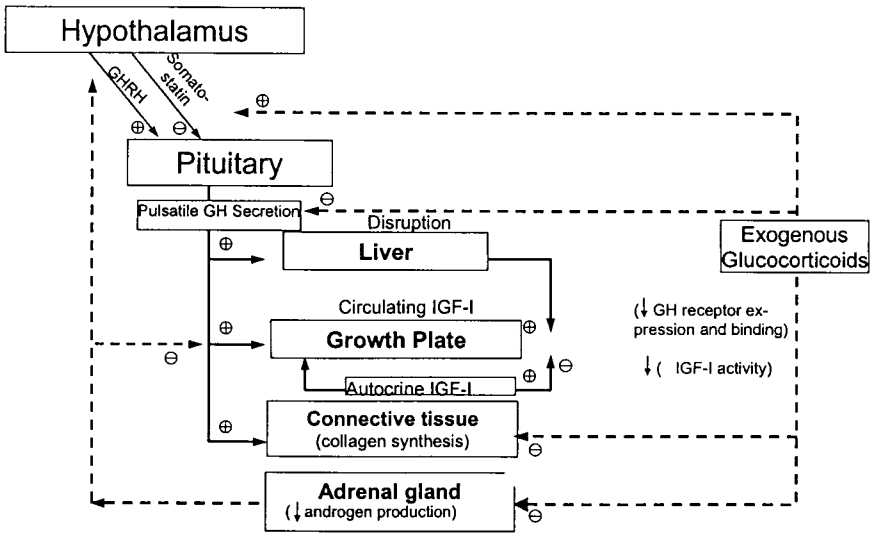

Figure 3. Possible mechanisms and pathways by which corticosteroids may influence growth. + = stimulatory effect, − = inhibitory effect.

children with normal growth during treatment with inhaled corticosteroids (82). Thus, at present, the mechanisms of growth inhibition remain unclear and there are no reliable measures that can be used to elucidate them further. The finding that GH treatment reverses corticosteroid-induced growth retardation does not necessarily indicate that changes in the GH axis are important in its pathogenesis (84), and further work is required in this area.

Design and Analysis of Growth Studies

Studies evaluating the effect of exogenous corticosteroids on growth are traditionally divided into: (*1*) growth marker studies, which measure corticosteroid-induced changes in various serum markers that are thought to reflect bone and collagen formation/degradation or growth; (*2*) short-term studies that assess growth over periods of 3 mo or less; (*3*) intermediate-term studies that evaluate growth over periods longer than 3 mo but do not assess final adult height; (*4*) long-term studies that assess growth for many years and also include final adult height in relation to predicted adult height.

It is important to remember these characteristics when assessing the clinical relevance of the results of clinical trials. Several studies have demonstrated poor correlations between short-term height velocity and annual height velocity (85–89), and between corticosteroid-induced changes in short-term lower leg growth rate and statural growth over the subsequent year. Lower leg length velocity over 1 mo does not correlate with the variation in annual statural height velocity (88, 89). In addition, the correlation between two consecutive annual height velocity measurements for normal prepubertal children is very poor. A low gain over 1 yr is not necessarily followed by a low gain the next year and vice versa (88). There is only a partial correlation between 1-, 2-, 3-, and 4-yr values (88), and height velocity over a 3- or 4-yr period in childhood only explains 34 and 38% of the variation in final height, respectively. Therefore, a change in growth markers or a significant effect on growth found in short- or intermediate-term studies is not necessarily equivalent to an effect on long-term growth or adult height.

Normal growth is nonlinear in the long-term and unpredictable in the short-term. Furthermore, growth in asthma is influenced by a host of factors, including disease severity, social and psychological factors, nutrition, age, puberty, genetic factors, exposure to smoking, and treatment. It is, therefore, extremely difficult to carry out an optimal study on the influence of inhaled corticosteroids on growth. Of course, the design of the study depends on the research question asked. In this respect, it is important to differentiate between: (*1*) studies designed to detect systemic effects of inhaled corticosteroids, and (*2*) studies designed to assess clinically relevant effects of inhaled corticosteroids on growth.

Both types of study should preferably be randomized, double-blind, and controlled for factors that are known to influence growth (e.g., age, sex, pubertal status, bone age, baseline growth rate, and height—preferably recorded for 6 to 12 mo prior to study entry, previous corticosteroid use, onset of wheezing, asthma severity, socioeconomic status, and exposure to smoking). Standing height is best measured using a stadiometer, and measurements should be made at the same time of the day to avoid diurnal variation and by a limited number of trained observers throughout the trial. Height measurements should be performed in triplicate, with only the most reproducible (or average) value retained for analysis.

The analysis of growth data is also important. Changes in growth rate are more sensitive than analysis of height after a treatment period. A linear regression of height against time, which requires at least four measurements, should be used to minimize the influence of random errors and seasonal variation.

The two most common methods for calculating growth over time are: (*1*) growth velocity (cm/yr), and (*2*) standard deviation score (SDS)—the difference between the subject's growth velocity and normal growth velocity divided by the normal growth velocity standard deviation for individuals of the same age and sex.

Growth velocity is easier to interpret and has a more direct applicability to clinical practice. It does not, however, take age and sex into account, which are important factors in assessing normal growth, so these factors should be built into the statistical model.

SDS is advantageous when growth rates are not linear across the age ranges that are studied. It allows a more direct comparison of treatment group differences of the population under study. The use of reference data for calculating SDS is not, however, without problems. Reference data are normally cross-sectional rather than longitudinal and they may be out-of-date or nonexistent for some populations. Furthermore, children with asthma do not grow at the same rate as normal children and therefore the reference group will not provide an appropriate comparison. Thus, in studies without a control group of asthmatics, it is not possible to determine whether a change in SDS is due to disease or to treatment.

Assessment of Measurable Systemic Effects of Inhaled Corticosteroids

Most studies into possible effects on growth to date have been designed to evaluate the systemic effects of inhaled corticosteroids. Typically, these studies are parallel group studies of short duration (1 yr or less). They include only children with mild asthma and in a limited age range (6 to 9 yr), and use a fixed dose of inhaled corticosteroid that is not adjusted to disease activity or severity. As discussed earlier, these factors all increase the likelihood of detecting an adverse effect on growth (children with mild asthma have a greater systemic exposure to the inhaled drug, children 6 to 9 yr of age are the most susceptible to the effect of exogenous corticosteroids, and the effect of an inhaled corticosteroid on growth seems to be more pronounced at the beginning of the treatment). Also, the growth-inhibiting effect of mild disease is minimal and, therefore, the likelihood of a possible beneficial effect on growth by improved asthma control is small.

The results of these studies conducted during a "narrow window of childhood growth" cannot be used to predict growth during long-term treatment in a clinical setting, when the dose of inhaled corticosteroid is titrated to disease severity and all age groups are treated for asthma (90). They are, however, suitable for (*1*) assessing the relationship between dose and the growth-inhibiting effects of individual inhaled corticosteroids or inhalers, (*2*) comparing the growth-inhibiting effects of different inhaled corticosteroids or inhalers, (*3*) comparing growth during treatment with an inhaled corticosteroid with that of and another class of drug, (*4*) defining the dose of inhaled corticosteroid that is most unlikely to be associated with any detectable adverse effects on growth.

Assessment of Clinically Relevant Effects

Studies designed to assess the clinically relevant effects of inhaled corticosteroids on growth are conducted over several years and include children of all ages. In addition, the dose of inhaled corticosteroid is titrated to the severity of the disease at regular intervals.

If only children with mild disease are included, such studies can be used to compare growth during treatment with an inhaled corticosteroid with growth during treatment with an-

other class of drug or placebo, or with another inhaled corticosteroid. If children with more severe disease are included, only the last option is feasible because inhaled corticosteroids are clinically markedly more effective than other classes of drugs or placebo. Attempts to compare inhaled corticosteroids with other drugs in these patients would lead to differences in dropout rates during the study and, by the end of the study, the groups would no longer be comparable with respect to disease severity. Poor asthma control is a common reason for withdrawal from clinical trials and, because children with uncontrolled asthma grow more slowly, such withdrawals may cause an upwardly biased estimate of the mean growth rate for the control group. Finally, this study design also allows more accurate predictions about possible effects on final adult height and assessments of growth effects at different ages.

Markers of Bone Formation and Resorption

Levels of various biologic markers of bone and collagen formation and resorption, or GH concentrations and activity, have been the most popular surrogate markers of statural growth. Levels of all markers are usually measurable, as normal bone and collagen are in a constant state of turnover, maintaining a balance between resorption and formation. In simple terms, an elevation of all markers could occur when there is increased bone turnover without net loss or gain in bone mass, whereas a reduction of all markers, which is normally seen with low doses of oral corticosteroids or high doses of inhaled corticosteroids, could signify a reduction in bone turnover with a constant bone mass. Therefore, it is probably most clinically relevant to consider the *net* effect of bone formation and bone resorption (91). If, for example, formation and resorption decrease to the same extent, the changes may not be important since the net effect may be zero. An elevation of markers of bone resorption alone supposedly suggests net bone loss, whereas an elevation of markers of bone formation alone suggests net bone formation.

Effect of inhaled corticosteroids. Several placebo-controlled crossover studies have assessed markers of bone and collagen resorption and formation. All the studies found that high daily doses of inhaled corticosteroids ($>$ 400 μg) had a statistically significant effect on some of these markers in children, suggesting a reduction in both bone formation and resorption. Daily doses of budesonide or fluticasone propionate of 400 μg or less had no effect in any of the studies (49, 61, 81, 83, 92–97). All studies were short-term and involved patients with relatively mild disease.

Blood levels of various biochemical markers such as GH, IGF-1, IGF-binding protein-3 (IGFBP-3), carboxyterminal propeptide of type-1 procollagen (PICP), and the amino terminal propeptide of type III procollagen (PIIINP) have been found to correlate to some extent with statural growth rate or lower leg growth velocity (98, 99). Treatment with low doses of prednisolone (2.5 to 5 mg/d) is associated with a significant reduction in the levels of some of these markers, whereas daily doses of inhaled corticosteroids of 400 μg or less are not (81, 93, 95, 96, 100). Furthermore, daily doses of BDP and budesonide of about 400 μg (range, 200 to 1,200 μg/d) do not adversely affect urinary GH excretion (101, 102).

Leptin is a recently discovered hormone, which is thought to play an important role in the regulation of body weight and possibly also growth. Systemic corticosteroids increase serum leptin levels, but budesonide, 800 μg/d via a pMDI plus large-volume spacer (Nebuhaler), had no effect (103).

Thus, inhaled corticosteroids at standard pediatric doses ($<$ 400 μg/d) have no reported adverse effects on markers of bone formation and degradation or on markers of growth. Higher doses may, however, cause significant changes, which suggest a reduced bone turnover rate. The importance of this has yet to be established since studies have failed to find any correlation between the levels of the various markers and bone mineral density, or between changes in levels of the various markers and changes in bone mineral density over 1 and 2 yr (104).

The clinical relevance of treatment-induced changes in growth markers also remains unknown. A recent study found no correlation between the levels of various markers or corticosteroid-induced changes in these markers and statural growth during budesonide treatment for 1 and 2 yr (104), indicating that the predictive value of corticosteroid-induced changes in these markers is low and that assessment of changes is not clinically useful. This is in good agreement with the observation that growth markers have been found to correlate poorly with growth rate in healthy children (105). Furthermore, a study to assess the clinical usefulness of the various markers in children suspected of corticosteroid-induced growth retardation and children with normal growth during treatment with inhaled corticosteroids found no clinically useful differences in GH secretion, serum cortisol, osteocalcin and IGF-1 levels, or bone mineral density between the two groups (82). Thus, the relevance of changes reported from short-term studies to long-term clinical outcomes remains to be demonstrated (106).

Changes in growth markers may also occur with other forms of treatment for asthma. Sodium cromoglycate has been found to be associated with significant effects on the excretion of GH in the urine (48) and markers of bone metabolism (49), and inhaled β_2-agonists have been found to adversely affect GH secretion (50, 51, 107). Although statistically significant, these findings are probably not clinically relevant.

Short-term Growth Studies

Knemometry measures changes in short-term linear growth of the lower leg within weeks and may be a valuable adjunct/alternative to traditional methods, because it enables the study design to be well controlled. To date, all children participating in placebo-controlled, double-blind, knemometry studies have had mild asthma, which has not required continuous treatment with inhaled corticosteroids (108–117). The results have shown that the effect of inhaled corticosteroids on lower leg growth rate is dose dependent with no detectable effect at low doses. Moreover, the dose-response curves for growth inhibition seem to differ between the various inhaled corticosteroids (Figure 4).

1. Budesonide, 200 μg/d via the dry powder inhaler Turbuhaler and 400 μg/d via a pMDI plus large-volume spacer (Nebuhaler), and 200 and 400 μg fluticasone propionate, via the dry powder inhaler Diskhaler, had no adverse effects on lower leg growth rates.
2. Budesonide, 800 μg/d via Nebuhaler and 400 μg/d via Turbuhaler, and BDP, 400 μg/d via Diskhaler, were associated with a significant reduction in lower leg growth rates.
3. Budesonide via Turbuhaler and fluticasone propionate via Diskhaler were compared in a recent dose-response study (112). It was found that, microgram for microgram, the two drug-delivery combinations had similar effects. Lower leg growth rate was not adversely affected by budesonide at doses of 200 μg/d, but it was associated with a slight reduction in lower leg growth at a dose of 400 μg/d, which was significant when compared with placebo but not when compared with fluticasone propionate.

As with growth markers, the clinical implications of the findings of knemometry studies still need further assessment,

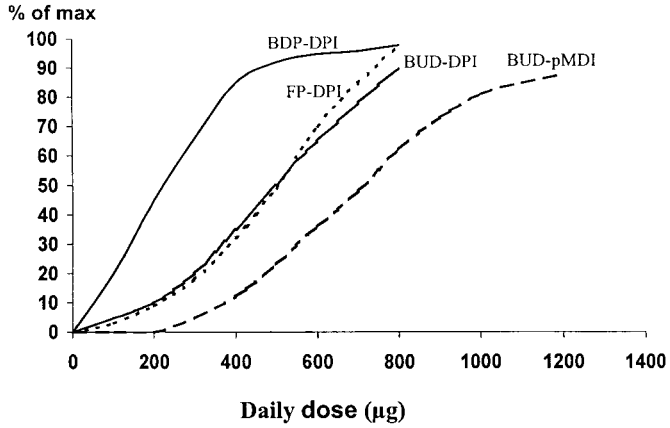

Figure 4. Dose-response curves of different inhaled corticosteroids and inhalers on the growth-suppressive effect on lower leg growth rate measured by knemometry. The curves have been constructed from the findings in randomized, placebo-controlled trials with treatment duration periods of 2 to 3 wk. Though this a not a formal meta-analysis the data convincingly show marked effects upon lower leg growth rate at quite low doses. They also suggest important differences between different drug/inhaler combinations.

since lower leg growth velocity over 1 mo and short-term corticosteroid-induced changes in lower leg growth rate do little to explain the variation in annual statural height velocity (88, 89). Treatment for 2 wk with oral prednisolone, 2.5 mg/d or 5 mg/d, or inhaled BDP, 400 μg/d, has been found to stop lower leg growth completely (118, 119). This suggests that knemometry is a very sensitive tool, which probably exaggerates the growth-stunting effects of exogenous corticosteroids. On the other hand, it also suggests that if an exogenous corticosteroid has no adverse effect on lower leg growth in a properly performed knemometry study, it is unlikely that such treatment will be associated with any growth suppression during long-term treatment. This assumption is supported by the finding that, so far, none of three well-powered growth studies that have been carried out have found any adverse effects of inhaled corticosteroids on statural growth at doses found not to adversely affect lower leg growth in well-designed knemometry studies.

Intermediate Term Studies

A large number of intermediate-term studies have evaluated the effect of inhaled corticosteroids on statural growth (14, 17, 43, 59, 65, 66, 72, 73, 120–143). Most have been carried out in schoolchildren, and none of those carried out before 1993 included a control group. Some investigations have been historical follow-up studies, whereas others have been prospective and, more or less, controlled. BDP was administered by pMDI or dry powder inhaler, and budesonide by pMDI plus large-volume spacer (Nebuhaler). None of these studies, comprising more than 3,500 children treated for mean periods of 1 to 13 yr, found any adverse effect of the inhaled corticosteroid on growth. In agreement with this, a meta-analysis of 21 studies representing 810 patients has to some extent corroborated these findings. The analysis compared the attained height with the expected height of children with asthma treated with inhaled or oral corticosteroids (144). Significant, though slight, growth impairment was found in children receiving oral corticosteroids, whereas children treated with inhaled corticosteroids attained normal height. Furthermore, there was no statistical association between inhaled corticosteroid therapy and growth impairment either at higher doses or during extended therapy.

A recent follow-up in family practices of a cohort of 3,347 children with asthma corroborated these findings, but also highlighted the complexity of the growth process. This study found that most children had normal growth rates and only those receiving daily doses of inhaled corticosteroids of 400 μg or above showed growth impairment. This effect on growth was, however, smaller than the effect of poor socioeconomic status or severe asthma (75). This study has illustrated how important confounding factors may be in growth studies, and such factors must, therefore, be accounted for in the analysis of the data.

Beclomethasone dipropionate (BDP). In contrast to these findings, several parallel-group studies conducted over the last few years have found significant growth retardation in children with mild asthma treated continuously for 9 to 12 mo with a fixed daily dose of BDP of 400 μg or above (11, 14, 21, 43, 145). As mentioned earlier, this dose is markedly higher than the dose normally required to control mild asthma. Furthermore, a dry powder inhaler or a pMDI was used for administration in all studies. These devices deposit a large amount of drug into the oropharynx, which is extensively absorbed (50%) into the systemic circulation through the gastrointestinal tract, resulting in a subsequent increase in systemic effect. It is likely that the growth-retarding effect in these studies would have been smaller if a spacer device and dose titration had been used for delivery instead of a fixed dose from a pMDI or a dry powder inhaler. The magnitude of the growth reduction in these trials has been rather consistent, ranging from 0.9 to 1.5 cm/yr of treatment.

In at least two of these studies, the difference in growth rate between BDP and placebo was mainly due to a markedly lower growth rate in the BDP-treated children during the first 3 mo of the study. After this, the growth rate in the BDP group was similar to that in the placebo group (21, 43).

Budesonide. A prospective study over 3 to 6 yr (17) measured growth in 216 children with asthma treated with inhaled budesonide and 62 asthmatic children not treated with corticosteroids. During the whole period, the annual increase in height was 5.6 cm in the control group and 5.5 cm in the budesonide group. Because the dose of budesonide varied in each individual child during the treatment period, the influence of the budesonide dose on growth could not be accurately assessed. However, when high doses were used ($>$ 400 μg/d), both growth rate and lung function were lower than during run-in and during treatment with 400 μg/d, indicating that either high doses or poor asthma control (or both) adversely affected growth.

A randomized study compared growth over 2 yr in children treated with a fixed dose of budesonide, 600 μg/d via pMDI, or placebo (143). Budesonide treatment was found not to adversely affect growth. Similar results were seen in another double-blind study in children with mild asthma. No differences were seen in growth velocity over a 9-mo period in 46 children treated with budesonide, 200 μg/d via Turbuhaler, 45 children treated with nedocromil sodium and 45 healthy children (104). In contrast, growth rate was significantly reduced in the budesonide-treated children when the dose was increased to 400 μg/d for a 3-mo period.

The largest (approximately 1,000 patients aged 5 to 12 yr of age) and longest randomized growth study conducted so far compared growth over 4.3 yr during treatment with budesonide, 400 μg/d via Turbuhaler, nedocromil, 16 mg/d, and placebo (60). In the first year of treatment, the mean growth rate in the budesonide group was significantly lower (about 1 cm/yr) than in the two other groups. The growth rate during the last 3 yr of the study was similar in all three groups and, at the end of the

TABLE 1. CONCLUSIONS FROM SHORT- AND MEDIUM-TERM GROWTH STUDIES IN CHILDREN RECEIVING INHALED CORTICOSTEROID THERAPY FOR ASTHMA

1. Controlled studies have not reported any statistically or clinically significant adverse effect on growth with orally inhaled corticosteroids at the usual childhood doses of 100 to 200 μg/d (8, 104, 145, 165).
2. Growth retardation may be seen with all inhaled corticosteroids when a sufficiently high dose is administered without any adjustment for disease severity and control.
3. Growth suppression in both short- and intermediate-term studies is dose-dependent.
4. Important differences seem to exist between the growth-retarding effects of various inhaled corticosteroids and inhalers (8, 149).
5. Different age groups seem to differ in their susceptibility to the growth-retarding effects of inhaled corticosteroids; children 4 to 10 yr of age are more susceptible than pubertal children (11, 59).
6. The growth-retarding effect of inhaled corticosteroid treatment seems to be more marked at the beginning of treatment and, in some way, becomes attenuated with continued treatment (21, 57–60).

study, bone age, projected final height, and Tanner stage in the two active treatment groups were similar to those in the placebo group. The investigators concluded that extrapolating the findings of 1-yr growth studies to subsequent years is inappropriate.

Fluticasone propionate. Fluticasone propionate, 100 μg/d, or 200 μg/d, was not found to adversely affect growth (13, 146). One study compared fluticasone propionate, 100 μg/d, with sodium cromoglycate 80 mg/d (13) in 60 children, whereas the other study (146) assessed growth rate in 300 children treated with either placebo or fluticasone propionate, 100 μg/d or 200 μg/d, for 1 yr. The reserchers concluded that prepubescent children treated with fluticasone propionate, 100 μg/d or 200 μg/d for 1 yr, grew at rates similar to placebo-treated children and at rates equal to the expected growth velocity for age.

Other inhaled corticosteroids. The effect of other inhaled corticosteroids on growth has not been thoroughly assessed. One retrospective study has found no adverse effects of triamcinolone on growth over 1 yr (134).

Conclusions from intermediate term studies. Although no formal dose-response studies have been conducted, the data suggest that the effect of inhaled corticosteroids on statural growth is dose dependent. Low doses are not associated with any detectable adverse effects, whereas higher doses normally are. Only one study compared growth rates during treatment with BDP at doses on the steep part of the growth suppressive dose-response curve. A daily dose of 800 μg was found to have a significantly greater growth suppressive effect (growth rate = 3.6 cm/yr) than a daily dose of 400 μg (growth rate = 4.6 cm/yr) (147). In good agreement with this, a recent pooling of growth data from ten randomized, controlled studies concluded that the growth-suppressive effects of inhaled corticosteroids were dose dependent.

Studies in Preschool Children

Budesonide nebulizing inhalation suspension (BIS) is the most carefully studied treatment in preschool children. In three randomized, 12-wk, double-blind, placebo-controlled studies, 223 subjects received control treatment and 447 received BIS at median total daily doses of 0.5 to 1.0 mg (148). In Study A, changes in height SDS differed significantly between the BIS-treated children and the control subjects (who did not receive inhaled corticosteroids), and there was a statistically significant decrease in growth velocity of 0.8 cm/yr in the BIS-treated group. No statistically significant differences were observed between the BIS and the control groups in changes in height SDS or in growth velocities in Studies B and C in which some of the control children also received inhaled corticosteroids.

The influence of other forms of administration and doses on growth in preschool children is less well studied. Children treated with budesonide, 200 to 300 μg/d via pMDI plus spacer (Nebuhaler), were reported to grow normally during continuous treatment for 3 to 5 yr (136). However, the conclusions of this study were weakened by the lack of a control group that did not receive inhaled corticosteroids.

Comparison of Different Inhaled Corticosteroids

A study compared annual growth rate in prepubertal children receiving either fluticasone propionate, 400 μg/d, or BDP, 400 μg/d (149). Growth rate was significantly higher during treatment with fluticasone propionate (4.99 cm/yr) than with BDP (4.09 cm/yr). This study emphazises that different corticosteroids have different potentials to inhibit growth.

In other studies, treatment with budesonide, 800 μg/d, adversely affected growth significantly more than fluticasone

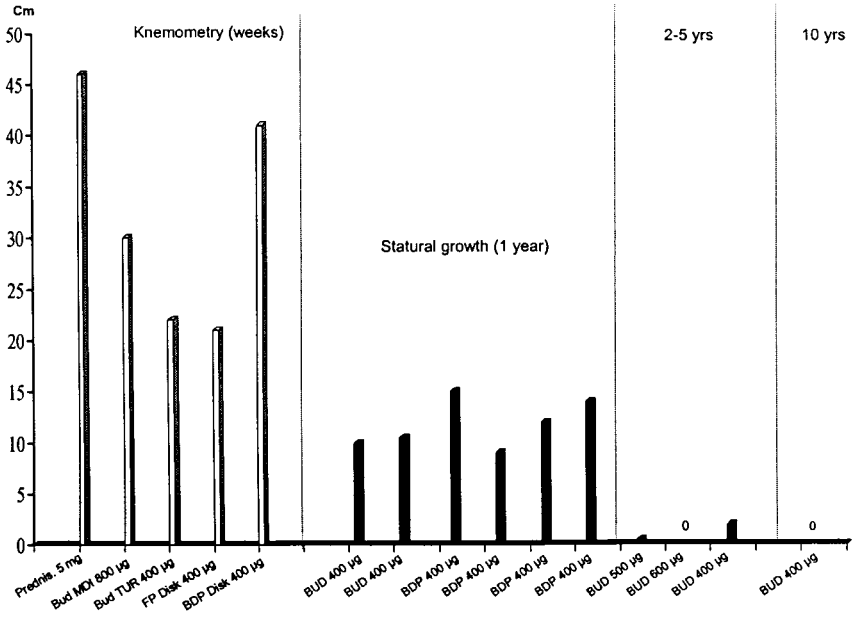

Figure 5. Expected effect that a treatment would have on attained adult height if the growth retardation measured in each individual study persisted during 10 yr of continued treatment. The data have been constructed from the findings in randomized controlled trials published as full-length papers. The expected effect of 10 yr of treatment on adult height has also been calculated on the basis of the results after 1, 4, and 10 yr of treatment in two long-term studies (9, 60). Findings in short-term studies seem to suggest a much more marked effect upon attained adult height than studies of longer duration. These calculations should be assessed in the light of the fact that all studies conducted so far (a total of six) have found that long-term treatment with inhaled corticosteroids has no adverse effect upon attained adult height.

propionate, 400 μg/d (150), and with BDP, 400 μg/d, had a significantly greater influence on growth than did fluticasone 200 μg/d (151). The differences in growth rate between the various treatments in these two studies may have been caused by differences in dose, drugs, or both.

Conclusions from Short- and Intermediate-term Growth Studies

Key conclusions from short- and intermediate-term growth studies are summarized in Table 1. These studies suggest that the growth-retarding effect of inhaled corticosteroid treatment is more marked at the beginning of treatment and, in some way, becomes attenuated with continued treatment (21, 57–60). Such a time-dependent effect on growth would explain the marked corticosteroid-induced reductions in lower leg growth rate observed in the knemometry studies (108, 109, 116, 118, 152, 153) compared with the smaller reduction in statural height found in studies of longer duration.

In an attempt to assess the possibility of a time-dependent growth-retarding effect of inhaled corticosteroids, the data from various randomized controlled growth studies of different durations have been used to calculate the expected effect a treatment would have on attained adult height if the growth retardation measured in each individual study persisted over 10 yr of continued treatment (Figure 5). Although this analysis does not lead to a firm conclusion, it strongly suggests the possibility of a time-dependent effect on growth.

Long-term Studies and Studies of Final Adult Height

Most physicians consider attained adult height to be the most important growth outcome and the key question with regard to effects on growth is whether the slowing in short-term growth rates leads, ultimately, to a diminished adult height. At present, few prospective long-term studies of attained adult height have been conducted. Because the number of studies is low, and the design and methods of the various studies vary, each study will be briefly summarized.

Retrospective studies. One study (154) compared the recorded adult heights of all pregnant women born in Sweden between 1960 and 1974 with the heights of all pregnant women with asthma (n = 2,738) born during the same period. The use of inhaled corticosteroids was very low in the study population, because inhaled corticosteroids were not available or reserved for more severe cases at this time. The adult height of women with asthma was significantly lower than the adult height of women without asthma, and patients who had been hospitalized with asthma early in life tended to be shorter than patients who had been hospitalized later in life. The investigators concluded that asthma may itself adversely affect adult height and that this effect may be more marked if the asthma is severe. This is in good agreement with the findings of other studies in children with asthma (59, 74) and the observations in children with other chronic diseases (155, 156), but contrasts with the findings in children with atopic dermatitis who, like children with asthma, may also have a prepubertal growth delay but no apparent adverse effect on adult height (157, 158). This is probably because atopic dermatitis is a less severe disease.

Other studies (74, 159–161) have compared the measured adult heights of corticosteroid-treated children with their target adult heights. One study found that the adult height of children with asthma treated with inhaled corticosteroids was not significantly different from that of adults with asthma who were not treated with corticosteroids (159). Another study (74) found that mean attained adult height in patients who received inhaled corticosteroids during childhood was the same as that in those who had never received such treatment. However, the difference between adult height and target height was significantly lower in corticosteroid-treated patients than in those who had never received inhaled corticosteroids. Furthermore, the difference between adult height and target height was lower in patients who had been hospitalized for asthma than in those who had never been hospitalized, indicating that asthma severity negatively influenced attained adult height. A third study (160) compared the measured adult heights of 97 children treated with inhaled corticosteroids during childhood with the adult heights of 70 non-corticosteroid-treated patients with asthma and 136 healthy control subjects. Survey-reported parental heights were used to calculate the target heights of the study population. Use of inhaled corticosteroids did not adversely affect adult height. Similar results were reported in a study that assessed the longitudinal growth of 97 children treated with BDP in daily doses of 300 to 800 μg for more than 8 yr (161). Adult heights were within the expected range, although no predicted adult heights were given.

Prospective studies. Balfour-Lynn (65, 66) followed 66 children with asthma for an average of 13.1 yr. No difference was found in overall growth rate between children who received inhaled BDP and those who did not. Final heights were reported to be within the expected range in the children treated with BDP. No data on predicted height estimated from parental height were given.

Recently, the findings of all these studies were corroborated by a 14-yr prospective, long-term study in which asthmatic children were treated with inhaled budesonide for several years in doses tailored to disease severity (59). There were 142 children who attained adult height after a mean of 9.2 yr of budesonide treatment at a mean daily dose of 412 μg. Mean cumulative dose was 1.35 g (range, 0.41 to 3.99 g) and 18 control children with asthma, who never received any inhaled corticosteroids, and 51 healthy siblings were also followed until adult height was attained. The budesonide-treated children attained their expected adult height to the same extent as their healthy siblings and the control children. Adult height was not influenced by the duration of budesonide treatment or the cumulative dose of budesonide. Height standard deviation scores (SDS) before treatment with budesonide correlated positively with percent predicted FEV_1, indicating that asthma severity influenced growth. Furthermore, adult height depended significantly upon height SDS before budesonide treatment (Figure 6). Growth rates were significantly reduced during the first 2 yr of budesonide treatment, but the reduction in annual growth

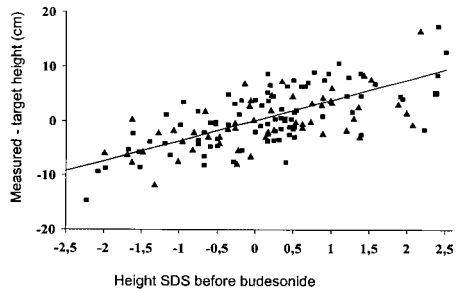

Figure 6. Correlation between height standard deviation score before budesonide treatment and the difference between measured and target adult height. The correlation was highly significant ($p < 0.001$), so that children who were short (had a low height standard deviation score) before treatment with budesonide tended to end up shorter than expected, whereas children who were tall before treatment with budesonide tended to end up taller than expected. The dose of inhaled budesonide and the duration of treatment before adult height was attained did not influence adult height.

rate did not persist, and the changes in growth rate during this period showed no relation to the differences between measured and target adult height (Figure 7).

The authors concluded that long-term treatment with inhaled budesonide did not adversely affect adult height, whereas poorly controlled asthma did. Furthermore, changes in growth rate during the first year of budesonide treatment were not useful in predicting adult height. These conclusions are in good agreement with the findings in the largest and longest randomized growth study conducted so far (60).

Although prospective studies of several years duration and retrospective analyses may be criticized for being less controlled than prospective, short-term studies, some conclusions from them about the effect of inhaled corticosteroids on adult height seem to be justified.

1. Uncontrolled or severe asthma seems to adversely affect growth and attained adult height.
2. Corticosteroid-induced changes in growth rate during the first 1 or 2 yr of treatment do not predict adult height.
3. Children with asthma treated with inhaled corticosteroids have consistently been found to attain normal final adult height.

Discrepancies between Intermediate- and Long-term Growth Studies

The reason for the apparent discrepancy between the findings of some intermediate-term studies and the conclusions of the studies on adult height is not clear. Intermediate studies with BDP have found a growth retardation of 1.5 cm/yr. An annual growth retardation of 1.5 cm, if persistent, would be expected to result in a cumulative mean reduction in measured adult height of 15 cm were the treatment given continuously for 10 yr. Such marked effects would be difficult to miss in the day-to-day clinic or in long-term prospective studies. Some possible explanations for the discrepancy are as follows:

1. As mentioned earlier, the correlation between two consecutive annual height velocity values for normal prepubertal children is poor. A low gain in 1 yr is not necessarily followed by a low gain the next year and vice versa (88). The correlation between 1-, 2-, 3-, and 4-yr growth velocities is only partial (88), and growth rate computed over a period of 3 or 4 yr in childhood explains only 34 and 38% of the variation in final height, respectively.
2. The growth retarding effect of exogenous corticosteroids is most pronounced during the first year of treatment (21, 57–60). Therefore, conclusions from rather short-term studies of 1 yr should not be extrapolated to the long-term situation (90).
3. Corticosteroids seem to retard bone maturation. If this occurs to the same extent as the retardation of growth, then final height should not be adversely affected (since bone age will correspond to height age). Such children will grow for a longer period than their peers and eventually attain normal final height.
4. The results obtained in prepubertal school children may not be valid in other age groups because prepubertal children may be more sensitive to the growth-retarding effect of inhaled corticosteroids (11, 59). If the pubertal growth spurt is not adversely affected, the effect on final height may be rather small.
5. In a real-life situation children with mild asthma are not treated continuously with a rather high, fixed dose of inhaled corticosteroid. The dose is adjusted to the severity of the disease. Only children with moderate or severe asthma would require continuous treatment with daily doses of 400 μg or more. The systemic effects in these children may be lower than in children with mild disease (52–55). Many clinics would also use spacers when administering inhaled corticosteroids with low first-pass metabolism.
6. Compliance may be lower during long-term "real life" treatment than during a controlled trial with several visits to the clinic, though when compliance was assessed in two studies it did not seem to explain the findings (59, 60).

More prospective studies are needed to assess the relative importance of these possibilities.

Problems in Growth Assessment: Individual Sensitivity to Corticosteroids?

Case reports suggest that individual children may be particularly sensitive to the growth-retarding effects of exogenous corticosteroids (162). When such reports are evaluated it must be remembered that growth is a complex process that may be affected by a host of factors, including disease severity, social and psychological factors, nutrition, body composition, age, puberty, genetic factors, and treatment.

Healthy children show spontaneous fluctuations in growth velocity, often with seasonal variations (Figure 8), with most children growing faster in the summer than in the winter (85). In some children fluctuations are not purely seasonal, but cycles of growth may span two or more years (86). This leads to

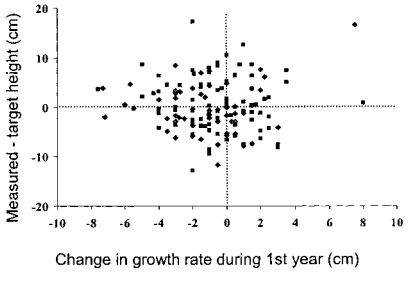

Figure 7. Association between changes in growth rate during first year of budesonide treatment and the difference between measured and target adult height in 142 children with asthma treated with inhaled budesonide for a mean of 10 yr. The changes in growth rate during the first year of treatment were not correlated with the differences between measured and target adult height ($p = 0.44$), emphasizing that inhaled corticosteroid induced changes in growth rate during 1 yr of treatment are unrelated to the attained adult height even if the inhaled corticosteroid treatment is continued for several years. So, even if a child grows 3 cm less during the first year of treatment with an inhaled corticosteroid, this will not influence adult height.

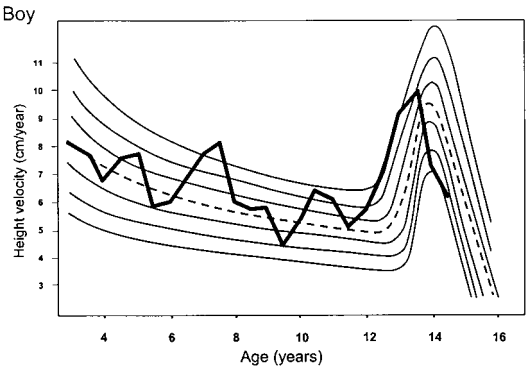

Figure 8. Individual growth velocity curve in a normal child. Marked variations are seen in annual growth rate. If an inhaled corticosteroid had been started at 7 yr of age and stopped at 9.5 yr of age, it would probably have been concluded that the treatment caused growth stunting, particularly because "apparent catch-up growth" is seen from 9.5 to 10.5 yr of age.

a very poor correlation between the growth velocity in 1 yr and that in the next year (87). These variations in combination with the standard error of the height measurement, which for trained observers is around 0.2 to 0.3 cm, and the abnormal growth pattern seen in many asthmatic children (which is unrelated to the use of inhaled corticosteroids), mean that case reports of apparently reduced growth in association with an asthma treatment should be interpreted with caution.

A recent study of final adult height in a cohort of 142 children did not find any evidence of a subgroup of patients who were more susceptible to the effects of long-term treatment with inhaled corticosteroids (59), indicating that this phenomenon is probably rare. Although increased individual sensitivity to the growth-retarding effects of inhaled corticosteroids probably exists, firm conclusions about cause and effect relationships in association with apparent changes in growth rates should be made with caution.

DISCUSSION AND SUMMARY

Inhaled corticosteroids have been used for the treatment of asthma in children for more than 20 yr. During this time, a substantial number of studies has been performed evaluating the safety and efficacy of this therapy. Generally, the results have been reassuring. Inhaled corticosteroids have a marked effect on both the immediate and the long-term aims of asthma therapy. In patients with mild and moderate asthma, low daily doses of around 100 to 200 μg/d of inhaled corticosteroid produce a clinical effect that, in most trials, is better than the effect of any comparator treatment. No adverse effects on growth have been associated with treatment in this dose range and idiosyncratic adverse reactions are rare. Yet, in the interest of "doing no harm," many clinicians are reluctant to prescribe inhaled corticosteroids for pediatric patients with asthma because of concerns about growth. Ironically, the available evidence suggests that perhaps the greater harm to children with asthma arises from the avoidance of the use of inhaled corticosteroids when they are needed (17, 163–166). Thus, avoidance of inhaled corticosteroid therapy has been observed to lead to poorer asthma control, poorer growth as result of poorer asthma control, increased morbidity and hospitalizations, and more frequent need for courses of treatment with systemic corticosteroids.

Undoubtedly, the reluctance to use inhaled corticosteroids is based on the results of growth data obtained in school children with *mild* asthma who have been overtreated, as they have not required the investigational doses of inhaled corticosteroid for optimal asthma control. However, conclusions from such studies should be applied with great caution to the day-to-day treatment of patients with mild or moderate asthma or of patients with more severe disease who may actually require the doses used in these studies to control their disease. *Clinically relevant safety data should be obtained in clinical trials that tailor the dose of inhaled corticosteroid to the severity of the disease.* Often, the conclusions of such "dose-tailored" studies seem to be different from those of studies in which patients are overtreated with a fixed (often high-dose) regimen that does not allow for dose adjustments as indicated by the individual's clinical picture.

Higher doses of inhaled corticosteroids consistently lead to a reduced growth rate during the first year(s) of treatment, particularly in patients with mild disease. However, attained adult height is not adversely affected, even if such doses are used for several years, although these children are likely to be 1 to 2 cm shorter than their peers for some years. This risk is also present if the asthma is not sufficiently controlled, but, in contrast to the growth retardation caused by high dose inhaled corticosteroids, the growth inhibition caused by uncontroled disease may also adversely affect adult height.

Growth studies with higher doses (> 200 μg/d) of inhaled corticosteroids should be performed in patients with moderate or severe disease in order to be clinically relevant. Such studies should mainly be performed to compare different corticosteroids or inhalers in order to define a therapeutic index or to provide evidence for deciding whether to increase the inhaled corticosteroid dose or to add other therapy (such as a long-acting β_2-agonist or a leukotriene receptor antagonist) in a child whose asthma is inadequately controlled. Findings in such studies are generally not relevant for decisions about choosing between inhaled corticosteroids and other asthma drugs, since doses of inhaled corticosteroids that are equieffective with other asthma drugs are normally lower ($\leqslant 200$ μg/d) than those used in these studies.

Because the occurrence of measurable systemic effects and risk of clinical side effects increases with dose, the lowest dose that controls the disease should always be used. Furthermore, inhaler-corticosteroid combinations with a high clinical efficacy/systemic effect ratio should be used. If a child is not sufficiently controlled on a low dose of inhaled corticosteroid it might be better to add another drug to the low dose inhaled corticosteroid treatment rather than to increase the corticosteroid dose. Further studies are needed to assess that and at which dose this should be done for the individual corticosteroid-inhaler combinations.

Finally, the literature on inhaled corticosteroids and growth calls for a reappraisal of which study designs that should be used when new inhaled corticosteroids are assessed. In all studies that have found a significant corticosteroid-induced effect on growth, this effect has been statistically significant already after 3 mo of treatment. Continuing the study for another 9 mo has not provided any additional information in any of the studies. Moreover, the available evidence suggests that growth during 1 yr is not useful in predicting growth during longer periods of time or attained adult height. Much longer studies are required for that. So why do 1-yr growth studies? A 3-mo study (or perhaps a knemometry study) seems to have the same power in detecting systemic effects of the inhaled corticosteroid treatment as a 1-yr study, and there is no evidence that the extra 9 mo of treatment would increase the predictive value about long-term growth or effect on adult height or make the study more clinically relevant. Clinically relevant growth studies should be of a totally different design and duration.

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