ORIGINAL ARTICLE

Monitoring growth in asthmatic children treated with high dose inhaled glucocorticoids does not predict adrenal suppression

K A Dunlop, D J Carson, H J Steen, V McGovern, J McNaboe, M D Shields

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See end of article for authors' affiliations

Correspondence to: Dr M D Shields, Dept of Child Health, The Queen's University of Belfast, The Institute of Clinical Science, Grosvenor Road, Belfast BT12 6BJ, Northern Ireland, UK; m.shields@qub.ac.uk

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Aims: To determine whether routine outpatient monitoring of growth predicts adrenal suppression in prepubertal children treated with high dose inhaled glucocorticoid.

Methods: Observational study of 35 prepubertal children (aged 4–10 years) treated with at least 1000 μg/day of inhaled budesonide or equivalent potency glucocorticoid for at least six months. Main outcome measures were: changes in HtSDS over 6 and 12 month periods preceding adrenal function testing, and increment and peak cortisol after stimulation by low dose tetracosactrin test. Adrenal suppression was defined as a peak cortisol $\leqslant$500 nmol/l.

Results: The areas under the receiver operator characteristic curves for a decrease in HtSDS as a predictor of adrenal insufficiency 6 and 12 months prior to adrenal testing were 0.50 (SE 0.10) and 0.59 (SE 0.10). Prediction values of an HtSDS change of −0.5 for adrenal insufficiency at 12 months prior to testing were: sensitivity 13%, specificity 95%, and positive likelihood ratio of 2.4. Peak cortisol reached correlated poorly with change in HtSDS ($\rho = 0.23$, $p = 0.19$ at 6 months; $\rho = 0.33$, $p = 0.06$ at 12 months).

Conclusions: Monitoring growth does not enable prediction of which children treated with high dose inhaled glucocorticoids are at risk of potentially serious adrenal suppression. Both growth and adrenal function should be monitored in patients on high dose inhaled glucocorticoids. Further research is required to determine the optimal frequency of monitoring adrenal function.

A significant proportion of asthmatic children are treated with high dose inhaled glucocorticoids.[1] Systemic side effects of inhaled glucocorticoids in childhood asthma have not been considered a problem at doses up to 400 μg/day of budesonide (BUD) or beclomethasone dipropionate (BDP) or equivalent,[2–4] and reviews have questioned the clinical relevance of adrenal suppression noted in children.[5 6] However, there are recent case reports of symptomatic adrenal suppression in asthmatic children treated with moderate to high dose inhaled glucocorticoid.[7–14] In some of these patients the symptomatic adrenal suppression was associated with normal linear growth.[8 11 14] As asthma guidelines recommend monitoring growth in children on inhaled glucocorticoids,[15] it is important to know whether growth rate predicts which children have adrenal gland suppression and need to carry a steroid card and take glucocorticoid supplementation during stressful illness. In this observational study of prepubertal asthmatic children treated with high dose inhaled glucocorticoids and undergoing adrenal function testing, we related changes in height standard deviation scores and body mass indices in the previous 6 and 12 months to adrenal function.

METHODS

This was an observational study. Children 10 years of age or younger attending specialist asthma clinics (1996 to 2002) at the Royal Belfast Hospital for Sick Children or the local Community Asthma Clinic who were identified as having severe asthma requiring very high doses of inhaled glucocorticoids (equivalent to at least 1000 μg/day of BUD) for more than six months were invited to take part. The age at which they first started inhaled glucocorticoid therapy was noted as was the duration of high dose therapy. They had no other chronic medical conditions except eczema or allergic rhinitis, and use of topical glucocorticoids was recorded. At clinic visits inhaler technique was optimised and the dose of inhaled glucocorticoid was tailored to current asthma severity. Children requiring continuous oral steroids were excluded. Informed parental consent was obtained for all tests.

Growth measurements

Height standard deviation scores (HtSDS) and body mass index standard deviation scores (BMISDS) were calculated retrospectively 6 and 12 months before and at the time of adrenal function testing. The change in HtSDS and change in BMISDS were calculated for the 6 months (ΔHtSDS–6 months, ΔBMISDS–6 months) and 12 months (ΔHtSDS–12 months, ΔBMISDS–12 months) prior to adrenal function testing. The height measurements were made on one of two Holtain stadiometers by one of three trained nurses whose measurement technique and measurement repeatability were regularly audited.

Adrenal function tests

Adrenal function was tested by low dose tetracosactrin test (0.5 μg/1.73 m^2 body surface area) starting at 9 am. Advice was given to omit inhaled glucocorticoid on the morning of the test. If a child had received systemic glucocorticoids within the past month adrenal function testing was delayed for at least four weeks. Serum cortisol was measured at 0 (basal), 20, 30, 45, and 60 minutes. Cortisol was measured by radioimmunoassay using reagents supplied by Diagnostic Products Corporation, Los Angeles; the intracoefficient of

Abbreviations: HtSDS, height standard deviation score; BDP, beclomethasone dipropionate; BMISDS, body mass index standard deviation score; BUD, budesonide; FP, fluticasone propionate; IQR, interquartile range; ROC, receiver operating characteristic; SE, standard error

variation for both assays was less than 7% for all levels. For the purposes of statistical analysis cortisol concentrations below the detection limit of 30 nmol/l were recorded as 20 nmol/l. There was no cross-reactivity of budesonide with cortisol for the assay. Children were defined as having adrenal suppression if, following tetracosactrin, a peak cortisol ⩾500 nmol/l was not reached.[16–19] The number of days for which each child required systemic prednisolone was obtained from the case notes, general practitioner records, and parental recall.

Statistical analysis

Descriptive statistics (median, interquartile range (IQR), and range) were calculated for the basal serum cortisol, rise in cortisol, peak cortisol level reached, and ΔHtSDSs and ΔBMISDSs over the 6 and 12 month periods before adrenal function testing. Spearman's correlation coefficient (ρ) or Pearson's R (as appropriate) was used to determine the association between ΔHtSDS and ΔBMISDS and adrenal function. The Mann-Whitney U test was used to determine whether ΔHtSDS or ΔBMISDS differed between those with and without adrenal suppression. Sensitivity, specificity, positive predictive values, and positive likelihood ratios were calculated using ΔHtSDS for the prediction of adrenal suppression. The area under the receiver operator characteristic (ROC) curve (with standard error (SE)) was calculated for ΔHtSDS. A p value of <0.05 was considered significant.

RESULTS

Thirty seven children were identified and invited to undergo adrenal function testing. Two parents refused to have the adrenal function test performed leaving 35 children studied (median age 8.6 years, IQR 7.3–9.6 years, range 4.2–10.6 years, 23 males). Fifteen had eczema and 15 allergic rhinitis, of whom 11 were using topical glucocorticoids intermittently. Twenty six were taking (FP) at doses ranging between 1000 and 2100 μg/day (median 1000 μg/day). Eleven used dry powder at a median dose of 1000 μg/day and 16 used the metered dose inhaler and spacer at a median dose of 1500 μg/day. Nine children were treated with BUD by dry powder at doses ranging from 1200 to 1600 μg/day (median 1600 μg/day). All children had been on inhaled glucocorticoid for more than two years. Thirty had been on high dose inhaled glucocorticoid for more than 12 months and 25 for more than 24 months.

Attempts were made to reduce the dose of inhaled glucocorticoid; some children had transient periods of treatment with lower doses (lowest dose achieved was 750 μg/day for FP and 800 μg/day for BUD). In addition, three children had periods when they were treated with nebulised BUD (2–4 mg/day) either instead of or additional to their usual inhaled glucocorticoid.

Twenty four children had been treated with at least one course of systemic steroids (prednisolone 1–2 mg/kg/day) for a median of 8 days (range 3–34 days) in total during the 12 months prior to adrenal function testing. ΔHtSDS and ΔBMISDS were calculated over intervals of 0.5 (median 0.47, IQR 0.29–0.58) and 1.0 (median 1.1, IQR 1.0–1.4) years before adrenal function testing. Table 1 summarises the results for all patients and by inhaled glucocorticoid (FP, BUD).

Sixteen (13 taking FP) of the 35 (46%) children had evidence of biochemical adrenal suppression as defined above. Four children on FP had both an undetectable basal cortisol and no increase after tetracosactrin stimulation (table 2).

No statistically significant differences in any of the growth measures were observed in those with or without biochemical adrenal suppression (table 3).

The correlations between peak cortisol and ΔHtSDS–6 months ($\rho = 0.23$, $p = 0.2$) or ΔHtSDS–12 months ($\rho = 0.33$, $p = 0.06$) and between peak cortisol and ΔBMISDS–6 months ($\rho = 0.20$, $p = 0.3$) or ΔBMISDS–12 months ($\rho = 0.32$, $p = 0.07$) were weak and not statistically significant.

The area under the ROC curves for ΔHtSDS–6 months and ΔHtSDS–12 months in the prediction of biochemical adrenal insufficiency were 0.50 (SE 0.10) and 0.59 (SE 0.10) respectively (fig 1). Using a ΔHtSDS–12 months cut-off point of −0.5 had a sensitivity of 13%, specificity of 95%, a positive likelihood ratio of 2.4, and positive predictive value of 66% for the prediction of adrenal suppression. Using a ΔHtSDS–12 months cut-off point of −0.3 had a sensitivity of 25%, specificity of 86%, a positive likelihood ratio of 1.7, and positive predictive value of 60% for the prediction of adrenal suppression.

Table 1 Summary results for all patients

	All patients (n = 35)	FP (n = 26)	BUD (n = 9)
ΔHtSDS–6 months			
Median (IQR)	0.08 (−0.09 to 0.23)	0.06 (−0.04 to 0.23)	0.1 (−0.2 to 0.2)
Range	−0.37 to 0.55	−0.32 to 0.55	−0.37 to 0.23
ΔHtSDS–12 months			
Median (IQR)	0.12 (−0.14 to 0.31)	0.22 (−0.1 to 0.31)	−0.04 (−0.34 to 0.34)
Range	−0.65 to 0.45	−0.63 to 0.45	−0.65 to 0.45
ΔBMISDS–6 months			
Median (IQR)	−0.03 (−0.44 to 0.35)	−0.13 (−0.46 to 0.25)	0.1 (−0.03 to 0.62)
Range	−1.5 to 0.97	−1.5 to 0.72	−0.77 to 0.97
ΔBMISDS–12 months			
Median (IQR)	0.07 (−0.46 to 0.58)	−0.02 (−0.53 to 0.58)	0.07 (−0.36 to 0.67)
Range	−1.4 to 2.62	−1.4 to 2.62	−1.4 to 1.0
Basal cortisol (nmol/l)			
Median (IQR)	197 (87 to 275)	188 (50 to 254)	257 (150 to 302)
Range	20 to 514	20 to 514	20 to 328
Rise in cortisol (nmol/l)			
Median (IQR)	258 (77 to 451)	249 (46 to 446)	260 (234 to 462)
Range	0 to 723	0 to 723	0 to 558
Peak cortisol (nmol/l)			
Median (IQR)	533 (250 to 714)	472 (122 to 747)	570 (395 to 653)
Range	20 to 1103	20 to 1103	237 to 763

Table 2 Summary of low dose tetracosactrin tests, age, HtSDS at time of test, and 12 months previous and inhaled corticosteroid (ICS) type and dosage in the four children with the most severe adrenal suppression

	Age	Basal cortisol (nmol/l)	Peak cortisol (nmol/l)	ICS dose (μg/m²/day)	HtSDS–12 months previously	HtSDS at time of tetracosactrin test
Case 1	4.18	<30	<30	3030.3 FP via spacer	0.09	−0.54
Case 2	8.14	<30	<30	520.8 FP via spacer	0.71	−0.32
Case 3	7.88	<30	<30	1595.7 FP via spacer + intermittent nebulised BUD	−0.79	−1.16
Case 4	7.64	<30	<30	1456.3 FP via spacer	0.84	0.34

DISCUSSION

We have found that ΔHtSDS at 6 and 12 months prior to adrenal function testing does not predict adrenal suppression in prepubertal asthmatic children treated with long term high dose inhaled glucocorticoids. The ΔHtSDS–12 months was the best measurement for predicting the presence of adrenal suppression with an area under the ROC of 0.59. However, the sensitivity of cut-off points (−0.5 and −0.3) of ΔHtSDS over 12 months were low at 13% and 25%, respectively, indicating that many children with biochemical adrenal suppression were not being detected.

Although endogenous and exogenous glucocorticoids are potent suppressors of growth, the data presented show that the routine monitoring of growth in children receiving high dose inhaled glucocorticoids will not predict those with adrenal suppression. Some children with normal growth have potentially serious adrenal gland suppression and other children with reduced growth have normal adrenal function. This suggests that the systemic effects of glucocorticoids on growth through the hypothalamic/pituitary/growth plate axis are dissociated from the effects on the hypothalamic/pituitary/adrenal cortex axis and the extent to which each axis is affected varies between individuals. It is known that high doses of glucocorticoids have a direct effect on growth plate physiology,[20] but in lower doses it is less clear what the relation is. Any relation between inhaled glucocorticoids and change in growth that could be used to predict adrenal suppression is likely to be complex and to be influenced by factors such as duration of treatment, differential tissue sensitivity, and inter-individual sensitivity to glucocorticoids.

Concern following our initial case series[7] lead us to invite all asthmatic children who had been treated with inhaled glucocorticoids (≥1000 μg/day) at our clinics for longer than six months to have adrenal function testing. Only two parents declined. This study reports near complete data ascertainment in a cohort of children with severe asthma attending specialist asthma clinics during a 6–7 year period where the prevalence of adrenal suppression (46%) was sufficient to give meaningful results. Only prepubertal children were included in an attempt to avoid the confounding effect of puberty on growth rate.

One of three children reported by Todd *et al*, one of four reported by Drake *et al*, and all three reported by Macdessi *et al* apparently had normal growth at the time of experiencing an adrenal crisis.[8 11 14] The majority of the other reported patients have had both growth and adrenal suppression.[7 9 12 13] From these case reports and small case series it is not possible to determine how frequently adrenal suppression occurs in a child with normal growth. It is likely that, in at least some cases, adrenal function was tested only after growth failure had been detected. A recent prospective one year Finnish study of 75 newly diagnosed asthmatic children aged 5.5–14.7 years, without previous exposure to inhaled glucocorticoids, found that mild adrenal suppression developed in a quarter of the children treated with moderate doses of inhaled glucocorticoids. Subnormal ACTH test results were not associated with growth retardation during the first four study months, but in children who used steroids for a year a subnormal ACTH test at 4 months was associated with one year growth suppression.[21] We found a non-significant trend for reduced growth at 12 months to be better than at 6 months for predicting adrenal suppression.

Height measurements can be problematic. To minimise measurement error in our study the height measurements were recorded on one of two stadiometers by one of three trained nurses whose height measurement technique was regularly audited. We used change in height standard deviation score (ΔHtSDS) as an appropriate measure of linear growth and superior to using height velocity standard deviation scores which would have multiplied any measurement errors incurred. We studied growth over 6 and 12 months prior to adrenal function testing, as making clinical decisions on the basis of short term growth data may be misguided.[22]

We have no indicator of how well the children were complying with the inhaled glucocorticoid therapy and hence did not analyse the data in detail for dose related effects. In addition, we have no information on adrenal function in

Table 3 Summary results for all categories

	Adrenal suppression (n = 16)	No adrenal suppression (n = 19)	
ΔHtSDS–6 months	0.06 (−0.04 to 0.20)	0.1 (−0.1 to 0.22)	p = 0.97
ΔHtSDS–12 months	−0.01 (−0.34 to 0.35)	0.22 (−0.09 to 0.31)	p = 0.38
ΔBMISDS–6 months	−0.35 (−0.47 to 0.25)	0.06 (−0.10 to 0.44)	p = 0.14
ΔBMISDS–12 months	−0.16 (−0.50 to 0.58)	0.15 (−0.30 to 0.77)	p = 0.22

Results are reported as median (IQR).

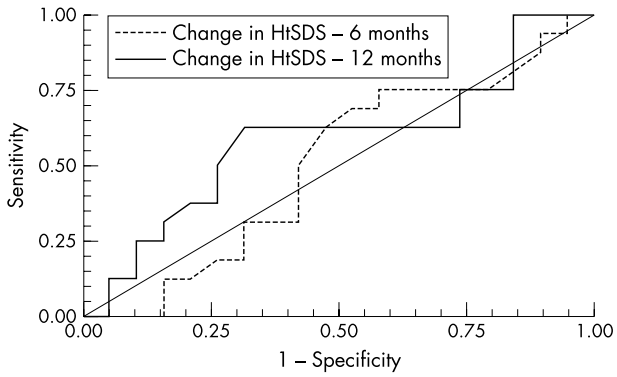

Figure 1 ROC curve using change in HtSDS at 6 months and 12 months to predict adrenal insufficiency. The 45° line is of chance prediction with an area of one half.

these children prior to our study period. All the children had been on long term inhaled glucocorticoids, and the transient reduction in growth velocity known to occur with initiating therapy would already have been experienced and is therefore unlikely to have led to bias in our study.[23] The majority of previous studies and reviews on adverse effects of inhaled glucocorticoids have considered growth and adrenal function separately and have not reported information that allows an estimate of having potentially severe adrenal suppression but normal growth. Our study shows that potentially severe adrenal suppression can occur in some asthmatic children who are growing at a normal rate while taking high dose inhaled glucocorticoids.

Inhaled glucocorticoids will continue to play a vital role in the management of childhood asthma and it is important to step down treatment when symptoms are controlled. We agree with Carlsen and Gerritsen's recommendation that all children receiving high dose inhaled glucocorticoids should have growth and adrenal function monitored.[24] Further research is necessary to elucidate the optimum frequency of adrenal function testing and at what dose of inhaled glucocorticoid usage is it required. With regards to the frequency of testing adrenal function the study reported by Nikolaizik *et al* is reassuring in that although nocturnal cortisol production was significantly reduced by 19% after one year of treatment, this was no greater than that observed after two and four weeks' treatment.[25] However, their patients were taking low to moderate doses of inhaled glucocorticoids (400 µg/day), and they did not look at adrenal reserve and therefore the capacity to respond to stress. An alternative approach would be to assume that all children on high dose inhaled glucocorticoid have adrenal suppression, and to issue them with steroid cards and recommend glucocorticoid supplementation during stressful illness.

The Committee on Safety of Medicines recently reinforced warnings regarding commonly used inhaled glucocorticoids, advising that symptoms and signs of adrenal suppression may be under recognised, particularly in children receiving higher than licensed doses.[26] Close attention must be paid to treating asthmatic children with the minimum effective dose of inhaled glucocorticoid to reduce the risk of adverse effects.

From our findings we conclude that monitoring growth over a one year period in children requiring high dose inhaled glucocorticoids is not an adequate screening test to identify those with adrenal suppression.

Authors' affiliations
K A Dunlop, D J Carson, H J Steen, V McGovern, J McNaboe, M D Shields, Royal Belfast Hospital for Sick Children, Belfast, Northern Ireland, UK

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