Effect of inhaled beclomethasone dipropionate and budesonide on growth in children with asthma

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Introduction

The decision to prescribe a medication long term to a child must be made with care because of possible detrimental effects on normal development. Current asthma guidelines advocate the use of inhaled corticosteroids in children with moderate or severe asthma (1,2). Corticosteroids administered systemically can impair linear growth (3,4) and height (5), possibly as a result of subnormal adrenal androgen and/or growth hormone (GH) production (6) and direct effects on bone and connective tissue growth (7). Although administering corticosteroids via inhalation is associated with fewer systemic effects compared with oral administration, there is recent evidence that consistent administration of inhaled corticosteroids can affect growth (8,9). The inhaled corticosteroids used most commonly in children with asthma are beclomethasone dipropionate (BDP) and budesonide. Following a brief review of mechanisms by which corticosteroids suppress growth, this article will summarise data pertaining to the effect of these two agents on growth in children with asthma.

Mechanism of Growth Suppression by Glucocorticoids

The pathogenesis of growth suppression by corticosteroids is complex and multifactorial, involving several steps in the cascade of events that leads to linear growth. These include inhibition of GH secretion and its subsequent action, insulin-like growth factor-I activity, collagen synthesis and adrenal androgen production (7). The mechanism(s) by which inhaled corticosteroids could exert a suppressive effect growth is not well characterised. In contrast to oral corticosteroids, inhaled corticosteroids have not been associated with alterations of the GH axis. No significant change in GH production was observed in 12 children treated with inhaled BDP and budesonide 400 µg daily for 2 weeks (10). Similarly, in a 1 yr longitudinal study involving 52 asthmatic children (some of whom exhibited slowed growth), inhaled BDP or budesonide had no effect on GH secretion (11).

Biochemical markers of bone growth and metabolism have not proved to be useful for predicting or detecting adverse effects of inhaled corticosteroids on growth. Osteocalcin concentration has a good correlation with growth but, even at dosages that have been shown to suppress growth in children, inhaled corticosteroids have minimal effect on serum osteocalcin concentrations and other biochemical markers of bone metabolism (12,13). These findings have lead to speculation that inhaled corticosteroids may have an effect on growth that is not mediated through an effect on bone (12).

Effects of inhaled corticosteroids on growth do not always correlate well with other measurements of systemic bioavailability, such as suppression of the hypothalamic-pituitary-adrenal axis. For example, Agertoft and Pedersen (13) found that treatment with fluticasone propionate 200 µg and 400 µg daily, or budesonide 400 µg daily, for 2 weeks in 24 children caused a significant reduction in urinary cortisol concentrations compared with placebo; however, only the budesonide 400 µg day⁻¹ dosage caused a significant reduction in mean lower-leg growth rate. Conversely, growth rate can be reduced in the absence of changes in cortisol production. In a 7 month study, Doull et al. (9) observed a significant reduction in mean linear growth rate in children treated with BDP, but these children had no significant change in cortisol production. Consequently, monitoring adrenal function or serum markers of bone metabolism is not useful for predicting
or detecting an effect of inhaled corticosteroids on growth; careful stadiometric measurements of treated children remain essential.

**Effect on Growth Rate**

When discussing studies of the effect of medication on growth in asthmatic children, it must be kept in mind that physiological delayed puberty and impaired growth rate have been observed in children with asthma who were not receiving inhaled or oral corticosteroid therapy (14). This delay in the growth process is thought to be due to effects of asthma itself and may result in slowing of early adolescent growth (15) but will not necessarily influence final adult height (16,17).

In studies examining the effect of inhaled corticosteroids on growth, growth rate has generally been assessed by measuring statural height or by knemometry (measuring the growth velocity of the lower leg). Although knemometry is useful for detecting changes in linear growth velocity over short periods of time, it does not accurately predict long-term statural growth (18).

**SHORT-TERM STUDIES**

The results of short-term studies of inhaled BDP and budesonide on growth rate are summarised in Table 1. It is difficult to form a consensus from these short-term studies because patient clinical characteristics differed significantly and small numbers of children were studied. Bisgaard (19) studied very young children who had recurrent wheezing. The children included in the three knemometry studies conducted by Wolthers and Pedersen (21–23) all had mild asthma and, therefore, might not constitute representative candidates for inhaled corticosteroids therapy according to current guidelines. In addition, the method of administering the inhaled corticosteroids differed between studies.

Results of knemometry studies have not been consistent even between two studies in comparable groups of children (similar age, mild asthma) receiving similar dosages of budesonide via the same delivery method. In a cross-over study comparing 18 day treatment periods of budesonide 200 and 800 µg day⁻¹, both dosages were found to reduce significantly the velocity of lower-leg growth compared with baseline (21). In contrast, a larger, parallel-group study found that budesonide 800 µg day⁻¹, but not 200 or 400 µg day⁻¹, had a significant effect on lower-leg growth rate compared with baseline (22). These inconsistencies probably reflect the sensitivity of the measurement technique in detecting the (normal) markedly irregular pattern of lower-leg growth from week to week.

Despite these shortcomings, knemometry may indicate short-term growth-suppressive effects of inhaled corticosteroids. Taken as a whole, these short-term studies suggest that the effect of inhaled corticosteroids on lower-leg growth rate is dose related, with a statistically significant impact being more common at dosages ≥400 µg day⁻¹. Reassuringly, the growth rate reduction associated with budesonide 800 µg day⁻¹ is still less than that associated with an oral prednisolone dosage of 2.5 mg day⁻¹ (24).

**LONGER-TERM STUDIES**

Until recently, most studies of growth in asthmatic children treated with inhaled corticosteroids have suffered from flaws in study design. In addition to reliance on measurement techniques that do not predict long-term growth (i.e. knemometry), these studies include a lack of evaluation of pubertal status, inappropriate stratification of pubertal status by age alone, lack of an adequate untreated control group, lack of baseline growth rate data and baseline differences in age and height between treatment groups. In the discussion of longer-term (i.e. >6 months) studies outlined below, however, aspects of study design are not analysed; rather, the authors’ conclusions regarding the data are presented and summarised in Table 2.

*Studies of beclomethasone dipropionate alone*

Awareness of potential growth-suppressing effects of BDP was raised by a cross-sectional study of 346 asthmatic children, 81 of whom were taking BDP 200–800 µg day⁻¹ (27). The patients in the BDP group were significantly shorter for their age than the control group receiving other treatments, although the authors stated that it was impossible to determine whether this was an effect associated with asthma or the treatment. Notably the children in the BDP group had a mean age of 10.9 years, compared with 6.6 years for the control group, and therefore were likely to be in the phase of physiological pre-pubertal growth deceleration, during which a temporary decline in height standard deviation scores would be expected.

Somewhat different results were obtained by Nassif et al. (28), who studied growth in 24 children receiving alternate-day prednisolone and 32 receiving inhaled BDP (mean dosage 532 µg day⁻¹) for a minimum of 6 months. Both groups of children were smaller than average, with initial mean heights on the 35th percentile. Final mean heights showed no change over the mean 2 yr follow-up. There was a trend towards an inverse correlation of height velocities and dosage of
<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Mean age (range)</th>
<th>Study design</th>
<th>Period of active treatment&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Daily dosage</th>
<th>Overall results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agertoft and Pedersen (13) (A)</td>
<td>24/24</td>
<td>9 (6–12) years/9 (6–12) years</td>
<td>r,d,d,co,pc</td>
<td>2 weeks</td>
<td>Budesonide or FP 200 μg&lt;sup&gt;c&lt;/sup&gt;; budesonide or FP 400 μg&lt;sup&gt;c&lt;/sup&gt;, Budesonide 200 μg&lt;sup&gt;e&lt;/sup&gt;; budesonide 800 μg&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Budesonide 400 μg had a significant effect on lower-leg growth rate compared with placebo; Budesonide 800 μg, but not 200 μg, had a significant effect on lower-leg growth rate compared with placebo.</td>
</tr>
<tr>
<td>Bisgaard (19) (F)</td>
<td>18</td>
<td>27 (13–36) months</td>
<td>r,co,pc</td>
<td>4 weeks</td>
<td>Budesonide 200 μg&lt;sup&gt;e&lt;/sup&gt;; Budesonide 800 μg&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Budesonide 400 μg had a significant effect on lower-leg growth rate compared with placebo.</td>
</tr>
<tr>
<td>MacKenzie and Wales (20) (L)</td>
<td>13</td>
<td>Not given</td>
<td>db,pc</td>
<td>4 weeks</td>
<td>BDP 200 or 400 μg&lt;sup&gt;c&lt;/sup&gt;</td>
<td>BDP 400 μg had a significant effect on lower-leg growth rate compared with baseline.</td>
</tr>
<tr>
<td>Wolthers and Pedersen (21) (F)</td>
<td>15</td>
<td>9.5 (6–13) years</td>
<td>r,d,co</td>
<td>18 days</td>
<td>Budesonide 200 or 800 μg&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Both dosages of budesonide had a significant effect on lower-leg growth rate compared with baseline.</td>
</tr>
<tr>
<td>Wolthers and Pedersen (22) (F)</td>
<td>43</td>
<td>10.2 (7–14) years</td>
<td>db,pg</td>
<td>8 weeks</td>
<td>Budesonide 200, 400 or 800 μg&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Only budesonide 800 μg had a significant effect on lower-leg growth rate compared with baseline (placebo).</td>
</tr>
<tr>
<td>Wolthers and Pedersen (23) (F)</td>
<td>19</td>
<td>10.7 (7–14) years</td>
<td>r,dh,co</td>
<td>15 days</td>
<td>BDP 400 or 800 μg&lt;sup&gt;c&lt;/sup&gt;; FP 200 μg&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Both dosages of BDP had a significant effect on lower-leg growth rate compared with FP.</td>
</tr>
</tbody>
</table>

<sup>a</sup> Number of patients who entered the trial.
<sup>b</sup> Duration of treatment with each regimen (excluding placebo run-in or wash-out).
<sup>c</sup> Administered as a dry powder formulation.
<sup>d</sup> Administered using a metered dose inhaler (MDI) with a spacer plus face mask.
<sup>e</sup> Administered using an MDI with a spacer.
### TABLE 2. Longer-term studies examining the effects of inhaled beclomethasone dipropionate (BDP) and budesonide on growth rate

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients</th>
<th>Mean age (range)</th>
<th>Study design</th>
<th>Period of active treatment</th>
<th>Daily dosage</th>
<th>Overall results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allen et al. (5) (F)</td>
<td>810</td>
<td></td>
<td>Meta-analysis of 21 studies</td>
<td></td>
<td>BDP, oral steroids</td>
<td>Growth impairment linked to oral corticosteroid treatment whereas inhaled BDP treatment linked with attaining normal final height</td>
</tr>
<tr>
<td>Balfour-Lynn (16) (F)</td>
<td>66</td>
<td>7-5 years at entry</td>
<td>o</td>
<td>13 yr</td>
<td>BDP up to 600 µg</td>
<td>No effect on adult height</td>
</tr>
<tr>
<td>Delacourt et al. (25) (A)</td>
<td>50</td>
<td>10-8 years</td>
<td>o</td>
<td>Mean 19 months</td>
<td>BDP 750-1500 µg</td>
<td>Physiological pre-pubertal growth deceleration only BDP caused significant growth suppression compared with placebo</td>
</tr>
<tr>
<td>Doull et al. (9) (F)</td>
<td>88</td>
<td>7-9 years</td>
<td>db,pc,r</td>
<td>7 months</td>
<td>BDP 400 µg Placebo</td>
<td></td>
</tr>
<tr>
<td>Insoue et al. (26) (A)</td>
<td>97</td>
<td>12 years</td>
<td>o</td>
<td>2-14 yr</td>
<td>BDP 300 µg SCG and/or SR theophylline</td>
<td></td>
</tr>
<tr>
<td>Littlewood et al. (27) (A)</td>
<td>346</td>
<td>10-9 years (BDP); 6-6 years (control)</td>
<td>c,cs,o</td>
<td>Up to 3 yr</td>
<td>BDP 200-800 µg</td>
<td>Analysis not possible because of non-matched controls STeroid groups smaller than controls, no effect on growth</td>
</tr>
<tr>
<td>Nassif et al. (28) (F)</td>
<td>56</td>
<td>13 years (BDP); 10 years (oral steroids)</td>
<td>co,o</td>
<td>At least 6 months</td>
<td>BDP 532 µg Oral steroids</td>
<td>All children had growth over 95% of the expected; high-dose BDP did not interfere with normal growth</td>
</tr>
<tr>
<td>Rizzo and Rizzo (29) (A)</td>
<td>10</td>
<td>8 years (4-12 years)</td>
<td>o</td>
<td>1 yr</td>
<td>BDP 1000, 1500, 2000 µg</td>
<td>Increasing the dose of BDP resulted in reduced height velocity; decreasing or stopping BDP resulted in increased height velocity Growth velocity suppression was noted with BDP (and more pronounced in boys); suppression was not associated with alterations in cortisol measurements</td>
</tr>
<tr>
<td>Thomas et al. (30) (F)</td>
<td>6</td>
<td>5-2 years</td>
<td>o</td>
<td>Up to 4.5 yr</td>
<td>BDP 200-300 µg (starting dose), increasing to 800 µg where necessary</td>
<td></td>
</tr>
<tr>
<td>Tinkelman et al. (8) (F)</td>
<td>195</td>
<td>6-16 years</td>
<td>c,db,pc,r</td>
<td></td>
<td>BDP 336 µg SR theophylline (dose titrated)</td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>No. of patients</td>
<td>Mean age (range)</td>
<td>Study design</td>
<td>Period of active treatment</td>
<td>Daily dosage</td>
<td>Overall results</td>
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<tr>
<td>Agertoft and Pedersen (31) (F)</td>
<td>216</td>
<td>3-11 years</td>
<td>c.o</td>
<td>3-6 yr</td>
<td>Budesonide 710 μg reduced to 430 μg</td>
<td>No changes in growth velocity observed with budesonide</td>
</tr>
<tr>
<td>Merkus et al. (15) (F)</td>
<td>40</td>
<td>12-8 years</td>
<td>c.db,r</td>
<td>22 months</td>
<td>Salbutamol 600 μg + budesonide 600 μg or placebo</td>
<td>Budesonide had no effect on growth velocity compared with placebo</td>
</tr>
<tr>
<td>Reid et al. (32) (F)</td>
<td>40</td>
<td>1-4 years (0.33-2.8 years)</td>
<td>o</td>
<td>6 months</td>
<td>Budesonide 1000-4000 μg via nebuliser</td>
<td>Treatment was not associated with reduced linear growth</td>
</tr>
<tr>
<td>Ruiz and Price (33) (A)</td>
<td>15</td>
<td>5-9 years (median)</td>
<td>cs</td>
<td>25 months</td>
<td>Budesonide 410 μg via spacer Budesonide 200 μg via spacer</td>
<td>No effect on growth or bone age</td>
</tr>
<tr>
<td>Varsano et al. (34) (F)</td>
<td>16</td>
<td>5 years</td>
<td>o</td>
<td>1 yr</td>
<td>Budesonide 700 μg</td>
<td>No effect on growth</td>
</tr>
<tr>
<td>Volovitz et al. (35) (F)</td>
<td>15</td>
<td>2-7 years</td>
<td>o</td>
<td>3-5 yr</td>
<td>Budesonide 200 μg via spacer</td>
<td>Following prolonged budesonide administration growth patterns were normal and pituitary adrenal function was unaffected</td>
</tr>
<tr>
<td>Crowley et al. (11) (F)</td>
<td>56</td>
<td>8-3 years (4-4-11.7 years)</td>
<td>o</td>
<td>1 yr</td>
<td>BDP Budesonide Oral prednisolone</td>
<td>All three treatments resulted in retardation of linear growth velocity, but this was not accompanied by significant changes in the GH axis</td>
</tr>
<tr>
<td>Ninan and Russell (36) (F)</td>
<td>58</td>
<td>Pre-pubertal</td>
<td>o</td>
<td>4-9 yr</td>
<td>Inhaled corticosteroids 200-1600 μg</td>
<td>No effect on growth</td>
</tr>
<tr>
<td>Saha et al. (37) (F)</td>
<td>201</td>
<td>4-4 years (1-11 years)</td>
<td>o</td>
<td>Up to 5 yr</td>
<td>BDP 500 μg (mean) Budesonide 500 μg (mean)</td>
<td>BDP and budesonide impaired growth velocity; this effect was not dose dependent but was linked to duration of treatment</td>
</tr>
</tbody>
</table>

A, abstract; c, controlled; co, cross-over; cs, cross-sectional; db, double blind; F, full paper; GH, growth hormone; o, open; pc, placebo controlled; r, randomised; SCG, sodium cromoglycate; SR, slow release.

* Number of patients who entered the trial.

* Duration of treatment with each regimen (excluding placebo run-in or wash-out).
oral and inhaled corticosteroids. However, the authors concluded that growth was affected by the disease but not by corticosteroid treatment.

Subsequent studies have supported the absence of a clinically significant growth-suppressing effect of BDP. In a study of 50 asthmatic children receiving BDP 750–1500 μg daily for a mean of 19 months, growth was found to be normal in 44 of the children (25). Four of the children who showed a decrease in height percentile were within the period of pre-pubertal growth deceleration and the decrease in height percentile was always less than 10 percentile points. Rizzo and Rizzo (29) conducted a longitudinal survey of 10 children (mean age 8 years) with severe asthma receiving ≥1000 μg inhaled BDP daily. Height was measured prior to beginning BDP treatment and following 1 yr of treatment. After 1 yr, all of the children achieved >95% of the growth predicted for them based on the pre-treatment height percentiles. Inoue et al. (26) conducted a retrospective analysis of linear growth in 97 asthmatic children. Height was measured annually from age 12 to 20 years. There were no significant differences in mean height at each age among the 61 patients who were treated with inhaled BDP (300 μg daily for 2–14 yr) and those treated with inhaled sodium cromoglycate and/or slow-release theophylline.

However, some recent studies, some with significantly improved study designs, have shown growth inhibition by BDP. A randomised clinical trial comparing BDP with oral theophylline in children, aged 6–17 years, with mild to moderately severe asthma demonstrated reduced growth in the BDP-treated patients (8). Thomas et al. (30) observed six pre-pubertal children receiving BDP (300–800 μg daily by MDI or dry powder device) who showed a significant reduction in mean height velocity during treatment. When the dosage was reduced or treatment stopped completely, mean height velocity increased. The authors believed the six children to be particularly sensitive to BDP. Finally, Doull et al. (9) conducted a parallel-group study comparing BDP (400 μg daily via dry powder device) with placebo in 94 pre-pubertal children (aged 7–9 years) with mild asthma. Over the 7-month study period, mean growth rate was significantly lower in the BDP group (0.79 mm week⁻¹). P<0.001 and catch-up growth did not occur during the 4-month wash-out period.

Little information is currently available regarding the influence of inhaled corticosteroids on growth during infancy and early childhood. Treatment for 6 months with BDP 200 μg daily, administered via an MDI and spacer plus mask (Aerochamber), had no effect on length or height in 12 very young children (mean age 1.22 years) (38). However, there is some debate over whether inhaled corticosteroids should be used in children <3 years of age because 30 yr follow-up studies have now provided evidence of increasingly severe asthma or deteriorating lung function in the absence of treatment (39).

The clinical relevance of growth suppression by inhaled corticosteroids depends more on the ultimate effect on height than (possibly) short-term reductions in growth rate. Because BDP was approved for use in children earlier than budesonide, more extensive data regarding the effect on height are available for BDP. Balfour-Lynn (16) followed 66 asthmatic children (mean age 7.5 years at entry) for a mean of 13.1 yr, 26 of whom were receiving inhaled BDP up to 600 μg day⁻¹. All grew normally until about 10 years of age. Eleven children whose dosage of BDP exceeded 400 μg day⁻¹ showed decelerating growth velocity during a period of delayed onset of puberty, but later demonstrated catch-up growth and achieved their predicted adult height. There was no significant difference between the final heights of children receiving BDP and those not receiving inhaled corticosteroid. Finally, a meta-analysis (of 21 studies in 810 asthma patients) of the effect of oral corticosteroid or inhaled BDP on growth showed a small but significant correlation between corticosteroid treatment in general and reduced final height (5). Growth impairment was linked to oral corticosteroid treatment whereas inhaled BDP treatment was associated with reaching normal height. The statistical evidence did not suggest a link between growth impairment and inhaled BDP at higher doses, for more prolonged treatment duration or among patients with more severe asthma.

Studies of budesonide alone

Of six studies examining budesonide in children with asthma, none has shown an adverse effect on growth. In a large controlled, prospective study (31), 216 children were followed at six-monthly intervals for 1–2 yr while not receiving inhaled budesonide and then for 3–6 yr while receiving inhaled budesonide (mean daily dosage decreased from 710 to 430 μg over the course of the study). No statistically significant changes in growth velocity were observed during budesonide treatment. Moreover, compared with the control group which did not receive inhaled budesonide, children in the budesonide group had improved lung function, suggesting that inhaled corticosteroid therapy can modify the course of the disease. Three small, longer-term studies of budesonide administered at standard dosages have also found no adverse effects on growth. Varsano et al. (34) followed 16 children (mean age 4 years 11 months receiving BUD 100 μg two to four times daily (via MDI plus spacer) over 1 yr. No abnormalities in growth or bone maturation were observed. Similarly, Ruiz and Price (33)
reported normal growth over 1 yr in 15 asthmatic children (median age 5-9 years) who had taken budesonide (mean dosage 410 µg daily via MDI used with a spacer) for a mean period of 25 months. Follow-up after 3–5 yr of a small number of pre-pubertal children treated with budesonide 200 µg day⁻¹ also showed no decrement in height percentiles (35).

Merkus et al. (15) conducted a randomised, double-blind study in 40 asthmatic adolescents (mean age 12.8 years) receiving salbutamol 600 µg daily and inhaled budesonide 600 µg daily or placebo for a median period of 22 months. Growth rates were matched with those of 80 controls. Budesonide treatment was not associated with a significant effect on growth velocity compared with placebo. Interestingly, males treated with either budesonide or placebo showed similar slowing of growth rates compared with controls, pointing again to a likely confounding effect of delayed puberty in the analysis of growth of children with asthma.

In an open study of 40 very young children (mean age 1-4 years) with severe asthma, nebulised budesonide (via a face mask) 1-4 mg daily for a mean duration of 6 months did not reduce linear growth (32). Indeed, budesonide treatment was associated with a small improvement in linear growth (statistically but not clinically significant according to the authors).

Studies of beclomethasone dipropionate, budesonide and other inhaled corticosteroid treated children

Studies investigating the effects of inhaled corticosteroids (BDP and/or budesonide as well as other corticosteroids) generally on growth in children with asthma have found contradictory results. Ninan & Russell (36) followed 58 pre-pubertal children receiving inhaled corticosteroids 200–1600 µg (mean 800 µg) daily for a mean of 4.9 yr. Height velocity changes were measured in boys until they were 11 years of age and in girls until they were 10 years of age and asthma control was assessed by symptom scores. The researchers concluded that poor asthma control affected growth but that the use of inhaled corticosteroids did not.

However, two other studies have reported evidence of impaired growth associated with inhaled corticosteroids. In the study by Saha et al. (37), prior to treatment with inhaled corticosteroids, mean growth velocity in 201 pre-pubertal asthmatic children (1–11 years) was found to be similar to that of healthy peers. Growth velocity was impaired in the asthmatic children during BDP or budesonide therapy (average dosage 500 µg day⁻¹). The growth-retarding effect of the inhaled corticosteroids was not dose dependent but a longer duration of therapy was linked to a greater growth suppression. Although these asthmatic children showed similar pre-treatment growth compared with healthy peers (suggesting that the disease itself did not modify growth), more severe asthma was associated with a greater reduction in growth rate.

Crowley et al. (11) performed a 1 yr longitudinal study of 56 asthmatic children aged 4-11.7 years. All 13 children not receiving inhaled corticosteroids had normal growth velocity whereas ten of 20 receiving BDP (mean dosage 560 µg day⁻¹ by dry powder device or MDI ± spacer) and four of 19 receiving budesonide (mean dosage 762 µg day⁻¹ by dry powder device or MDI ± spacer) had an impaired growth rate. Children receiving inhaled corticosteroids and oral prednisolone were much more likely to grow slowly: three of four showed slow growth. While growth delay was also detected in children who did not receive corticosteroids, it was more marked in those receiving inhaled corticosteroids, who were also more likely to have more severe disease.

Conclusions

To date, no comparative studies of the effects of therapeutically equivalent doses of BDP, budesonide and other inhaled corticosteroids on long-term growth have been conducted. Most short and long-term studies have been confounded by differences in the inhaled corticosteroid dosages, delivery devices and the patient populations studied. Short-term studies indicate that dosages of inhaled BDP and budesonide ≥100 µg day⁻¹ can affect lower-leg growth rate evaluated over a period of 2–8 weeks; however, these data do not accurately predict long-term growth or final height attained. The overall data from longer-term studies suggest that dosages of inhaled BDP and budesonide <400 µg day⁻¹ do not adversely affect growth rate in asthmatic children. Rarely, growth failure will occur during conventional dose inhaled corticosteroid therapy, reflecting interindividual differences in sensitivity to systemic corticosteroid effects following inhalation (40). The risk of more frequent and profound growth suppression can be expected to increase incrementally with uninterrupted administration of doses in excess of 400 µg/day. In children with allergic rhinitis, clinicians must consider total corticosteroid burden during concurrent therapy with intranasal corticosteroid.

Disparities in the results of recent prospective studies (showing growth suppression by BDP) and retrospective studies (showing minimal or no effect on growth rate or height) might be reconciled by considering the difference in inhaled corticosteroid dose and consistency of administration required to achieve disease control rather than symptom control (41). Well-designed, prospective studies, with closely
monitored and consistent dosing capable of achieving disease control, have shown 1–1.5 cm yr⁻¹ reductions in growth rate during BDP therapy 400 µg day⁻¹. On the other hand, most patients reduce drug exposure over time by titrating medication to achieve symptom control only, perhaps accounting for the lack of effect of real-life prescriptions of BDP 400 µg day⁻¹ on retrospective growth rates or final adult stature. Marked discrepancies between adherence to prescribed therapy as reported by patients and actual compliance has been convincingly demonstrated (42). Consequently, whether long-term continuous administration of inhaled corticosteroids at a disease-controlling dosage could reduce final height remains unknown.

No reliable surrogate marker for predicting the effect of inhaled corticosteroids on growth has yet been identified. Careful monitoring of growth of children receiving continuous inhaled corticosteroid therapy using a wall-mounted stadiometer is a sensitive indicator of this adverse effect and should occur regularly at 3–4 month intervals. As with any drug, the dosage of inhaled corticosteroid should be tailored to the minimum amount that provides reliable control of asthmatic symptoms. Moreover, because the growth-inhibiting effects of corticosteroids vary not only with dosage but with dose frequency and time of exposure, receptor affinity, drug absorption and metabolism, lipophilicity and other factors, each new strategy in inhaled corticosteroid therapy (e.g. higher dosage, institution earlier in life, use of more potent formulations) requires that questions regarding side-effects of inhaled corticosteroids be addressed anew (41).

References


