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REVIEW

Long-, intermediate- and short-term growth studies in asthmatic children treated with inhaled glucocorticosteroids

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Long-, intermediate- and short-term growth studies in asthmatic children treated with inhaled glucocorticosteroids. O.D. Wolthers. ©ERS Journals Ltd 1996.

ABSTRACT: During recent years, new auxological techniques have been introduced for assessment of the risk of growth suppression in asthmatic children treated with exogeneous glucocorticosteroids. Assessment of lower leg growth rates with the knemometer has made short-term studies of growth processes under strictly controlled conditions possible. However, short-term lower leg growth rates cannot be used for estimations of intermediate-term height growth rates or long-term evaluations of final height. Consequently, the distinctions between the various types of growth studies in asthmatic children treated with inhaled glucocorticosteroids have become important and need to be discussed.

The present paper presents a review of the long-, intermediate- and short-term growth studies available. The bulk of evidence from intermediate- and short-term evaluations indicates that growth rate is not affected when standard paediatric doses of inhaled glucocorticosteroids are used. However, further focus needs to be placed on differences between specific glucocorticosteroids, doses and delivery systems. Intermediate- and short-term growth data should be evaluated in the long-term perspective.

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During recent years, it has become widely accepted that symptoms and severity of bronchial asthma are correlated to features of inflammation [1, 2] . Since topical glucocorticosteroids have marked anti-inflammatory effects in the bronchial mucosa, these drugs are increasingly recommended for early treatment in the management of asthma [1, 3–5]. Consequently, the risk of serious adverse effects, such as growth retardation in children, has attracted more attention. New methods and techniques have been introduced for assessment of the risk of growth supression. This paper reviews the data available on growth effects of inhaled glucocorticosteroids in asthmatic children and comments on the interpretation of results from various types of growth studies.

Regulation of growth

Normal growth is regulated by complex interactions of hormonal influences, tissue responsiveness and nutrition [6]. The final outcome of growth, adult height, depends on three distinct age-related components: 1) Growth during infancy. The rapid growth of the first 2–3 yrs of life. To some extent this phase is controlled by the same factors which stimulate foetal growth, the main one being nutrition; 2) Childhood growth. Longitudinal growth occurring from 3 yrs of age to puberty, which is mainly dependent on pituitary secretion of growth hormone; and 3) Growth during puberty. The pubertal growth spurt, which in addition to growth hormone is stimulated mainly by the sex glucocorticosteroids.

Outcome measures of growth

When the effect of exogeneous glucocorticosteroids on growth is evaluated, it is convenient to apply the following definitions of long-, intermediate- and short-term growth studies [7]. The long-term growth study starts in infancy or childhood and is completed when adult height has been achieved. The intermediate-term growth study evaluates growth in longer periods than 6 months but does not include assessment of final height. The observation period in a short-term growth study is 6 months or less.

The clinically important outcome measure, final adult height, can only be assessed in a long-term study. It is expressed as the observed height in relation to expected final height, allowing for sex and mid-parental height differences.

Though final height is the clinically relevant outcome measure of growth, it is not always possible to follow the child until adult height has been achieved. Therefore, most studies of growth in children treated with inhaled glucocorticosteroids have used observation periods of one or several years but have not included assessment of final height. Analysis of annual height measurements in glucocorticosteroid-treated children may provide important information on treatment effects, which may lead to withdrawal of the treatment or changes in treatment regimens. Furthermore, annual measurements may also identify individual responses to treatment.

The outcome measures of intermediate-term studies are height growth rate and statural height compared to

age- and sex-matched standards for normals (height percentiles, height standard deviation scores). Since the error of height measurement is approximately 0.3 cm, shorter than annual measurement intervals should not be applied. It is important to be aware that due to seasonal variations in growth, to spontaneous variations in growth rate throughout childhood, and to variations in the timing and size of the pubertal growth spurt, growth rates from intermediate-term studies are not reliable for prediction of final height [8–11].

The short-term growth study requires auxological techniques with smaller measurement errors than those observed for statural height, such as knemometry or modified knemometry for use in early life [12, 13]. The knemometer measures the length of the lower leg with an accuracy of approximately 0.1 mm. Compared to long-term and intermediate-term growth studies, there are three important advances of knemometry studies: the observation periods may be very short (weeks); controlled, randomized, double-blind conditions can be applied; and cross-over trials can be performed [14]. Direct effects of exogeneous glucocorticosteroids on growth can be assessed, and detailed insight into the biology of the growth process may be provided [14, 15]. The outcome measure in short-term growth studies is lower leg growth rate. Short-term lower leg growth rates cannot be extrapolated to intermediate- or long term height growth rates [16, 17]. This is probably due to influences from the soft tissue componenent in the lower leg length measurements and to seasonal and spontaneous variations in growth of the lower leg [15, 16, 18, 19].

Asthma and growth

As in other chronic childhood diseases, impairment of growth may be seen in asthmatic children [20]. This has been suggested to be due to different factors: hormonal [21]; nutritional [21–23]; psychological and socioeconomic factors [21, 24]; hypoxaemia [21, 23]; pulmonary infections [25]; and treatment with systemic glucocorticosteroids [26]. Only the latter has been established as a significant risk factor. The growth suppressive effect of oral glucocorticosteroids is correlated to duration of treatment, dosage and regimen [26–34]. When a twice daily administration regimen is used, daily doses from approximately 2.5–5 mg prednisolone suppress intermediate-term statural growth in children with asthma [35–37]. When the treatment is withdrawn, catch-up growth may occur compensating for the retardation [28]. Age and pubertal stage at withdrawal of the glucocorticosteroid appear to be important for the final outcome of growth. The risk of permanent stunting can be reduced when the treatment is withdrawn before the pubertal growth spurt occurs [38]. Reduction of final height has been seen after several years of treatment with low daily doses of prednisolone [37].

Though many studies have aimed to evaluate to what extent asthma severity may be associated with growth retardation, there are no data available to prove any causal relationship [23–25, 34, 39–44]. On the contrary, growth impairment has been observed in asthmatic children not on glucocorticosteroids regardless of the severity of their disease [40–42]. Since similar observations have been made in children with allergic rhinitis [41] and atopic dermatitis [45, 46] it has been suggested that the retardation of growth may represent a physiological pattern associated with the atopic condition *per se* [41, 45].

Growth delay is most frequent in preadolescent children [24, 39, 40, 42], and a large proportion of boys are delayed in puberty [25, 39, 40, 47]. This explains the deceleration of growth velocity in late maturing children with asthma [39, 40]. The deviant growth pattern is associated with retarded bone age corresponding to the retardation in statural height, indicating the existence of a relative growth potential [39]. In accordance with this, the children continue to grow for a longer period as compared with their peers. It seems that in most of them final height within the normal range is obtained [24, 25, 39, 40, 44, 48].

Considering the many variables that may influence growth in children with asthma, it seems obvious that a meaningful assessment of the relationship between treatment with inhaled glucocorticosteroids and growth depends on carefully selected control or comparative groups.

Inhaled glucocorticosteroids and growth

Long-term growth

One long-term follow-up study reported final height to be within the expected range in children treated with beclomethasone dipropionate (table 1) [40]. However, no specific data were given on predicted height estimated from parental height.

Intermediate-term growth

Details and results of various intermediate-term growth studies in children treated with inhaled glucocorticosteroids are presented in the table 1. Most of the follow-up studies have been in children with severe asthma [40, 44, 49–56] and have not included control groups. In the studies that have used control groups, the prepubertal growth deceleration may have complicated the interpretation of the results. This is illustrated by the study reported by Littlewood *et al*. [57], in which the deviant growth pattern probably reflected the physiological growth deceleration in the beclomethasone-treated children rather than growth suppressive effects of the inhaled treatment. In the study by Nassif *et al*. [56], intermediate growth in groups of children treated with inhaled beclomethasone dipropionate and alternate-day prednisolone was compared with non-glucocorticosteroid-treated asthmatics and normal children. A preponderance of low growth rates was seen in the groups treated with glucocorticosteroids. However, the study design did not allow any evaluation of whether that was caused by the treatment or the more severe disease activity in the glucocorticosteroid-treated groups.

In the studies of beclomethasone dipropionate, the dose often varied and, in one study [51], the treatment was withdrawn for some months during the observation period. Some of the children in the studies had received oral glucocorticosteroids until the inhaled therapy was

Table 1. – Conventional growth studies in children with asthma treated with inhaled glucocorticosteroids

First author	Year	[Ref]	Age yrs	Pts n	Drug	Dose $\mu g \cdot day^{-1}$	Dose regimen	Mode of administration	Method	Obs. period yrs	Outcome measure	Effect
Godfrey	1974	[50]	4–15	26	BDP	100–800	NG	P-MDI	H/P; NC	1	Mean height growth rate	None
Francis	1976	[51]	6–17	15	BDP	300	NG	P-MDI	P; NC	2.5–3	Height percentiles	None
Kerrebijn	1976	[52]	7–9	7	BDP	300	*t.i.d*	P-MDI	H/P; NC	1.5	Height growth rates, height-SDS	None None
Godfrey	1978	[53]	5–11	19	BDP	100–800	NG	P-MDI	H/P; NC	3–5.3	Height percentiles	None
Graff-Lonnevig	1979	[54]	3–10	31	BDP	200–400	*t.i.d.*	P-MDI	H; NC	1.3–3.3	Mean height-SD	None
Brown	1980	[55]	NG	75	BDP	450	*t.i.d.*	P-MDI	H; NC	NG	Height percentiles	No conclusion
Balfour-Lynn	1986	[40]	NG	26	BDP	?–600	NG	P-MDI	H/P; NC	1.1–12.3	Height percentiles, final height	None None
Nassif	1987	[56]	10–16	32	BDP	300–750	NG	NG	H/P; C	2.1	Mean height percentile Mean height growth rate	No conclusion No conclusion
Littlewood	1988	[57]	8–13	81	BDP	200–800	NG	NG	CS; C	NG	Mean height-SDS	Suppression
Littlewood	1988	[57]	NG	16	BDP	200–800	NG	NG	H; NC	3.5	Mean height-SDS	Suppression
Verini	1990	[62]	NG	10	BDP	300	*t.i.d.*	P-MDI	H; C	1	Height percentiles Mean height growth rate	None None
Phillip	1992	[63]	6–16	8	BDP	300–450	NG	P-MDI	H; NC	0.5–3	Height growth rates	None
Brown	1989	[61]	6–17	82	TRI	400–1200	*q.i.d.*	P-MDI	H; NC	1	Mean height percentile	None
Ribeiro	1987	[59]	7–12	19	BUD	200	*b.i.d.*	P-MDI + a tube inhalation device	P; NC	1	Height percentiles	None
Varsano	1990	[49]	3–7	16	BUD	200–400	2–4 *q.d.*	P-MDI + a spacer	P; NC	1	Height percentiles	None
Ninan	1992	[44]	NG	58	BDP/BUD	200–1600	NG	P-MDI + a spacer/ dry powder inhaler	H; NC	1–5.1	Height growth rate-SDS	None
Ribeiro	1993	[64]	4–13	52	BUD	400	*b.i.d.*	P-MDI + a tube inhalation device	P; NC	1	Height-SDS	None
Merkus	1993	[65]	12–16	40	BUD	600	*t.i.d.*	P-MDI	P; C	1.6	Height growth rates	None
Tinkelman	1993	[58]	6–16	195	BDP	330	*q.i.d.*	P-MDI	P; C	1	Height growth rates	Suppression
Agertoft	1994	[60]	3–11	216	BUD	430–710	NG	P-MDI + a spacer/ dry powder inhaler	H; C	3–6	Height-SDS Height growth rates	None None
Ruiz	1994	[66]	4–7	18	BUD	200–800	NG	P-MDI + a spacer	H; NC	1	Height growth rate-SDS	None

Pts: patients; obs. period: observational period; BDP: beclomethasone dipropionate; TRI: triamcinolone acetonide; BUD: budesonide; P-MDI: pressurized metered-dose inhaler; P: prospective follow-up; H: historical follow-up; CS: cross-sectional; C: control group; NC: no control group; SDS: standard deviation score; NG: not given.

introduced [50–54], and continued to do so intermittently [50, 53]. In the study by TINKELMAN *et al*. [58], the beclomethasone dipropionate-treated children were compared with theophylline-treated children, who grew somewhat faster than expected during the study period. One of the budesonide studies included children who had been treated with inhaled beclomethasone dipropionate until budesonide was introduced [59]. Another study of budesonide included children who had received oral glucocorticosteroids shortly before entry into the study [49]. Intermittent treatment with oral glucocorticosteroids was allowed in several of the budesonide studies [49, 59, 60]. In the study of triamcinolone acetonide, a majority of patients were on oral glucocorticosteroids when the inhaled therapy was introduced [61].

Short-term growth

In a randomized, single-blind, cross-over study of 14 children aged 1–3 yrs with mild, recurrent wheezing, a handheld knemometer was used for assessment of lower leg growth rates during treatment with 200 and 800 μg budesonide inhaled *via* a spacer with a face mask [67]. Treatment with 800 μg budesonide was associated with reduced growth rate, whereas treatment with 200 μg was not. The results should be interpreted with some reservation, since a wash-out period was not interposed between the two 4 week budesonide treatment periods.

Two randomized, double-blind knemometry studies have evaluated the influence of inhaled budesonide delivered from the Nebuhaler® in prepubertal 6–14 year olds with mild asthma [68, 69]. In the cross-over study, 14 children were measured twice weekly during periods of 2.5 weeks [68]. In the parallel group study, 38 children were measured once a week during 4 weeks run-in and 8 weeks treatment [69]. In both studies, daily doses of 200-400 μg were found to have no adverse effect on growth. Furthermore, data from these studies were pooled with data from two other knemometry studies [70]. Analysis of growth rates in 61 children failed to show any growth suppression by budesonide in doses up to 400 μg [70]. In contrast, 800 μg budesonide statistically significantly reduced lower leg growth rates to approximately 50% of the run-in values [68, 69].

Beclomethasone dipropionate and fluticasone propionate from a Diskhaler were compared in a randomized, double-blind, three period, cross-over knemometry trial in 17 prepubertal 7–14 year olds with mild asthma [71]. Knemometry was performed twice weekly during periods of 2 weeks. Beclomethasone dipropionate, 400 and 800 μg, caused almost total suppression of lower leg growth rates during 2 week observation periods.

Discussion

A conspicuous paucity of data on the final outcome of growth, adult height, exists in children treated with inhaled glucocorticosteroids. Most of the intermediate-term studies available have been in schoolchildren. However, since the regulation of growth varies from infancy to puberty, conclusions from these studies may not be valid for other age groups. Therefore, extrapolations of growth results from one age group to another should be avoided, and effects of exogeneous glucocorticosteroids on growth rates should be assessed separately in all three age groups.

Interpretation of the results of the intermediate-term growth studies is complicated by the difficulties in establishing randomized, controlled, double-blind study conditions. Influences from differences between various inhaled drugs, dosages, administration regimens, change of delivery systems during the observation period, intermittent use of other antiasthma medications, fluctuations in disease severity and compliance are difficult to control in follow-up studies of several years duration. On the other hand, it may be argued that such conditions are more similar to the clinical situation than are the strictly controlled conditions applied in short-term growth studies. However, though reservation is necessary when trying to evaluate growth effects of inhaled glucocorticosteroids in children from the intermediate-term studies available, the bulk of evidence suggests that height growth rate is not affected by inhaled glucocorticosteroids when low doses are used.

The results of the short-term growth studies have emphasized the importance of being specific with respect to doses, glucocorticosteroids and inhaler systems used. Intermediate- and short-term evaluations of budesonide taken from the Nebuhaler unanimously indicate that doses up to 400 $\mu g \cdot day^{-1}$ do not adversely affect growth rates in prepubertal children. The cause for the discrepancy between these findings and the findings in the short-term study of beclomethasone dipropionate administered from the Diskhaler seems to be differences in systemic activity between the two drugs. Such differences have been reported in studies using other measures of systemic activity of inhaled glucocorticosteroids [72, 73]. However, to some extent, it may also be due to the use of different inhalers. Administration of a glucocorticosteroid from a spacer device causes less systemic activity than a Diskhaler or a metered-dose inhaler [74]. Thus, no conclusions can be made from one specific glucocorticosteroid to others administered from different delivery systems, whether in similar or different doses. Finally, short-term growth studies of insufflated glucocorticosteroids have suggested that the dose regimen also influences the risk of growth suppressive effects of topical glucocorticosteroids [75, 76]. Once daily dosing appears to be associated with a lower leg growth sparing effect as compared to twice daily dosing.

Intermediate- or long-term growth effects cannot be estimated from the short-term findings of supressed growth rates during treatment with 800 μg budesonide from the Nebuhaler and 400 and 800 μg beclomethasone dipropionate from the Diskhaler. The finding of suppressive effects on short-term growth of a similar magnitude during beclomethasone dipropionate treatment and during treatment with 2.5 mg prednisolone in comparable study designs [14, 71] indicates that short-term knemometry may amplify and, so to speak, exaggerate the growth retarding effect of exogeneous glucocorticosteroids. This is probably due to soft tissue effects, as indicated from concomitant observations of catabolic effects on collagen turnover [77, 78]. On the other hand, findings of no adverse effects of inhaled glucocorticosteroids on knemometric growth rates have been confirmatory to results

from intermediate-term studies of height growth rates. Therefore, if an inhaled glucocorticosteroid is not associated with any detectable suppressive effect on short-term knemometric growth rates, it appears to be most unlikely that such treatment will cause any detectable suppressive effect on height growth rates in the intermediate-term perspective.

Conclusions

No firm conclusions can be drawn with respect to the important outcome of childhood growth, adult height, in children treated with inhaled glucocorticosteroids. However, adverse effects on final height from treatment regimens that have been found not to be associated with any suppressive effects in the short- and intermediate-term perspectives seem unlikely. Evaluation of final height in children in whom inhaled glucocorticosteroids are introduced and continued during one or all three phases of growth are needed.

Though the results of the intermediate-term growth studies available are generally reassuring with respect to height growth rates, these data should be interpreted with caution, since most of the studies have used uncontrolled designs. Suitable controlled conditions are difficult to establish.

Inhaled budesonide from the Nebuhaler in doses up to 400 $\mu g \cdot day^{-1}$ does not adversely affect short- or intermediate-term growth rates in prepubertal children. The finding of reduced short-term lower leg growth rates during treatment with 800 μg budesonide from the Nebuhaler does not imply a similar effect on intermediate-term growth in height.

Treatment with inhaled beclomethasone dipropionate, 400 and 800 μg, from the Diskhaler suppresses short-term lower leg growth rates, but no firm conclusions can be drawn with respect to intermediate- or long-term growth effects.

When new topical glucocorticosteroids, administration forms, application systems or dose regimens are introduced in the management of children with asthma, short-term knemometry can be used for assessment of the dose level at which growth suppressive effects should be looked for.

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