

Effects of inhaled corticosteroids on growth

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Inhaled corticosteroids are an established treatment for asthma in childhood. The risk of adverse events associated with conventional doses of inhaled corticosteroids is low, but in children with asthma concern remains about the potential effects of these compounds on growth. Short-term growth in children can be measured with knemometry. This technique measures changes in lower leg length that can be detected over periods as short as days or even intradaily. However, nonlinearity of lower leg growth and the complexity of statural growth confound any attempts to derive a predicted height from short-term measurements of the lower leg. Knemometry is better at detecting growth suppression than growth promotion. With knemometry, inhaled fluticasone propionate 200 µg/day had no effect on lower leg growth, but beclomethasone propionate 400 µg/day significantly reduced lower leg growth. Inhaled budesonide also caused a dose-dependent reduction in lower leg growth, but this only reached significance at the 800 µg/day dose. Long-term growth in children is measured with stadiometry. Growth velocity can only be determined from measurements of height taken over a period of at least 1 year. There is no evidence that inhaled corticosteroids at conventional doses have an adverse effect on the final height of children, but it is important to be aware of the growth-impairing effect of poorly controlled asthma. All children with asthma receiving inhaled corticosteroids should have their growth monitored, and any deviation from the expected pattern should be investigated. The effect of early intervention with inhaled steroids in childhood warrants further investigation. (*J Allergy Clin Immunol* 1998;101:S451-5.)

Key words: *Inhaled corticosteroids, childhood asthma, growth, knemometry, stadiometry*

Inhaled corticosteroids are an established treatment for asthma in childhood. Their success is based on their ability to improve control of asthma, to allow a reduction in the dosage of other drugs such as oral corticosteroids, and their potential role in limiting the risk of long-term decline in lung function. These impressive benefits are achieved at the risk of a few relatively common, minor unwanted local effects such as oral candidiasis and dysphonia. The clinical relevance of the systemic changes detected when inhaled corticosteroids are used at very high doses remains unclear.

The most important properties of all inhaled corticosteroids are high topical potency¹ combined with low systemic bioavailability,² and this is particularly true of the new agent, fluticasone propionate. The risk of adverse events associated with treatment is low, and there

Abbreviations used

BDP: Beclomethasone dipropionate
FP: Fluticasone propionate

are no reports of any life-threatening events. There is limited knowledge of the true benefits and risks of inhaled corticosteroids at various doses, and full dose-response curves for the therapeutic effects of inhaled corticosteroids in children have not been established.

Studies examining growth in children with asthma are confounded by many factors including the effect of the disease itself, if poorly controlled, on growth. There is no evidence of an adverse effect on statural growth with conventional inhaled steroids at doses <800 µg daily, and accumulating evidence with FP is also reassuring on this issue. The clinical relevance of knemometric studies to long-term growth has yet to be fully determined.

SHORT-TERM GROWTH (KNEOMETRY)

The first reports of the systematic observation of short-term growth phenomena date back to the early 18th century, when Wasse described variations in his own height during the course of a day³ and Montbeillard reported his son's loss of height after an all-night party.⁴ Since then, there have been many attempts to accurately assess short-term growth, and thus in the early 1980s, the knemometer was designed by Valk. The device takes its name from the Greek *knēmh*, meaning the lower leg, and was designed to measure lower leg growth with a precision not previously achievable. Independent groups in the United Kingdom, Germany, the Netherlands, Canada, and Denmark have evaluated the device,⁵⁻¹⁰ and knemometry now has an accepted role in the measurement of growth rate changes on a weekly or even daily basis. Over longer time intervals, however, this technique offers no more information than conventional auxological methods.^{5, 9, 11}

METHODOLOGY

The principle of this measurement is in the use of an electronic ruler to measure a highly stable aggregate of bones between the upper surface of the knee and the sole of the foot. In this region there is very little interposing soft tissue and hence estimated changes in the length of the lower leg represent true bone growth or compression. Much of the apparatus is designed to ensure highly reproducible orientation and positioning of the limb at each visit to maximize the precision of the measurement. The child is seated on an adjustable, moveable chair with the feet placed on an individually

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TABLE I. Short-term lower leg growth velocities of children with asthma during treatment with inhaled corticosteroids in two clinical studies

Study	Lower leg growth velocity (mm/week) (No. of subjects)			
	Washout	FP 200 µg/day	BDP 400 µg/day	BDP 800 µg/day
Wolthers and Pedersen (1993) ²⁴	0.61 (n = 17)	0.34 ± 0.29 (n = 17)	0.09 ± 0.34 (n = 17)	0.06 ± 0.21* (n = 17)
MacKenzie and Wales (1991) ²⁵	Run-in	FP 200 µg/day	BDP 200 µg/day	BDP 400 µg/day
	0.38 ± 0.12 (n = 13)	0.62 ± 0.34 (n = 7)	0.34 ± 0.20 (n = 13)	0.20 ± 0.16† (n = 13)

Results are expressed as mean ± SD.

* $p < 0.05$, significantly different compared with washout period.

† $p < 0.05$, significantly different compared with FP 200 µg/day.

drawn template. A frictionless measuring plateau is lowered onto the upper surface of the knee, which is flexed to 90 degrees. The lower leg is then moved from side to side and backward and forward until the maximum reading is obtained. This technique is accurate to 0.1 mm. At each visit, four separate recordings of the child's lower leg length are made, and the mean or modal^{5, 7} measurement is used to represent lower leg length.

Valk described the intradaily variation in lower leg length with postural compression tending to occur in the morning and after physical exertion.¹² Thus ideally, children should be measured at the same time of day and after similar levels of activity on each occasion. In practical terms this means measuring children at the end of the school day on the same day of the week throughout the period of observation.

Knemometry as described above can be reliably performed on cooperative children between the ages of 3.5 years and puberty. The neonatal knemometer, developed by Fleischer Michaelsen et al.,¹³ offers the opportunity to study lower leg growth from birth to early childhood, but this method is highly dependent on an experienced observer.¹⁴ The teenage years remain inaccessible to this technique because the dynamics of short-term growth at puberty have not been studied sufficiently to permit meaningful analysis. The recently described portable knemometer¹⁵ is very similar to original design by Valk but uses a standardized seat position, making it easier and quicker to use.

Wales and Milner⁵ assessed the operational characteristics of the knemometer designed by Valk by performing duplicate measurements on a group of children without knowledge of previous recordings. They demonstrated that the knemometer provided a precise, reproducible, and observer-independent assessment of lower leg length. The coefficient of variation of their measurements was 0.09%, which translates to a machine precision of 0.2 mm for a standard lower leg. Subsequent studies have used single observers, but measurements continue to be made blind from previous recordings. The mean lower leg growth rate obtained by this method

(mean 0.43 mm/week; range 0.32 to 0.57 mm/week) was highly comparable to the velocity previously determined by radiographic means. Thus the knemometer can detect actual changes in lower leg length over very short periods of time.

Lower leg growth can be analyzed by calculation of the growth velocity (in millimeters per week) by linear regression through the observations of leg length against time. This produces a traditional plot of distance traveled against time as used in a standard growth chart. This type of analysis is used widely,^{5, 16-24} but Hermanussen et al.²² prefer a rolling plot of 4-week velocity against time. This method produces a plot that can undergo waveform analysis, although the method is prone to show artifactual effects. Hermanussen et al. also described the process of lower leg growth occurring in a series of mini-growth spurts and lulls. The nonlinearity of lower leg growth and the irregularity of the growth process confound any attempts to derive a predicted height velocity from short-term measurements of the lower leg.^{5, 9, 11} Moreover, as a clinical tool, knemometry is better at detecting growth suppression than growth promotion.^{16, 18}

KNEMOMETRY AND INHALED CORTICOSTEROIDS

As part of a double-blind study designed to assess the efficacy and safety of FP administered with a dry powder inhaler, the lower leg growth of 13 children with asthma receiving either FP 200 µg/day or placebo was studied.²⁵ There was no significant difference ($p = 0.7$) in lower leg growth rate between FP and placebo (Table I). The lower leg growth rate during treatment with FP was highly variable, with an apparent mean velocity of 0.62 mm/week, which is just above the normal range. There were only seven children in this treatment group, and a probable mini-growth spurt was observed in one child, which may account for the apparent growth promotion.

The lower leg growth rate of the same 13 children during treatment with two doses of beclomethasone dipropionate 200 µg/day and 400 µg/day, by means of a dry powder inhaler, was also studied.²⁵ The lower leg

growth rates before treatment and during treatment with the lower dose of BDP were at the lower end of the range found in nonasthmatic children.⁵ However, there was a significant reduction ($p = 0.033$) in lower leg length during treatment with BDP 400 $\mu\text{g}/\text{day}$ compared with baseline.²⁵

In a similar study, Wolthers and Pedersen²⁴ investigated short-term growth in 19 school children with asthma during treatment with FP 200 $\mu\text{g}/\text{day}$ or BDP 400 or 800 $\mu\text{g}/\text{day}$, all given by a dry powder inhaler. It was found that BDP 800 $\mu\text{g}/\text{day}$ significantly reduced in growth velocity compared with FP (Table I).

Wolthers and Pedersen^{21, 26} have also measured lower leg growth in children with asthma receiving inhaled budesonide. Knemometrically derived lower leg growth rates were reduced by budesonide in a dose-dependent manner (Fig. 1); these findings were very similar to our own results. The pretreatment growth rate was higher in the Danish study, possibly reflecting the fact that the Danish children had milder asthma at study entry. The same authors also reported their experience using an intranasal dry powder budesonide preparation in children with allergic or perennial rhinitis and found no evidence of short-term growth suppression during 4 weeks of treatment with budesonide 200 or 400 $\mu\text{g}/\text{day}$ taken once daily.²⁷

Bisgaard²⁸ used an adapted handheld knemometer to study the effect of inhaled budesonide on lower leg growth in a group of children with asthma who were 13 to 36 months of age. In this blinded, randomized, crossover study, children received placebo or budesonide 200 or 800 $\mu\text{g}/\text{day}$, for 4 weeks, administered with a pressurized metered dose inhaler with spacer and face mask. The lower leg growth rate during the high-dose treatment was suppressed significantly compared with placebo, but the growth rate during low-dose treatment was not significantly different from placebo.

LONG-TERM GROWTH (STADIOMETRY)

It is well recognized that the long-term use of oral corticosteroids in childhood results in permanent stunting of growth²⁹ and that asthma itself can impair growth.³⁰ Studies of the interaction of inhaled corticosteroids and growth are subject to a number of confounding factors such as disease severity, seasonal variation in growth rate, pubertal status, and socioeconomic factors.

Height is the most reliable of classic anthropometric techniques⁴ but artifactual variations in this measure still occur.³¹ Accurate and precise measurement of stature is central to growth assessment and can only be ensured by careful calibration of the height measurement instrument and by obtaining at least two measurements of the individual child at each attendance. The coefficient of variation on a measurement can be as little as 0.1%. The accuracy of measurements can also be improved by using a single observer.³¹

Normal growth patterns in children are a good clinical indicator of general well-being although not an absolute

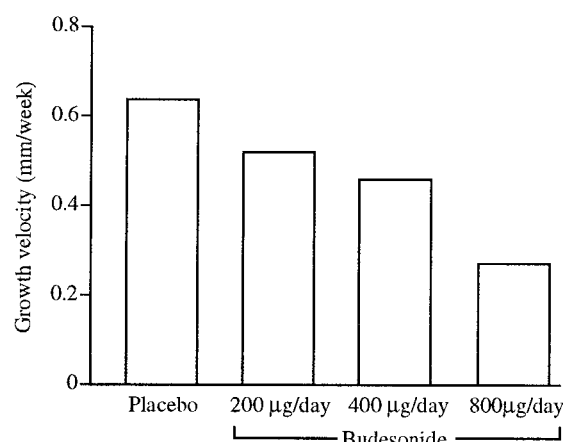


FIG. 1. Dose-dependent reduced lower leg growth velocities of 14 children with asthma, 6 to 13 years of age, during 4 weeks of treatment ($p = 0.03$) with placebo and budesonide 200, 400, and 800 $\mu\text{g}/\text{day}$. Results are expressed as mean values.²¹

indication of the absence of disease. Stadiometry provides an accurate, noninvasive clinical tool that is universally available, relatively inexpensive, and requires little formal training in its use. It does not provide rapid answers to questions about growth rates or the effect of different treatments on growth, but it does provide useful long-term information when it is used correctly.

Possible effects on growth in children with asthma receiving inhaled corticosteroids have been extensively studied, but as yet there has been no definitive conclusion, although it is generally agreed that poorly controlled asthma is the single most detrimental influence on growth.³² Although children with asthma may have retardation of growth and maturation, they will ultimately attain the height and weight predicted from their parental range. Children with mild asthma may actually become taller and heavier than their nonasthmatic peers.³³

While there is some evidence that higher doses of inhaled corticosteroids may result in short-term reduction in growth velocity and delayed puberty, there is no evidence of any reduction in the final height attained by children treated with inhaled corticosteroids at doses up to 800 $\mu\text{g}/\text{day}$. Recent clinical studies of growth rates during 1 year of treatment with FP 100 to 200 $\mu\text{g}/\text{day}$ have shown no adverse effect on growth.³⁴⁻³⁶

EARLY INTERVENTION WITH INHALED CORTICOSTEROIDS

The possible risks and benefits to the developing lung associated with the introduction of inhaled corticosteroid therapy during early postnatal life are currently much debated and, so far, unproven. The natural course of asthma itself may lead to the loss of lung function, as reported in cohort studies of young children followed through adolescence into adulthood.^{37, 38} It has therefore been suggested that asthma persisting throughout childhood may contribute to chronic obstructive pulmonary disease in late adulthood. Relatively little research

has been performed concerning the inflammatory changes that characterize childhood asthma. Most studies have focused on adults with mild asthma, but the pathological changes in children are thought to be similar. Research has shown the presence of bronchial inflammation in patients with asymptomatic and mild asthma, together with collagen deposition and fibrosis being observed in the airways of these patients.^{39, 40} It is likely that chronic inflammation causes remodeling of the airways, with mucosal thickening and smooth muscle hypertrophy. The presence of bronchial hyperreactivity may reflect airway remodeling and serve as a surrogate marker for the disease process. Any treatment strategy should be directed at reducing ongoing airway inflammation. Inhaled corticosteroids are the most effective drugs currently available for suppressing the inflammatory component of asthma, and they have been shown to prevent many of the pathological changes seen in the airways of asthma patients.⁴¹ Continued asthma control requires regular inhaled corticosteroid maintenance treatment.^{42, 43}

Clinical studies have shown that suboptimally treated asthma may result in airway obstruction and that effective treatment with inhaled corticosteroids can reduce this and possibly even prevent irreversible airway obstruction if the treatment is started early after the onset of symptoms.^{44, 45} Early intervention with inhaled corticosteroids reduces the undertreatment of asthma that is often observed in mild cases of asthma in childhood and also facilitates long-term control of the disease. In the study by Agertoft and Pedersen⁴⁵ it was also suggested that early treatment with inhaled corticosteroids had no adverse effect on growth.

Since the effect of inhaled corticosteroids may depend on the time between onset of symptoms and start of treatment, many clinicians now consider the use of inhaled steroids in all but the mildest cases, in the hope of preventing any irreversible decline of lung function.

CONCLUSIONS

The clinical relevance of markers of the systemic effects of inhaled corticosteroids in children with asthma remains uncertain because the scientific literature suggests that there are no clinically significant changes in the various parameters with doses of inhaled corticosteroids <800 µg/day. Given the difficulties in collecting appropriate blood and urine specimens from children, the lack of robust age- and sex-specific normal ranges, and the confounding influences of the disease itself, the routine use of blood and urine tests is an unattractive option.

Knemometry provides a powerful tool for accurate measurement of growth and can detect changes in lower leg growth on a daily or even intradaily basis. The device is designed to provide highly reproducible measurements with a precision of 0.2 mm. Maximum reproducibility is achieved by taking measurements at the same time of day and after similar levels of activity. Knemometry is better at predicting growth suppression than growth promotion and, using this technique, short-term

growth suppression has been observed in children receiving oral corticosteroids and those receiving dose of inhaled corticosteroids that are at the top of the dose-response curve. The significance of short-term growth changes on long-term growth patterns has yet to be determined.

The measurement of growth with the use of stadiometry provides a noninvasive tool that is widely applicable both in hospital and in the community, but it does not provide useful information over periods of less than 1 year. The effect of early intervention with inhaled corticosteroids in childhood requires further study. All children with asthma receiving inhaled corticosteroids should have their growth monitored, and any deviation from the expected pattern should be further investigated.

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