REVIEW ARTICLE

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Clinical Safety of Inhaled Corticosteroids for Asthma in Children

An Update of Long-Term Trials

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Abstract

Inhaled corticosteroids are established as the mainstay of maintenance therapy for chronic asthma. However, there remains some debate regarding the safety of long-term use of these agents, particularly in children. This concern mainly stems from the findings of short-term studies assessing the effects of inhaled corticosteroids on lower leg growth rate or the hypothalamic-pituitary-adrenal axis. However, the clinical relevance of these findings to long-term treatment is unknown and significant uncertainty exists regarding the predictive value of changes in cortisol levels and clinically relevant changes in growth or bone mineral density.

To assess the safety of long-term use of inhaled corticosteroids in children with asthma, a systematic review of the literature was performed focusing on randomised, controlled studies of ≥12 months' duration, to obtain data with maximum relevance to clinical practice. Specific searches were conducted to identify studies examining each of the following three areas: growth, bone mineral density and cortisol levels.

Fourteen studies met the inclusion criteria for statural growth, four for bone mineral density, and ten for cortisol levels. There was some evidence of a small decrease in statural growth during the initial period of inhaled corticosteroid therapy. This effect was more marked at daily doses of >200μg and did not apply to all treatment regimens. Studies examining final attained adult height found no

difference between patients treated with inhaled corticosteroids and those receiving nonsteroidal therapy. None of the studies investigating effects on bone mineral density found any adverse effects of inhaled corticosteroid therapy. Finally, recommended doses of inhaled corticosteroids generally had little or no effect on plasma- or urinary-cortisol levels versus nonsteroidal therapy.

In conclusion, this literature review supports the theory that recommended doses of inhaled corticosteroids can be administered to children for the long-term management of asthma with minimal risk of clinically relevant adverse effects on growth, bone density or cortisol levels.

Systemic exposure to increased concentrations of corticosteroids can potentially cause a variety of adverse events, including suppression of adrenal function, impairment of growth and skeletal formation, and increased risk of fracture.[1] Concerns relating to the risk of adverse effects of increased systemic concentrations of corticosteroids date from the time when corticosteroids were administered orally to treat persistent asthma. With oral administration, high systemic concentrations of the drug are required to achieve effective drug concentrations at the receptors in the airways. As a result, long-term treatment of asthma with corticosteroids has been the subject of considerable debate, particularly in children. However, when inhaled corticosteroids are used, the drug is delivered directly to the airways. Therefore, much lower doses can be used and systemic corticosteroid exposure is markedly reduced.[2] Furthermore, most inhaled corticosteroids are cleared more rapidly from the body than the older oral corticosteroids.

Over the last three decades, numerous studies have established inhaled corticosteroids as the most effective medications for controlling persistent asthma and, as a result, all international treatment guidelines now recommend inhaled corticosteroids for all patients with persistent asthma.[3-5] However, several surveys show that these recommendations are not being followed.[6,7] An important reason for this seems to be the misconception that inhaled corticosteroids are no different from oral corticosteroids or the steroids that athletes use for doping.[8] To put these misconceptions and beliefs into perspective, this paper will focus on the documented long-term (≥1 year) effects of inhaled corticosteroids on growth, bone mineral density and cortisol levels in children.

Before individual studies and topics are discussed, it should be emphasised that with respect to safety no other asthma drug class has been as carefully studied as inhaled corticosteroids. Over the years, approximately 130 studies with inhaled corticosteroids have had safety assessment as the main outcome. In comparison, there are 20 safety studies with cromones and 15 studies with antileukotrienes. There is also vast long-term clinical experience with inhaled corticosteroids, as they have been used for >25 years with an estimated total of 87 million patient-treatment years up until early 2004.[9,10]

Inhaled corticosteroids are often used long term and the appropriateness of extrapolating safety data from short-term trials to long-term treatment is questionable. Cross-sectional or epidemiological studies are prone to reduced data quality, mainly as a result of inadequate adjustment for confounders, such as oral corticosteroid use or variations in disease severity, age, sex, use of other medication, duration of disease, physical activity, bone age and diet. Therefore, it was decided to focus mainly on prospective, randomised, controlled studies of at least 12 months' duration. Such an approach has not been used before in review papers. To identify references meeting these criteria, an initial search of MEDLINE was performed using the following search terms: 'inhaled corticosteroi*', 'asthma', 'child' OR 'children', and 'pediatri*' OR 'paediatric*'.

The results were searched manually to identify the relevant studies, followed by supplementary MEDLINE searching for improved coverage, with the following example for bone mineral density: 'inhaled corticosteroi*' OR 'fluticasone' OR 'budesonide' OR 'beclomethasone' OR 'mometasone' OR 'triamcinolone' AND 'asthma'

AND 'child' OR 'children' OR 'paediatri*' OR 'paediatri*' AND 'bone'. All subcategories were selected for each search term.

The BIOSIS database was searched for studies meeting the selection criteria but published only in abstract form. Recent comprehensive review articles were also checked and the results from the papers fulfilling the strict search criteria were compared with the results of other long-term studies not fulfilling the strict criteria. All searches were completed by July 2005.

1. Statural Growth

1.1 Clinical Relevance of Controlled Studies

When trying to extrapolate from clinical trials data on the effects of inhaled corticosteroids on growth, it is important to appreciate that growth may be divided into three distinct stages.[11]

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

The potential influence of inhaled corticosteroids appears to differ between these stages with, for example, a more marked effect in prepubertal than in pubertal schoolchildren.[11]

The vast majority of inhaled corticosteroid safety studies include children with mild asthma and a limited age range (6–9 years), and use a fixed dose of inhaled corticosteroid (often higher than the dose needed for optimal asthma control), which is not adjusted to disease activity or severity. Moreover, the study duration is normally <1 year. This increases the likelihood of detecting an adverse effect on growth because patients with mild asthma have greater systemic exposure to the inhaled drug, children aged 6–9 years 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 according to disease severity and all age groups are treated for asthma. Most randomised, controlled studies do not allow the use of nasal corticosteroids, which are also absorbed systemically to some extent (differs from one inhaled corticosteroid to the other). In a clinical setting, children with co-existent asthma and allergic rhinitis are likely to be treated with nasal corticosteroids in addition to the orally inhaled corticosteroids. The clinical importance of this combined therapy is not known: although likely to increase the systemic effect, its use over a period of years has been found not to influence final adult height.[11,12]

1.2 Results of the Literature Review

Fourteen studies of statural growth met the selection criteria (randomised, prospective, ≥12 months' duration) [table I]. Stadiometry was used for height measurement in all except two of these studies – neither Merkus et al.[13] nor Roux et al.[14] specified their methodology. None of the five studies comparing low-dose inhaled corticosteroids (100–200 μg/day) with placebo or nonsteroidal therapy found that inhaled corticosteroids exert any adverse effect on statural growth: fluticasone propionate administered via dry-powder inhaler compared with placebo;[15] fluticasone propionate dry-powder inhaler compared with nedocromil;[14] fluticasone propionate via pressurised metered dose inhaler compared with sodium cromoglicate (cromolyn sodium),[16,17] and budesonide dry-powder inhaler compared with placebo.[18] Although a small, significant reduction in growth velocity was observed at 12 months in budesonide recipients aged 7–11 years in the last of these studies, there was no overall effect on growth and the authors concluded that budesonide was safe and effective.

Among studies of higher daily doses of inhaled corticosteroids, budesonide administered via pressurised metered dose inhaler at a dose of 600 μg/day

Table I. Summary of randomised, prospective studies of the effects of ≥12 months' inhaled corticosteroid therapy on childhood growth

Study	Year	Inhaler type	Drug regimen	Study duration (months)	Age (years)	Principal growth outcomes
Merkus et al.[13]	1993	pMDI	BUD 600 μg/day plus salbutamol (albuterol) 600 μg/day vs placebo plus salbutamol 600 μg/day	22	9–14	No significant between-group differences in growth
Roux et al.[14]	2003	DPI	FP 200 μg/day vs nedocromil 8–16 mg/day	24	6–14	No between-group differences in growth
Allen et al.[15]	1998	DPI	FP 100 μg/day vs 200 μg/day vs placebo	12	4–11, prepubertal	Growth not significantly impaired in children receiving FP 100 μg/day or 200 μg/day
Price et al.[16]	1997	pMDI	FP 100 μg/day vs sodium cromoglicate (cromolyn sodium) 20mg qid	12	4–10, prepubertal	No significant between-group differences in growth velocity or growth velocity standard deviation scores
Bisgaard et al.[17]	2004	pMDI	FP 200 μg/day vs sodium cromoglicate 5mg qid	12	11–47 months	No between-group differences in growth
Jonasson et al.[18]	2000	DPI	BUD 100 μg/day vs 200 μg/day vs placebo	27	7–16	Growth not significantly affected, except in 7–11 year olds at 12 months
Childhood Asthma Management Program Research Group[19]	2000	DPI	BUD 400 μg/day vs nedocromil 16 mg/day vs placebo	4–6 years	5–12	Small, transient reduction in growth velocity with BUD compared with placebo or nedocromil (22.7 vs 23.8 vs 23.7cm, respectively, over 5 years)
Verberne et al.[20]	1997	DPI	BDP 400 μg/day vs salmeterol 100 μg/day	12	6–16	Smaller height increase with BDP vs salmeterol (4.7 vs 6.1 cm)
Tinkelman et al.[21]	1993	pMDI	BDP 336 μg/day vs theophylline	12	6–17	Significantly slower growth in the BDP group (4.2 vs 5.5 cm/year)
Simons[22]	1997	DPI	BDP 400 μg/day vs salmeterol 100 μg/day vs placebo	12	6–14	Significantly slower growth in the BDP group than with either salmeterol or placebo (3.96 vs 5.40 and 5.04 cm/year, respectively)
Skoner et al.[23]a	2000	Nebuliser	BUD 500–1000 μg/day vs non-ICS	12	5 (approx.)	Small decrease in growth with BUD (6.55 vs 7.39 cm/year)
Visser et al.[26]b	2004	DPI	FP 200 μg/day (constant dose) vs 1000 μg/day step-down (100 μg/day from 6 months)	2 years	6–10	Growth velocity significantly lower in the step-down group at 2 months, significantly higher at 1 year, with no significant difference at 2 years
de Benedictis et al.[28]	2001	DPI	FP 200 μg/day vs BDP 200 μg/day	12	4–11	Growth velocity faster with FP
Rao et al.[29]	1999	pMDI	FP 200 μg/day vs BDP 400 μg/day	20	5–10	Significantly slower growth observed in the BDP group (4.94 vs 5.75 cm/year)

a This study also published by Irani et al.[24] in 2002 and by Scott & Skoner in 1999.[25]

b This study published with shorter follow-up by Visser et al.[27] in 2001.

BDP = beclometasone; **BUD** = budesonide; **DPI** = dry-powder inhaler; **FP** = fluticasone propionate; **ICS** = inhaled corticosteroid; **pMDI** = pressurised metered-dose inhaler; **qid** = four times daily.

was found to have no impact on growth over 22 months compared with placebo.[13]

The remaining studies of higher doses of inhaled corticosteroids all found some degree of apparent growth retardation in children treated with inhaled corticosteroids. A large study (1041 children recruited) demonstrated a small, transient decrease in growth with 4–6 years of budesonide dry-powder inhaler therapy compared with nedocromil or placebo (mean increase in height during the study was 1.1cm less with budesonide, which was attributable mainly to reduced growth during the first year).[19] Three 12-month studies comparing beclometasone (336–400 μg/day) with nonsteroidal therapy or placebo also reported a small reduction in growth with beclometasone (1.08–1.44 cm/year).[20-22] A 12-month study comparing nebulised budesonide 500–1000 μg/day with other therapies excluding inhaled corticosteroid treatment, indicated a 0.8 cm/year reduction in growth velocity with budesonide.[23] In patients in whom nebulised budesonide was compared with any available therapy for asthma, including inhaled glucocorticosteroids, nebulised budesonide did not adversely affect growth.[23]

Finally, a comparison of fluticasone propionate dry-powder inhaler 200 μg/day with step-down fluticasone propionate (1000 μg/day with reductions every 2 months to 500, 200 and 100 μg/day) indicated that growth velocity was reduced in the step-down group during the high-dose period.[26] However, growth velocity rebounded when the dose had been reduced to 100 μg/day, so for a period it was significantly greater than in the constant-dose group. Standing height increased comparably in both groups throughout the study.

Two randomised comparisons of different inhaled corticosteroids were identified, both of which compared fluticasone propionate with beclometasone.[28,29] A significantly higher growth rate was reported among children receiving fluticasone propionate 200 μg/day via dry-powder or pressurised metered dose inhaler, compared with beclometasone 200 μg/day via dry-powder inhaler or 400 μg/day via pressurised metered dose inhaler.

The results of growth studies not meeting the present criteria for selection as well as unpublished recent abstracts generally support the findings discussed in this section. Daily doses of inhaled corticosteroids ≤200μg are reported to have no adverse effect on statural growth, whereas daily doses of ≥400μg seem to have some effects particularly at the beginning of treatment in children <12 years of age with mild asthma.[11,30,31]

1.3 Final Height

The effects of long-term inhaled corticosteroid treatment on final adult height are arguably more clinically relevant than the effects of ≥12 months' therapy on growth velocity. However, randomised, prospective studies with final height as an endpoint are almost impossible to perform, so the data on this outcome are necessarily based on less strictly designed studies. Six studies have compared final height among individuals treated with inhaled corticosteroids for asthma with healthy controls or asthma patients treated with nonsteroidal drugs.[12,32-36] All of these studies defined normal/appropriate final height in relation to the final height of the parents. Moreover, they included the final height of comparator groups of children (siblings, controls, noninhaled corticosteroid-treated children) calculated in the same way to ensure the appropriateness of the final height assessment.

Two studies examined budesonide therapy,[12,32] one examined beclometasone[33] and in three studies the corticosteroids were not specified.[34-36] In summary, all six studies found that long-term treatment with inhaled corticosteroids did not adversely affect final adult height. The reason for the apparent discrepancy between this finding and the results of some 1-year growth studies is not known. The only prospective study, which followed 142 children treated with inhaled corticosteroids for many years (mean 9.2 years) found that, like the Childhood Asthma Management Program study,[19] the growth-slowing effect of exogenous corticosteroid was most pronounced during the first year(s) of treatment.[12] Therefore, results from studies of 1–3 years' duration do not predict long-term growth or final adult height. It seems that some inhaled corticosteroid-treated children may experience reduced growth for a couple of years; however, they are likely to grow for longer than their peers and eventually end up at a normal adult height (figure 1).[11,12]

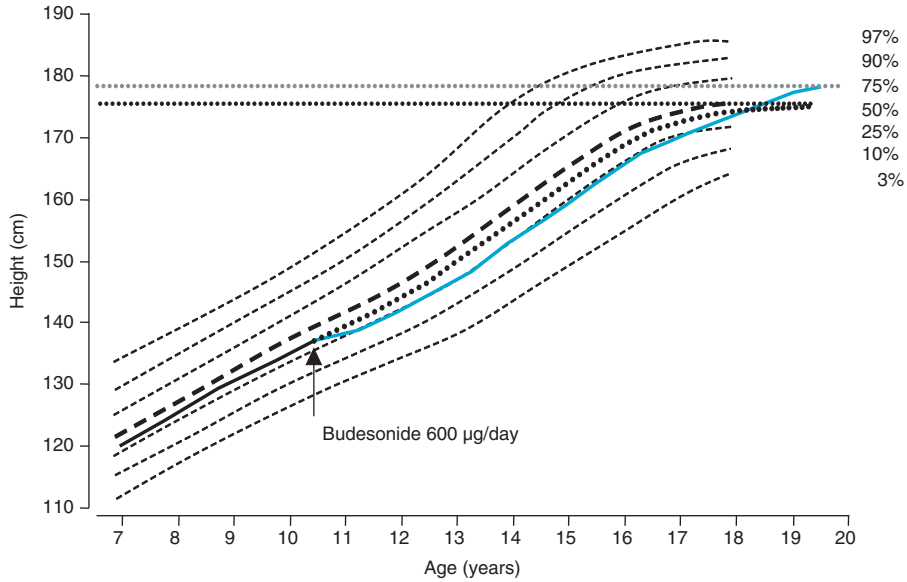

Fig. 1. Growth of a typical child treated with an inhaled corticosteroid. In this case, asthma was not diagnosed until 10 years of age. At 10.5 years (arrow), inhaled-corticosteroid treatment was initiated. The blue line shows the boy's growth thereafter: there is an initial reduction in growth but the child grows for longer than expected and final height is a little greater than expected. Black lines show the expected adult height. The percentage values are the height percentiles, with the 50% percentile marked by the horizontal dashed lines. These data are based on previously published findings.[31]

2. Bone Mineral Density

2.1 Clinical Relevance of Controlled Studies

Excess systemic exposure to corticosteroids can suppress bone formation and increase (or decrease) bone resorption, resulting in a net decrease in bone mass.[37] Therefore, there has been some concern that the use of inhaled corticosteroids as long-term asthma-maintenance therapy in children could have a detrimental effect on bone mass, bone mineral density or risk of fractures.

Most studies in adults have found that bone mineral density or risk of fractures are not affected by low to moderate doses of inhaled corticosteroids.[38] However, it is not valid to extrapolate findings from adults to children: bone turnover in children is much higher than for adults, and skeletal mass increases during childhood and adolescence, whereas it declines during adulthood.

The most clinically relevant outcome for the effects of inhaled corticosteroids on bones in children is an increased risk of fracture. This is almost impossible to study in randomised, prospective trials. Instead, biochemical markers of bone metabolism and bone mineral density have been studied as surrogate indicators of increased susceptibility to fracture. In this respect, bone mineral density has some power to predict fracture;[39] however, there is no evidence of a correlation between or predictive value of changes in metabolic markers and changes in bone mineral density or fracture risk.[40] Therefore, prospective, randomised, long-term (≥12 months) controlled trials using clinically relevant doses of inhaled corticosteroids with adjustment for confounders and with fracture or bone mineral density as an endpoint seem to be the best way to assess the risk of clinically important long-term adverse effects on the skeleton. However, even if oral corticosteroids or a sedentary life can cause significant effects on bone mineral density over 12 months, this time period may be too short to detect small effects of inhaled corticosteroids on bone mineral density.

2.2 Results of the Literature Review

Only four prospective studies met the present inclusion criteria (table II). The duration of these

Table II. Summary of randomised, prospective studies of the effects of ≥12 months' inhaled corticosteroid therapy on bone mineral density (BMD) in children

Study	Year	Inhaler type	Drug regimen	Study duration (months)	Age (years)	Principal effects on bone density
Roux et al.[14]	2003	DPI	FP 200–400 μg/day vs nedocromil 8–16 mg/day	24	6–14	No between-group differences in BMD
Childhood Asthma Management Program Research Group[19]	2000	DPI	BUD 400 μg/day vs nedocromil 16 mg/day vs controls	4–6 years	5–12	No between-group differences in BMD
Visser et al.[26] a	2004	DPI	FP 200 μg/day (constant dose) vs FP 1000 μg/day step-down (100 μg/day from 6 months)	2 years	6–10	No between-group differences in BMD (spine)
Rao et al.[29] b	1999	pMDI	FP 200 μg/day vs BDP 400 μg/day	20	5–10	No between-group differences in BMD (lumbar spine and total body BMD increased as expected in both study groups)

a This study published with shorter follow-up by Visser et al.[27] in 2001.

b This study also published by Gregson et al.[42] in 1998.

BDP = beclometasone; **BUD** = budesonide; **DPI** = dry-powder inhaler; **FP** = fluticasone propionate; **pMDI** = pressurised metered-dose inhaler.

studies ranged from 20 to 60 months. All four trials found that inhaled corticosteroid therapy had no significant effect on bone mineral density. The largest, involving 1041 asthmatic children treated for 4–6 years with nedocromil, placebo or budesonide dry-powder inhaler, found no significant difference in bone mineral density increases between the three groups.[19] In addition, cross-sectional analysis of the baseline characteristics of participants in the study found no significant effect of previous inhaled corticosteroid use on bone mineral density.[41]

A 24-month study comparing fluticasone propionate dry-powder inhaler with nedocromil reported no significant between-group difference in the increase in bone mineral density of the lumbar spine or femoral neck.[14] The third study on 23 corticosteroid-naive children found no differences between the increases in bone mineral density in children treated with fluticasone propionate 200 μg/day via pressurised metered dose inhaler and those receiving beclometasone 400 μg/day via pressurised metered dose inhaler.[29] Furthermore, bone mineral density increased at normal rates in both groups. Finally, a comparison of dry-powder inhaler administration of constant-dose fluticasone propionate 200 μg/day with 1000 μg/day step-down (100 μg/day from 6 months) showed no significant between-group differences at any stage of the study.[26]

These findings are in agreement with the two cross-sectional studies that have assessed fracture risk in children treated with inhaled corticosteroids.[43,44] In one study, inhaled corticosteroid use in children presenting with a fracture was compared with age- and sex-matched controls.[43] No significant differences in risk of fracture, or the distribution of number of fractures per patient, were found between the 3744 cases and 21 757 controls, all aged 5–17 years.

In the other study, the incidence of fractures was assessed in children with asthma using inhaled corticosteroids (n = 97 387), children with asthma using bronchodilators only (n = 70 984) and control children (n = 345 758).[44] Children using inhaled corticosteroids or bronchodilators only had comparable risks of fracture (adjusted relative risk among inhaled corticosteroid users: 1.03; 95% CI 0.97, 1.10). Compared with the controls, the adjusted fracture risk odds ratio (OR) was 1.03 (95% CI 0.93, 1.15)

for inhaled corticosteroid-treated children and 1.13 (95% CI 0.92, 1.38) for bronchodilator-treated children. No dose-response was found between adjusted OR for fracture and daily dose of inhaled corticosteroid: 200μg, 0.96 (95% CI 0.83, 1.12); 201–400μg, 1.07 (95% CI 0.93, 1.24); >400μg, 1.17 (95% CI 0.93, 1.45).

In both studies, the distribution of fracture sites was similar in controls and inhaled corticosteroid-treated children. The authors of both studies concluded that inhaled corticosteroid use does not increase the risk of fracture in children. In contrast, the use of oral corticosteroids was found in a large cross-sectional study to be associated with a statistically significant, dose-dependent increase in fracture risk in children.[45]

The vast majority of studies on inhaled corticosteroids and bone mineral density not meeting the present selection criteria (including almost 1000 children) support the findings of the long-term, controlled studies. This is also true for the results of randomised, prospective studies that have so far been published only in abstract form, including a 3-year prospective study in 3000 children in which fracture rate (budesonide = 2.4% and controls = 2.8%), distribution of fracture sites and number of fractures per child were similar in controls and inhaled corticosteroid-treated children.[46]

No long-term, randomised controlled studies have assessed the effect of high doses of inhaled corticosteroids (>400 μg/day) on bone mineral density in children. Two cross-sectional studies, on 76 and 110 children, respectively, found significantly lower bone mineral density among children receiving high daily doses of inhaled corticosteroids.[47,48] Another study found that bone mineral density in 157 children treated for 5 years with a mean daily dose of budesonide 500μg was not reduced compared with the bone mineral density of 111 children with asthma not treated with inhaled corticosteroids.[49] Furthermore, no dose-response effects between inhaled corticosteroid dose and bone mineral density were detected.

Finally, 12-month increases in total and lumbar vertebral bone mineral density were significantly smaller in 48 asthmatic children treated with budesonide 200–800 μg/day or beclometasone 200–800 μg/day compared with nine control children not treated with inhaled corticosteroid.[50]

More studies are needed before any firm conclusions can be made on the effect of high doses (>400 μg/day) of inhaled corticosteroids and bone mineral density. Nevertheless, the absence of increased fracture risk in the large cross-sectional studies is reassuring, as is the finding that growing children seem to be able to repair corticosteroid-induced bone loss.[45,48,51]

It is not known whether preventive strategies, such as weight-bearing exercise or increased calcium intake, should be emphasised in children treated with high doses of inhaled corticosteroids. Weight-bearing exercise has been shown to improve bone mineral density in healthy children, whereas increased calcium intake has not.[52] On the other hand, children allergic to cow's milk have been found to have reduced bone mineral density if they do not take enough calcium supplements, which emphasises the importance of sufficient calcium intake in such children. Inhaled corticosteroid treatment increases physical activity in children when the asthma control improves. This and the reassuring findings in children treated with recommended daily doses indicate that weight-bearing exercise or increased calcium intake are not generally necessary. However, more studies on this issue are needed in children treated with high doses of inhaled corticosteroids (>400 μg/day).

3. Cortisol Levels

3.1 Clinical Relevance of Controlled Studies

When investigating the safety of inhaled corticosteroids, it is particularly important to distinguish between measurable systemic effects and clinically important adverse effects, such as Cushingoid features and increased risk of hypoglycaemia or adrenal insufficiency. These aspects have been extensively studied for many years without being clearly defined. This is unfortunate because a measurable systemic effect is not necessarily equivalent to a clinically important adverse effect.

Whether a systemic effect is measurable or not depends entirely on the sensitivity of the method used for measurement. For any given inhaled corti-

Table III. Summary of randomised, prospective studies of the effects of ≥12 months' inhaled corticosteroid therapy on cortisol levels in children

Study	Year	Inhaler type	Drug regimen	Duration (months)	Age (years)	Findings
Price et al.[16]	1997	pMDI	FP 100 μg/day vs sodium cromoglicate (cromolyn sodium) 20mg qid	12	4–10	No significant between-group differences in urinary cortisol levels
Bisgaard et al.[17]	2004	pMDI	FP 200 μg/day vs sodium cromoglicate 5mg qid	12	1–3	Reduced cortisol serum and urinary cortisols levels with FP, but the number of children with below-normal values decreased
Tinkelman et al.[21]	1993	pMDI	BDP 336 μg/day vs theophylline	12	6–17	Morning cortisol levels were similar in the two groups at baseline, 6 months and 12 months
Visser et al.[26] a	2004	DPI	FP 200 μg/day (constant dose) vs 1000 μg/day step-down (100 μg/day from 6 months)	24	6–10	Urinary cortisols were significantly reduced in the step-down group during high-dose therapy (1000 and 500 μg/day); no significant differences thereafter
de Benedictis et al.[28]	2001	DPI	FP 200 μg/day vs BDP 200 μg/day	12	4–11	No between-group differences in serum or urinary cortisol
Rao et al.[29]	1999	pMDI	FP 200 μg/day vs BDP 400 μg/day	20	5–10	During the study, serum cortisol level reduced significantly in the BDP group but not in the FP group
Leflein et al.[53]	2002	Neb	BUD 500 μg/day vs sodium cromoglicate 20mg qid	12	2–6	No between-group differences in basal or ACTH-stimulated cortisol levels
Scott & Skoner[25] b	1999	Neb	BUD 500–1000 μg/day vs non-ICS	12	0.4–9	No significant between-group differences in basal or ACTH-stimulated cortisol levels
Bacharier et al.[55]	2004	DPI	BUD 400 μg/day vs nedocromil 16 mg/day	36	5–12	Cortisol levels (urinary- and ACTH-stimulated serum) were the same in both study groups
Verona et al.[56]	2003	DPI	FP 200 μg/day vs 400 μg/day	12	4–11	Overnight urinary cortisol level unchanged or increased from baseline with both groups

a This study published with shorter follow-up by Visser et al.[27] in 2001.

b This study was also published by Irani et al.[24] in 2002 and by Skoner et al.[54] in 2000.

ACTH = adrenocorticotrophic hormone; **BDP** = beclometasone; **BUD** = budesonide; **DPI** = dry-powder inhaler; **FP** = fluticasone propionate; **ICS** = inhaled corticosteroids; **neb** = nebuliser; **ns** = not specified; **pMDI** = pressurised metered-dose inhaler; **qid** = four times daily.

costeroid, there is a lower threshold dose below which there are no measurable effects on the hypothalamic-pituitary-adrenal (HPA) axis. It is normally assumed that inhaled corticosteroid doses not associated with any measurable systemic effects are clinically safe with respect to HPA-axis function. Beyond this, there is a dose range within which systemic effects can be detected if sensitive methods are used; the inhaled-corticosteroid threshold dose at which measurable effects become evident is well documented. However, these effects merely seem to reflect small changes within the normal biological range that have no proven clinical relevance. Finally, there is an upper threshold dose, above which there is an increased risk of clinically important adverse effects. Few data are available on the magnitude and duration of change in HPA-axis function required for clinically important systemic effects to emerge.

Different assessments can be used to assess the HPA-axis, all of which have their limits. Undoubtedly, assessment of the axis' response to a physiological stress stimulus is the most relevant and a sensitive measure. However, this test is also the most demanding on the patients and therefore most studies use other assessments, such as a measurement of morning plasma cortisol or urinary free-cortisol levels. A single measure of plasma-cortisol level at 08.00 hours is liable to miss the true peak cortisol level. Urinary free-cortisol is valuable for assessing adrenal over-secretion of cortisol, but has poorer sensitivity and specificity for detection of adrenal hypofunction. Furthermore, if the measurement method cross-reacts with the therapeutic inhaled corticosteroid, the finding of a 'normal' cortisol excretion may be misleading. However, in spite of these reservations, several short-term studies have demonstrated clear dose-dependent reductions in urine-cortisol excretions in patients treated with inhaled corticosteroids.[57-61]

3.2 Results of the Literature Review

The findings of the effects of inhaled corticosteroids on cortisol levels in randomised, prospective studies of ≥12 months' duration are summarised in table III. In general, studies of recommended doses of inhaled corticosteroids found little or no effect on the chosen measures of HPA-axis function over treatment periods of ≥12 months. For example, a study of nebulised budesonide versus sodium cromoglicate, which included 335 children, reported no HPA-axis suppression in either group.[53]

A second large study (n = 670) compared budesonide inhalation suspension (500–1000 μg/day) with 'conventional asthma therapy' (notably, inhaled corticosteroids were permissible in two of the three conventional-therapy cohorts).[25] No significant difference in cortisol levels between the two groups was reported.

Another study of budesonide dry-powder inhaler (part of the Childhood Asthma Management Program study) indicated that there is no emergence of HPA-axis suppression over 36 months' treatment.[55] Similarly, no significant difference was reported between fluticasone propionate 100 μg/day, administered by pressurised metered dose inhaler, and sodium cromoglicate in a study of urinary free-cortisol levels.[16]

A larger study comparing dry-powder inhaler administration of fluticasone propionate 200 μg/day with administration of 400 μg/day (n = 528) demonstrated no between-group differences in urinary cortisol levels, and there were no decreases relative to baseline values over the 12-month treatment period.[56] A comparison of dry-powder inhaler delivery of fluticasone propionate 200 μg/day with fluticasone propionate 1000 μg/day step-down found some degree of reduction in urinary cortisol levels during the administration of fluticasone propionate 1000 and 500 μg/day, although cortisol levels rebounded with subsequent administration of lower doses of fluticasone propionate so there were no further significant between-group differences.[26]

The only beclometasone study meeting the selection criteria compared this inhaled corticosteroid from a pressurised metered dose inhaler with non-steroidal therapy, and indicated that it has no impact on morning cortisol levels during 12 months' therapy.[21]

Two of the randomised, prospective studies compared the effects of two different inhaled corticosteroids on cortisol levels. In the first, there were no apparent differences between fluticasone propionate 200 μg/day and beclometasone 200 μg/day, both administered by dry-powder inhaler, in terms of their effect on urinary-cortisol levels.[28] The second study compared fluticasone propionate via pressurised metered dose inhaler with a therapeutically equivalent dose of beclometasone via pressurised metered dose inhaler. Mean serum cortisol levels showed a significant reduction versus baseline in the beclometasone group from week 10 to month 20, whereas there was no reduction in the fluticasone propionate group.[29]

A recent study of fluticasone propionate 200 μg/day delivered via pressurised metered dose inhaler with a spacer in preschool children reported reductions in cortisol levels (10% serum, 14% urinary) compared with sodium cromoglicate.[17] However, the number of children with cortisol levels below the normal limit was reduced during the study.

Several of the selected studies included assessment of growth as well as cortisol levels, and correlation between the two endpoints was poor. A de-

crease in cortisol levels does not necessarily seem to be accompanied by impaired growth,[17] and reduced growth does not necessarily seem to be accompanied by a reduction in cortisol levels.[21,25,28] Similarly, changes in cortisol levels may not be consistent with changes in bone mineral density.[29] Therefore, measurement of changes in HPA-axis function does not seem to be a useful surrogate marker for the risk of clinically important adverse effects on these outcomes.

In contrast to these reassuring data, there have been several reports of symptomatic adrenal crisis in association with high-dose inhaled corticosteroids. The most extensive publication, by Todd et al.,[62] reported 28 paediatric cases from a UK-wide survey, the majority presenting with acute hypoglycaemia. All but two were associated with high-dose fluticasone propionate treatment and the authors contrasted this with the overall distribution of prescriptions in the UK, fluticasone propionate accounting for only 13%. However, this comparison might be confounded because among UK children aged <16 years, the proportion of inhaled-corticosteroid prescriptions (>1500 μg/day of beclometasone or equivalent) that were for fluticasone propionate (Flixotide® [1] or Seretide®) was 84%.[63] Therefore, more information on the risk of clinically important adverse effects on the HPA-axis by high-dose inhaled corticosteroid treatment is needed. There have been no reports of adrenal crisis in any clinical trial of inhaled corticosteroids in children.

The results from the present selection of studies also differ from some previous reports of recommended doses of inhaled corticosteroids. Comprehensive review articles, which included shorter term studies and data obtained from inpatients using sensitive techniques under controlled laboratory conditions, have found clear dose-related reductions in cortisol levels.[64,65] Therefore, the clinical relevance of such data for long-term maintenance therapy seems questionable.

4. Discussion

Although large numbers of studies have investigated the safety of inhaled corticosteroids, relatively few provide data on the clinical safety of long-term therapy in children. In preschool children, only two studies met the present selection criteria and for these patients it is not appropriate to extrapolate from the findings of studies in older children. Therefore, more paediatric safety studies are needed, particularly in young age groups and concerning long-term inhaled corticosteroid therapy (several years).

This review was focused on the clinical effects of long-term inhaled corticosteroid therapy on growth, bone mineral density and cortisol levels in children. These effects are dependent on the pharmacokinetics of the inhaled corticosteroid, particularly the systemic bioavailability after administration. There are considerable differences between inhaled corticosteroids in this regard. For example, the oral bioavailability of the more recent generation of inhaled corticosteroids (e.g. fluticasone propionate, budesonide and ciclesonide) is low compared with older inhaled corticosteroids (e.g. beclometasone, triamcinolone and flunisolide).[66-69] Therefore, the overall quantity of systemically available drug is mostly attributable to absorption from the lungs with the newer inhaled corticosteroids. Some inhalers are more effective than others in depositing the drug within the lungs, further affecting overall systemic bioavailability. In addition, the airways are relatively narrow in young children, reducing the proportion of drug reaching the airways. Given these factors, more obvious differences between inhaled corticosteroids may have been expected in the present review.

The possibility of less common adverse effects with inhaled corticosteroids (e.g. relating to the skin, cataracts and blood vessels) has not been studied or reported in children in long-term, randomised, controlled trials. Nevertheless, the available data in children suggest that these phenomena are not increased in children >5 years of age treated with low and moderate doses of inhaled corticosteroids for several years.[19,70] This assumption is supported by the findings in the 3000 children who received budesonide or placebo for ≤5 years in the START (Steroid Treatment As Regular Therapy) study.[71]

When the results from studies measuring effects on the HPA axis are assessed it must be remembered that dynamic tests of response to a stimulus provide

1 The use of trade names is for product identification purposes only and does not imply endorsement.

the more relevant and sensitive measure of HPA-axis function. Of the ten cortisol studies meeting the literature search inclusion criteria, only three included adrenocorticotrophic hormone (ACTH) testing. None of these used the low-dose ACTH test, which is the most sensitive test to detect small effects, so more long-term data with this test are needed.

Finally, this review only included published papers and in this respect there is always a risk of publication bias. At present, there is no way to know the extent of this; however, this will hopefully be less of a problem in the future, when results from all controlled trials must be made public – if not in scientific journals then on the internet.

5. Conclusions

Despite these reservations and the rather small number of long-term studies, the existing data are consistent in suggesting that doses of inhaled corticosteroids that control asthma in the majority of patients with mild to moderate asthma are not associated with any clinically relevant adverse effects on growth, bone mineral density or cortisol levels. Several studies found that inhaled corticosteroid treatment markedly reduced the need for oral corticosteroids. In contrast to inhaled corticosteroids, oral corticosteroids have been associated with growth impairment and dose-dependent increase in risk of fracture. Therefore, the risk of systemic adverse effects with inhaled corticosteroids must also be balanced against the risks of uncontrolled asthma and frequent oral corticosteroid use affecting growth, bone mineral density and risk of fracture.[11,44] The available data indicate that daily doses of inhaled corticosteroids up to 400μg can be used for long-term therapy in children with asthma without clinically relevant systemic adverse effects.

The data on long-term use of higher doses all come from less well controlled studies. Although the findings from these studies suggest that such doses are not associated with any adverse effect on bone mineral density, risk of fracture or final adult height, more studies are needed before firm conclusions can be drawn. Idiosyncratic cases of adrenal crisis during high-dose therapy seem rare, but they should always be kept in mind by healthcare professionals treating children who may need high doses of inhaled corticosteroids (>400 μg/day) for long periods of time.

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