Eur Respir J 2006; 27: 316–320
DOI: 10.1183/09031936.06.00071905

The effect of inhaled budesonide on adrenal and growth suppression in asthmatic children

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ABSTRACT: The present authors evaluated adrenal reserve in asthmatic children on long-term inhaled corticosteroids and whether possible adrenal suppression could be predicted by growth retardation.

Low-dose synacthen test (0.5 μg·1.73 m^{-2}) was performed in 72 asthmatic children with a median age of 9.4 (range 4.2–15.7) yrs on long-term treatment (median 18 (range 6–84) months) with low-to-moderate doses (median 363 (range 127–1012) μg·m^{-2}) of inhaled budesonide, as well as in 30 controls. Adrenal suppression was considered as a peak serum cortisol <495 nmol·L^{-1}. The current authors calculated height standard deviation score (HSDS) at the time of testing and height velocity SDS (HVSDS) in the preceding year.

Mean HSDS was 0.06±1.3 and HVSDS was -0.9±2.3. Adrenal suppression was disclosed in 15 asthmatic children (20.8%). There were no differences in HSDS and HVSDS between children with and without adrenal suppression. There was no correlation between peak cortisol response and dose or duration of treatment. However, a positive relationship between HVSDS and duration of treatment was noted.

These data suggest that long-term treatment of asthmatic children with low and moderate doses of inhaled budesonide may result in mild adrenal suppression that cannot be predicted by growth deceleration. The negative influence of inhaled corticosteroids on growth becomes less the longer the duration of treatment.

KEYWORDS: Adrenal function, asthma, children, growth, inhaled budesonide

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Received:
June 18 2005
Accepted after revision:
October 31 2005

Inhaled corticosteroids (ICS) are the cornerstone in the management of persistent asthma. It is widely accepted that ICS are a safe mode of treatment because they act directly on the target organ, *i.e.* the lungs, whereas their systemic bioavailability is small due to their limited oral absorption and high hepatic first pass metabolism [1]. However, clinicians are often reluctant to prescribe ICS because of their potential side-effects [2]. Indeed, a number of studies reported growth retardation and/or mild adrenal suppression in asthmatic children treated with ICS [3–6]. Recently, there were reports of symptomatic adrenal insufficiency in children on chronic ICS treatment [7–9]. The vast majority of these children were treated with high doses of inhaled fluticasone.

Adrenal function can be assessed by various methods, *e.g.* by measuring morning serum cortisol [10] or 24-h excretion of cortisol and its metabolites in urine with gas chromatography-mass spectroscopy [1, 10]. More recently, the corticotrophin-releasing hormone test was also used to assess the function of the hypothalamic-pituitary-adrenal axis [11]. Adrenal response in a stress situation is mainly assessed by the insulin tolerance test (ITT) and the synthetic adrenocorticotrophic hormone (ACTH) (synacthen) stimulation test [12]. However, ITT has been linked to deaths in children as a result of the insulin-induced hypoglycaemia or its treatment [13]. In contrast, the dosage of ACTH used in the standard (0.25 mg) synacthen test (SST) produces supraphysiological ACTH levels that are never found in a real-life stress situation. In recent years, the low-dose (0.5 μg·1.73 m^{-2} body surface area) synacthen test (LDST) has been used as a more physiological stimulus to the adrenal gland [14] that is more sensitive than SST in detecting mild adrenal suppression [15, 16].

Linear growth has been shown to be temporarily compromised by conventional doses of ICS [17].

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

Recently, reductions in height gain were documented in children taking daily doses of budesonide as small as 200 μg, suggesting that even low doses may have measurable systemic effects [18].

There are conflicting reports on the correlation of the effects of ICS on hypothalamic-pituitary-adrenal axis and growth. KANISTO *et al*. [19] studied children who used ICS for a whole year and they found that a subnormal ACTH test was associated with growth suppression. In another more recent 12-month observational study of 35 pre-pubertal asthmatic children requiring $\geqslant$1,000 μg·day^{-1} of budesonide or equal potency of fluticasone propionate, DUNLOP *et al*. [20] reported that 46% of the subjects had evidence of biochemical adrenal suppression after LDST. Monitoring growth suppression alone was not adequate enough to reveal those at risk of the more severe adrenal suppression. It appears that possibly different levels of susceptibility to growth retardation and adrenal suppression to the different doses and types of ICS might exist.

The hypothesis of the present study was that growth monitoring could reveal mild adrenal suppression in asthmatic children on long-term treatment with low and medium doses of ICS. To test this hypothesis, the current authors investigated a cohort of asthmatic children on long-term treatment with inhaled budesonide looking at adrenal reserve by LDST and whether possible adrenal suppression could be predicted by growth retardation.

PATIENTS AND METHODS

Subjects

A total of 72 asthmatic children (42 males) who regularly attended the outpatient clinic of the Dept of Allergology-Pulmonology of Penteli Children's Hospital (P. Penteli, Greece) participated in the current cross-sectional study with a retrospective evaluation of data on growth and lung function. Inclusion criteria for the study were: 1) long-term (>6 months) continuous treatment with inhaled budesonide *via* turbuhaler at a dose up to 800 μg·day^{-1} or 1,000 μg·m^{-2} body surface area·day^{-1}; and 2) no usage of other inhaled corticosteroid treatment in the past, as well as no topical or systemic corticosteroids for the last 3 months. Children with a history of other chronic illnesses were excluded from the study.

Height measurements were made according to established techniques by the same experienced nurse with a Harpenden calibrated stadiometer (Holtrain Ltd, Crymych, UK). Height was measured to the nearest 0.1 cm and was expressed as height standard deviation score (HSDS). All past growth measurements were also made by the same nurse. Height velocity in the year preceding the time of the study was calculated in 55 children that were pre-pubertal at the time of the study and expressed as height velocity standard deviation score (HVSDS).

Lung function testing was performed at each visit if the child was able to complete reproducible and satisfactory flow–volume curves according to the standards of the American Thoracic Society [21]. Values are expressed as a percentage of predicted for sex and height. Atopic status was assessed by skin-prick testing and/or radioallergosorbent test. A battery of 20 common inhaled allergens was tested.

A total of 30 healthy nonasthmatic children matched for age and sex recruited from a general population sample served as controls to define the range of normal values of peak serum cortisol response to LDST. They also completed the spirometry and the skin-prick testing.

The present study was approved by the ethics committee of Penteli Children's Hospital and informed consent was obtained by the parents of each child that participated in the study.

Assessment of adrenal reserve

In order to assess adrenal reserve, the LDST (0.5 μg·1.73 m^{-2}) was performed in both the asthmatic children and controls. Serum cortisol was measured at baseline, 30 and 60 min after *i.v.* injection of diluted synacthen. LDST was performed between 09:00 h and 11:00 h. The normal response was considered the value that corresponded to, or above, the 3rd percentile of the serum cortisol response to LDST of controls.

Adrenal reserve testing along with spirometry was deferred if the child had suffered a respiratory tract infection within the past 3 weeks.

Statistical analysis

Differences of HSDS and HVSDS between children with and without adrenal suppression were determined using the independent samples t-test. Multivariate linear regression analysis with stepwise method was also performed for HSDS, HVSDS and peak serum cortisol level. Correlated variables were age, sex, forced expiratory volume in one second (FEV_1) at the time of initiation of the inhaled budesonide treatment, as well as the day of LDST, dose and duration of ICS treatment and atopic status. The relationships between HSDS and HVSDS and peak serum cortisol level were analysed using Pearson's correlation coefficient. The level of statistical significance was at 5%.

RESULTS

Demographic data and the other characteristics of patients and controls are shown in table 1.

A total of 15 asthmatic children (20.8%) demonstrated biochemical adrenal suppression, *i.e.* they had a peak serum cortisol response to LDST <495 nmol·L^{-1}, the value that corresponded to the 3rd percentile of controls. No patient presented symptoms suggestive of adrenal insufficiency.

There were no significant differences in HSDS (difference 0.35; 95% confidence interval (CI) -0.6–1.3), HVSDS (difference -0.79; 95% CI -2.6–1.0), FEV_1 at the time of treatment initiation (difference -1.29%; 95% CI -7.9–5.3) and FEV_1 at the time of LDST performance (difference -2.39; 95% CI -8.5–3.7) between children with and without adrenal suppression.

When multivariate linear regression analysis was performed, no significant correlation between peak cortisol response and the other parameters studied (age, sex, FEV_1 at the time of treatment initiation, dose of inhaled budesonide, duration of treatment) was found after stepwise analysis.

The height of asthmatic children was not different from that of the general population as the mean±SD HSDS was 0.06±1.3. There was a positive correlation between HSDS and FEV_1 at the time of treatment initiation ($t=2.51$; $p=0.015$) and a

TABLE 1 Characteristics of asthmatic children and controls

	Asthmatics	Controls	p-value
Subjects n	72	30	
Male	42 (58.3)	18 (60)	NS
Age yrs	9.4 (6.1–14.8)	9.2 (5.7–14.1)	NS
Chronic rhinitis ever	22 (30.5)	6 (20.0)	NS
Eczema ever	17 (23.6)	4 (13.3)	NS
Sensitisation	37 (51.4)	5 (16.7)	<0.01
Dose of budesonide			
μg·day^{-1}	400 (200–800)		
μg·m^{-2}·day^{-1}	363 (127–1022)		
Duration of treatment months	18 (6–84)		
HSDS	0.06±1.3		
HVSDS$^{\#}$	-0.9±2.3		
FEV$_1$ % pred	89.9±10.1¶	96.9±6.1	0.002
	97.3±9.2^{+}		NS

Data are presented as n (%), median (range) or mean±SD. HSDS: height standard deviation score; HVSDS: height velocity standard deviation score; FEV$_1$: forced expiratory volume in one second; NS: nonsignificant; % pred: per cent predicted. $^{\#}$: n=55; ¶: values at the beginning of treatment; $^{+}$: values at the time of low-dose synacthen test.

negative correlation between HSDS and dose of inhaled budesonide (t=-2.28; p=0.026; fig. 1) after stepwise analysis.

During the year preceding the time of the study, height velocity was low as mean HVSDS was -0.9±2.3. Multivariate linear regression analysis revealed a positive correlation with duration of treatment (t=2.66; p=0.011; fig. 2).

There was a borderline correlation between HSDS and HVSDS (Pearson's correlation coefficient r=0.26; p=0.054), but no correlation between HSDS or HVSDS and peak cortisol response was detected (fig. 3).

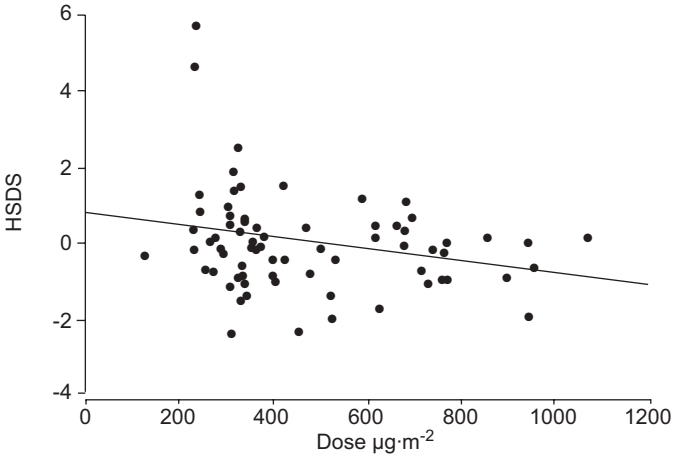

FIGURE 1. Negative correlation between height standard deviation score (HSDS) and dose of inhaled budesonide (t=-2.80; p=0.026).

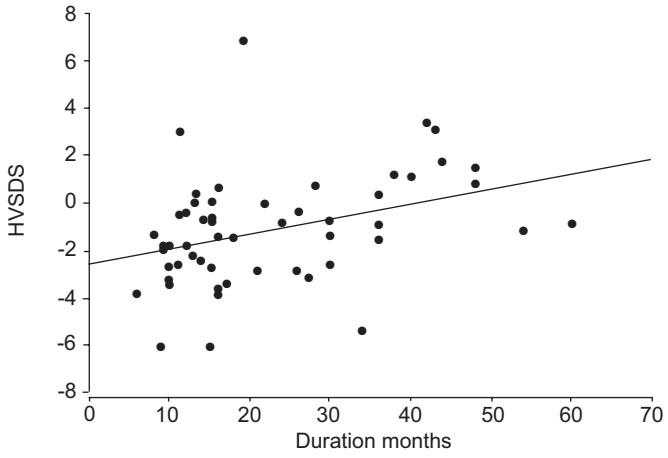

FIGURE 2. Positive correlation between height velocity standard deviation score (HVSDS) and duration of treatment (t=2.66; p=0.011).

DISCUSSION

The presented data show that a considerable number of asthmatic children on long-term treatment with inhaled budesonide presented mild adrenal suppression, as it is disclosed by the LDST, which was not related to dose and duration of treatment. Furthermore, no association of adrenal suppression with growth deceleration was detected.

Adrenal suppression was only biochemical, since none of these children presented symptomatic adrenal insufficiency during stress conditions (*e.g.* infections, trauma) by the time of the present study, suggesting that adrenal hyporesponsiveness is not clinically significant in a real-life stress situation. There are only a few studies on adrenal function of children on chronic ICS treatment. PRIFTIS *et al*. [22] reported a dose-dependent reduction in the urinary cortisol metabolites of asthmatic children treated with beclomethasone dipropionate (200–900 μg·day^{-1}). Cortisol metabolite levels tended to fall below the normal range when beclomethasone was given at a

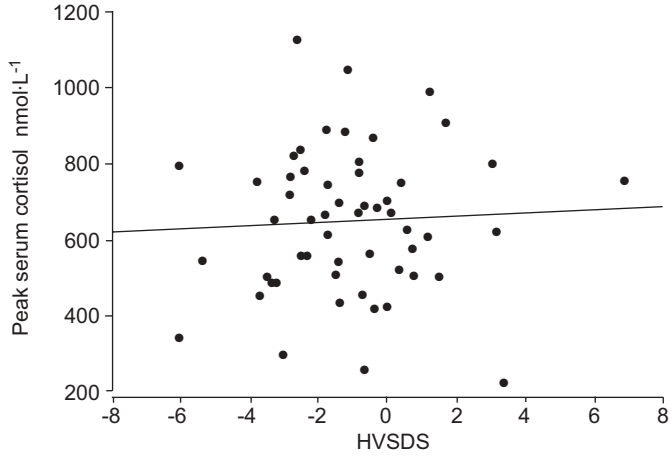

FIGURE 3. No correlation between height velocity standard deviation score (HVSDS) and peak serum cortisol response was detected (Pearson's correlation coefficient r=0.05; p=0.707).

dose >400 $\mu g \cdot m^{-2} \cdot day^{-1}$. YIALLOUROS *et al*. [23] reported dose-dependent suppression of adrenal function reflected in urinary cortisol metabolites in children taking budesonide in the higher range of 400–900 $\mu g \cdot m^{-2} \cdot day^{-1}$. In a study of asthmatic children treated with budesonide (400–800 $\mu g \cdot day^{-1}$), SHAPIRO *et al*. [24] found that 9–12% of the children had subnormal levels of basal plasma cortisol. However, in other studies where adrenal suppression was determined by the LDST, 23–35% of asthmatic children on moderate doses of beclomethasone dipropionate, budesonide or fluticasone propionate showed a subnormal response [14, 24], while higher doses of ICS revealed adrenal suppression in up to 46% [18]. The data from the current study of adrenal suppression in 20.8% of asthmatic children on mild and moderate doses of budesonide are in general agreement with the literature. The present authors do not know whether these children would present symptomatic adrenal insufficiency if they were treated with much larger doses of budesonide, such as children on large doses of fluticasone who reportedly experienced adrenal crisis [7–9, 25–27].

An important finding in the present study is that adrenal suppression did not correlate with the dose of budesonide and/or the duration of treatment highlighting the idiosyncratic sensitivity of some children to ICS. The latter probably explains symptomatic adrenal insufficiency in children even on moderate doses of ICS [8]. Moreover, there are case reports of iatrogenic Cushing's syndrome in children even on conventional doses of ICS [27, 28]. However, the current authors cannot exclude the possibility of a dose-dependent adrenal suppression if a greater number of the presented patients were on large doses of budesonide.

A low cortisol response in some of the asthmatics could also be attributed to better compliance to treatment [29]. However, all children participating in the present study were followed up regularly and the course of the disease, as well as lung function, at the time of testing was not different between children with normal and low response to adrenal stimulation suggesting a similar level of compliance.

Mean height of asthmatic children was not different compared with that of the population; however, HSDS was negatively correlated with the severity of asthma as estimated by lower FEV_1 values at the beginning of treatment and higher doses of budesonide (fig. 1). This is in accordance with the known relationship between the severity of symptoms and the degree of growth retardation [30, 31]. Height velocity in the year preceding the time of the study was low; however, deviation of HVSDS from normal was smaller the longer the duration of ICS treatment (fig. 2). This is in agreement with previous reports describing faster growth after the first period of treatment with ICS [18, 32, 33]. In a recent study, it was found that children on a low dose of inhaled budesonide for 3 yrs presented greater reductions in height in the first year (0.58 cm), than years 2 and 3 (0.43 cm and 0.33 cm, respectively) [18]. It is unclear whether the small reductions in height during ICS treatment may be compensated later on in life, or may result in some loss in final height. Although the data on adult height are reassuring [32, 33], the evidence is still insufficient as to whether long-term ICS treatment in childhood may allow the attainment of the full genetic growth potential.

PRICE *et al*. [34] reviewed 21 papers looking at the effects of asthma treatment on childhood growth and they found that the results from the majority of published growth studies with inhaled corticosteroids must be interpreted with a degree of caution owing to their potential susceptibility to important confounding factors.

Growth was considered as a sensitive indicator of the systemic bioavailability of ICS. TINKELMAN *et al*. [35] examined growth and adrenal response to the ACTH test in asthmatic children treated with inhaled beclomethasone or theophylline. Height velocity was significantly lower in those receiving beclomethasone, whereas adrenal response was normal in both groups. Growth in relation to adrenal reserve was also assessed by KANNISTO *et al*. [19]. Children with a subnormal response to LDST had a decrease of 0.4 inches in height compared with only 0.08 inches in the children with a normal LDST response.

The present data show no correlation between HVSDS and response to LDST in asthmatic children on long-term inhaled budesonide treatment in low and medium doses. Therefore, adrenal insufficiency cannot be predicted by decreased growth rate. This is in accordance with the recently reported observation by DUNLOP *et al*. [20] that monitoring for growth suppression in asthmatic children requiring high doses of ICS was not adequate enough to reveal those at risk of adrenal suppression. Lack of correlation of growth and adrenal response to ICS may be due to increased or decreased sensitivity of the glucocorticoid receptors to exogenous corticosteroids. Preliminary data suggest that polymorphisms in the glucocortocoid receptor might affect corticosteroid sensitivity in a tissue-specific manner [36].

The fact that at least two of the major target tissues of exogenous glucocorticosteroids, *i.e.* adrenal glands and bones, are adversely affected by moderate doses of budesonide suggests that physicians should prescribe ICS at the lowest effective doses. The findings of the present study confirm that prolonged ICS have no additive effect on adrenal suppression and in that view they may be used for as long as necessary.

In conclusion, 20.4% of asthmatic children on long-term treatment with low and moderate doses of inhaled budesonide demonstrated mild biochemical adrenal suppression which was not related to dose or duration of treatment. Although inhaled budesonide treatment may result in growth deceleration, the latter does not predict adrenal suppression. Moreover, the negative influence of inhaled corticosteroids on height velocity reduces as the duration of treatment increases. Thus, inhaled corticosteroids should be used at the lowest effective doses for as long as necessary.

ACKNOWLEDGEMENTS

The authors would like to thank G. Tzavelas (an expert statistician) and the staff in the Dept of Allergology-Pulmonology of Penteli Children's Hospital for their help with this project.

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