

PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Hypothalamic-Pituitary-Adrenal Axis Suppression in Asthmatic School Children

Ekkehard Werner Zöllner, Carl J. Lombard, Ushma Galal, F. Stephen Hough, Elvis M. Irusen and Eugene Weinberg

Pediatrics; originally published online November 12, 2012;

DOI: 10.1542/peds.2012-1147

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/early/2012/11/06/peds.2012-1147>

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2012 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



Hypothalamic-Pituitary-Adrenal Axis Suppression in Asthmatic School Children



WHAT'S KNOWN ON THIS SUBJECT: Hypothalamic-pituitary-adrenal axis suppression caused by inhaled corticosteroids is considered rare. Adrenal crisis has been described in children treated with high doses of inhaled fluticasone propionate. It was recommended that doses licensed for children should not be exceeded.



WHAT THIS STUDY ADDS: Biochemically confirmed hypothalamic-pituitary-adrenal axis dysfunction may occur in two-thirds of children treated with corticosteroids. Suppression may occur at low doses and especially with concomitant nasal steroids. Children with poor adherence or obesity may be less prone to adrenal crisis.

abstract

BACKGROUND AND OBJECTIVE: Hypothalamic-pituitary-adrenal axis suppression (HPAS) when treating children with corticosteroids is thought to be rare. Our objective was to determine the prevalence of and predictive factors for various degrees of HPAS.

METHODS: Clinical features of HPAS, doses, adherence, asthma score, and lung functions were recorded in 143 asthmatic children. The overnight metyrapone test was performed if morning cortisol was >83 nmol/L. Spearman correlations coefficients (r) were calculated between 3 postmetyrapone outcomes and each continuous variable. A multiple linear regression model of $\sqrt{\text{postmetyrapone}}$ adrenocorticotrophic hormone (ACTH) and a logistic regression model for HPAS were developed.

RESULTS: Hypocortisolemia was seen in 6.1% (1.8–10.5), hypothalamic-pituitary suppression (HPS) in 22.2% (14.5–29.9), adrenal suppression in 32.3% (23.7–40.9), HPAS in 16.3% (9.3–23.3), and any hypothalamic-pituitary-adrenal axis dysfunction in 65.1% (56.5–72.9). Log daily nasal steroid (NS) dose/ m^2 was associated with HPAS in the logistic regression model (odds ratio = 3.7 [95% confidence interval: 1.1–13.6]). Daily inhaled corticosteroids (ICSs) + NS dose/ m^2 predicted HPAS in the univariate logistic regression model ($P = .038$). Forced expiratory volume in 1 second/forced vital capacity $<80\%$ was associated with HPAS (odds ratio = 4.1 [95% confidence interval: 1.0–14.8]). Daily ICS + NS/ m^2 dose was correlated with the postmetyrapone ACTH ($r = -0.29$, $P < .001$). BMI ($P = .048$) and percent adherence to ICS ($P < .001$) and NS ($P = .002$) were predictive of $\sqrt{\text{postmetyrapone}}$ ACTH ($R^2 = .176$).

CONCLUSIONS: Two-thirds of children on corticosteroids may have hypothalamic-pituitary-adrenal axis dysfunction. In one-third, central function had recovered but adrenal suppression persisted. Predictive factors for HPAS are NS use, BMI, and adherence to ICS and NS. *Pediatrics* 2012;130:e1512–e1519

AUTHORS: Ekkehard Werner Zöllner, MB ChB, MMed (Paed), DCH, DTM&H, DPH,^a Carl J. Lombard, PhD,^b Ushma Galal, MSc,^b F. Stephen Hough, MB ChB, FCP, MMed, MD,^c Elvis M. Irusen, MB ChB, PhD,^d and Eugene Weinberg, MB ChB, FCP^e

^aPaediatric Endocrine Unit, Tygerberg Children's Hospital, ^eEndocrine Unit, Department of Medicine, and ^dPulmonology Division, Tygerberg Hospital, University of Stellenbosch, Cape Town, South Africa; ^bBiostatistics Unit, Medical Research Council, Cape Town, South Africa; and ^cAllergy Unit, Red Cross Children's Hospital, University of Cape Town, Cape Town, South Africa

KEY WORDS

pituitary-adrenal-function tests, adrenal insufficiency, steroids/adverse effects, asthma

ABBREVIATIONS

11DOC—11-deoxycortisol
ACTH—adrenocorticotrophic hormone
AS—adrenal suppression
BDP—beclomethasone dipropionate
BSA—body surface area
CI—confidence interval
FEV₁—forced expiratory volume in 1 second
FVC—forced vital capacity
HP—hypothalamus and pituitary gland
HPA—hypothalamic-pituitary-adrenal axis
HPAS—hypothalamic-pituitary-adrenal axis suppression
HPS—hypothalamic-pituitary suppression
HV—height velocity
ICS—inhaled corticosteroid
NS—nasal steroid
MDI—metered dose inhaler
OCS—oral corticosteroid
ONMTP—overnight metyrapone test
SDS—SD score
TS—topical steroid
WV—weight velocity

(Continued on last page)

Hypothalamic-pituitary-adrenal axis suppression (HPAS) when treating asthmatic children with inhaled corticosteroids (ICSs) or nasal steroids (NSs) was believed to be uncommon.^{1–6} The insulin tolerance and metyrapone tests do not confirm this belief.^{7,8} Regarding the former, a cohort study revealed that when asthmatic children are treated with a beclomethasone dipropionate (BDP) chlorofluorocarbon metered dose inhaler (MDI) without a spacer at a dose of 250 to 600 $\mu\text{g}/\text{m}^2$ per day, all children can be expected to have a suppressed hypothalamic pituitary axis (HPA) after 6 to 42 months.^{8,9} When the metyrapone test was performed on asthmatic children treated with a budesonide, chlorofluorocarbon, or hydrofluoroalkane MDI (with or without a spacer), as well as with nasal BDP, the prevalence of HPAS was 35% (95% confidence interval [CI]: 17–56).¹⁰ There are many possible explanations for the difference in the findings of these 2 studies,¹⁰ 1 of which is highlighted later. Suppression of the hypothalamus and pituitary due to exogenous corticosteroids precedes inactivity and atrophy of the adrenal glands. On removal of corticosteroids, central recovery precedes peripheral recovery, which often requires “supernormal” plasma adrenocorticotrophic hormone (ACTH) levels. Adrenal function might take a minimum of 9 months to normalize.¹¹ The metyrapone test is ideally suited to distinguish between the various levels of suppression of the HPA.¹² In atopic children, steroid omission by the child or the caregiver may trigger the recovery of the hypothalamus and pituitary gland (HP). This could lead to some children presenting with impaired adrenal (inadequate rise of 11-deoxycortisol [11DOC] on metyrapone testing) rather than impaired HP function (inadequate rise of ACTH on metyrapone testing). Patients with hypopituitarism respond differently. In these patients, the adre-

nals may not have lost their function yet, because HP impairment did not occur long enough or was only mild. Consequently, far more patients can be expected to have hypothalamic pituitary suppression (HPS) without concomitant adrenal dysfunction.¹³

In our recently published pilot study, we identified the concomitant use of NSs, the cumulative dose of ICSs, and body size as contributing factors to the development of HPAS in asthmatic children treated with ICSs. Confirmation in a larger study became necessary. We, therefore, performed a study to determine the prevalence of and the predictive factors for various degrees of HPAS in asthmatic children treated with corticosteroids in the allergy units of academic children's hospitals in Cape Town, South Africa.

METHODS

One hundred forty-three asthmatic children, 5 to 18 years old on ICSs with or without additional corticosteroid therapy, were recruited from the allergy units of Tygerberg Children's Hospital, Red Cross Children's Hospital, and the Lung Institute over a 2-year period (Table 1). Every eligible patient ≥ 11 years and every second eligible patient < 11 years was included, and informed consent was obtained. Children who were known to have HPA dysfunction, had untreated hypothyroidism or liver disease, and who were treated with phenobarbital, phenytoin, rifampicin, amitriptyline, chlorpromazine, neomercazole, or hormone replacement therapy were excluded. Symptoms compatible with past (hypoglycemia, shock, depressed level of consciousness, and seizures) and present HPAS (anorexia, nausea, vomiting, diarrhea, weakness, lassitude, and dizziness) were documented. The daily and cumulative dose of ICSs, NSs, topical steroids (TSs), and oral corticosteroids (OCSs) were recorded. ICS, NS, and OCS doses were corrected for body surface area (BSA) and converted

to hydrocortisone equivalents.^{14,15} All TSs were converted, on weight for weight basis, to hydrocortisone potency equivalents.¹⁶ Adherence to corticosteroid therapy was assessed by 2 different investigators at different times by inquiring how many doses had been omitted in the preceding week. The highest number of omissions was recorded. The asthma control questionnaire was administered, lung functions (forced expiratory volume in 1 second (FEV₁), forced vital capacity (FVC), and peak expiratory flow rate established, and the asthma score was determined.¹⁷ Height, weight, and change in systolic blood pressure, as measured with an electronic blood pressure measuring device, were recorded. The annualized height velocity (HV) and weight velocity (WV) were calculated by extracting the height and weight data of ~ 1 year earlier from the records. The following growth standards were used: the UK 1990 weight, height, and BMI standards; the UK 1966 HV standards for HV; and the Gerver 2001 WV standards for WV. Anthropometric measurements and velocities were recorded as SD scores (SDSs). Fasting blood between 8 am and 9 am for cortisol and ACTH was taken. The overnight metyrapone test (ONMTPT) was performed if the fasting morning serum cortisol was > 83 nmol/L. An adequate response was defined by a rise of ACTH from baseline to > 106 pg/mL (23.3 pmol/L),¹⁸ an 11DOC rise to > 208 nmol/L,¹⁹ or an 11DOC + cortisol rise to > 400 nmol/L.^{19,20} Because the assays used in this study were different from the assays in the original description, the published cutoffs were modified by correlation studies, done either in-house (11DOC) or by the manufacturer (ACTH).

Assays

Serum cortisol was measured with the ADVIA automated chemiluminescent assay (Bayer, Dublin, Ireland). The analytical sensitivity was 5.5 nmol/L. At

TABLE 1 Demographics and Therapy

Variable	Amount/Type
Total <i>n</i>	143
Boy:girl	77:66
Age, median (range), y	11 (5.2–17.5)
Ethnic group, <i>n</i>	
Mixed ancestry	138
Caucasian	4
African	1
ICS and device, <i>n</i>	
BUD Hfa MDI and spacer	128
BUD Hfa MDI	11
BUD Hfa vortex based MDI	1
FP DPI	3
Daily ICS dose/m ² , median (range)	
BUD equivalent, μg	439 (108–1058)
HC equivalent ^a , mg	5.5 (1.3–13.2)
Cumulative ICS dose/m ² , median (range), HC equivalent, mg	275.5 (10.3–38770.3)
Duration of ICS therapy, median (range), mo	41 (2–157)
Steroid sparing medication	
Salmeterol	28
Montelukast	5
Theophylline LA	1
<i>n</i> on NS (% of total)	122/143 (85)
NS	
BDP	118
BUD	4
Daily NS dose/m ² , median (range)	
BUD equivalent, μg	118 (54–468)
HC equivalent, mg	1.5 (0.7–5.9)
Cumulative NS dose/m ² , median (range), HC equivalent, mg	1548.6 (66.1–13601.6)
Duration of NS therapy, median (range), mo	36 (2–136)
<i>n</i> on OCS (% of total)	5/143 (3)
Daily OCS dose/m ² , median (range), HC equivalent, ^b mg	125.5 (17.5–187.3)
<i>n</i> on OCS previously (% of total)	93/143 (65)
Cumulative OCS dose/m ² given previously, median (range), HC equivalent, mg	1181.4 (201.0–11267.7)
<i>n</i> on TS (% of total)	60/143 (42)
TS	Fluocinolone, betamethasone, methylprednisolone aceponate, hydrocortisone
Cumulative TS dose/m ² , median (range), HC potency wt equivalent, g	4237.5 (23.77–11 5087.0)
Duration of TS therapy, median (range), mo	30 (0.25–356)
<i>n</i> on steroid eye drops (% of total)	4/143 (3)
Steroid eye drops, <i>n</i>	
Fluorometholone	3
Dexamethasone	1
% Adherence, median (range)	
ICS	85.7 (0–100)
NS	57.1 (0–100)
TS	75.0 (0–100)
OCS	100.0 (33.3–100)

BUD, budesonide; DPI, dry powder inhaler; FP, fluticasone propionate; HC, hydrocortisone; Hfa, hydrofluoroalkane; TS, topical steroids.

^a Eighty micrograms BUD is comparable to 1 mg HC in potency.

^b One milligram prednisone equates to 4 mg HC in potency.

107.05 nmol/L, the intraassay coefficient of variation (CV) was 3.69%, whereas the interassay CV was 5.45%. No cross-reactivity to fluticasone, budesonide, beclomethasone, or prednisone is

known. ACTH was measured by an automated sequential chemiluminescent immunometric assay (Immulite 2000, Siemens Healthcare Diagnostics, Flinders, NJ). Its analytical sensitivity was 5

pg/mL (1.1 pmol/L), whereas the precision at 23 pg/mL (5 pmol/L) ranged from 8.7% (within run) to 10% (run-to-run). No cross-reactivity has been reported. Levels of plasma 11DOC were established by utilizing the Biosource competitive radioimmunoassay. Its analytical sensitivity was 0.1 nmol/L; 0.1% cross-reactivity with cortisol has been reported. The intraassay CV at 82 nmol/L was 7.8%, and the interassay CV at 95 nmol/L was 14.1%.

Statistical Analysis

Growth velocities were analyzed by Growth Analyzer, version 3.5 (Rotterdam, The Netherlands). Age-adjusted prevalence of HPAS, hypothalamic-pituitary suppression (HPS), adrenal suppression (AS), and the corresponding CIs were calculated. Spearman correlations (*r*) were calculated between the post-metyrapone ACTH, 11DOC, 11DOC + cortisol, and each continuous variable. The Fisher's exact test was used to establish the statistical significance of nominal variables. To model ACTH on daily ICS + NS/m² dose, a quantile regression of fractional polynomials of order -2 and -1 was used. The CI of the median ACTH prediction was also obtained. Based on the most significant Spearman correlations, multiple linear regression was carried out to test for associations with postmetyrapone ACTH. A square root transformation of postmetyrapone ACTH was used in the modeling to improve the normality of the model variance. Univariate and multivariate logistic regression was used to test for associations with HPAS. The multiple linear regression and multivariate logistic models were adjusted for baseline characteristics (age and BMI). Linear and quadratic models were fitted to test for significance of nonlinear associations. Mathematical corrections for multiple comparisons were not made. Except for the age-adjusted prevalence of HPAS, HPS, and AS, which was carried

out in Stata (Stata Corp, College Station, TX), all other statistical analyses were done with R (www.r-project.org).

RESULTS

Prevalence

The prevalence varied with the degree of suppression of the HPA (Table 2). Hypocortisolemia (serum basal cortisol <83 nmol/L) was least common, and AS (postmetypapone 11DOC <208 nmol/L or 11DOC + cortisol <400 nmol/L) was most common. The prevalences of HPS (postmetypapone ACTH <106 pg/mL [23.3 pmol/L] and HPAS (postmetypapone ACTH <106 pg/mL [23.3 pmol/L] and postmetypapone 11DOC < 208 nmol/L and postmetypapone 11DOC + cortisol <400 nmol/L) were similar. The whole or part of the axis was suppressed in two-

thirds of patients. Nausea, vomiting, and diarrhea occurred while on therapy in only 2 of 8 patients with overt hypocortisolemia ($P = .016$). Moreover, the symptoms of anorexia, weakness, lassitude, fatigue, or dizziness, as well as an HV <25th percentile, WV < -2 SDS, or orthostatic hypotension (a fall in systolic blood pressure of ≥ 20 mm Hg from standing to recumbent), were not prevalent in the suppressed children.

Predictors of Suppression

Some variables were weakly, but significantly, correlated to postmetypapone ACTH, 11DOC, and/or 11DOC + cortisol (Table 3). No correlation was found with the cumulative OCS, ICS, NS, or TS/m², the monthly TS/m² and the asthma score. There was no significant association between HPAS and the number of

OCS courses administered in the preceding year ($P = .355$). There was also no significant (Rue de l'Industrie, Nivelles, Belgium) difference in the average postmetypapone $\sqrt{\text{ACTH}}$, $\sqrt{11\text{DOC}}$, and $\sqrt{11\text{DOC} + \text{cortisol}}$ between those who received potent TS (betamethasone) and those who did not (P values were .711, .829, and .700, respectively).

The quantile regression line based on fractional polynomials, with ICS adherence as additional covariate, in the scatter plot (Fig 1) of postmetypapone ACTH versus the daily ICS + NS/m² confirms a mild inverse correlation to the dose of corticosteroid (model $R^2 = .115$). At physiologic doses (equating to a normal cortisol production rate of 3.0–10.6 mg/m² per day²¹), the median ACTH response is nonlinear, whereas at supraphysiologic doses (area to the right of the vertical dotted line) the response is linear. The CI around the median predicted ACTH level straddles 106 pg/mL (cutoff between an adequate and inadequate ACTH response), indicating that the ACTH-dose effect is nonsignificant at these levels.

A univariate logistic regression analysis also identified the daily ICS + NS dose/m² as a significant determinant of HPAS ($P = .038$). The cumulative ICS + NS dose/m² and the cumulative ICS + NS dose/m² for the previous year were, however, not significant ($P = .450$ and .380, respectively).

Only 84 subjects, not treated with TS, were considered for the prediction models. A linear regression model of $\sqrt{\text{postmetypapone ACTH}}$ was found to explain 17.6% ($R^2 = .176$) of the variance (Table 4). It identified poor adherence to ICS and NS, as well as the BMI as significant protective factors for an inadequate ACTH response. As indicated by the effect size, a child, who was only 50% adherent to his ICS treatment, can be expected to have a postmetypapone ACTH level 125 pg/mL (27.5 pmol/L) higher than a child who is 100% adherent. Similarly, the postmetypapone

TABLE 2 Age-Adjusted Prevalence Estimates for Various Degrees of HPAS

Category	n	% ^a	95% CI
Basal C <83 nmol/L ^a	8/142	6.1	1.8–10.5
HPS ^b : ACTH <106 pg/mL (23.3 pmol/L)	27/133	22.2	14.5–29.9
AS ^c : 11DOC <208 nmol/L	63/135	47.5	38.5–56.5
11DOC + C <400 nmol/L	62/129	45.8	36.7–55.0
Both	43/129	32.3	23.7–40.9
HPAS ^d	20/127	16.3	9.3–23.3
All ^e	91/140 ^f	65.1	56.5–72.9

C, cortisol.

^a Duration of ICS and NS therapy is 4 to 226 (median 25) and 2 to 167 (median 36) months, respectively.

^b Hypothalamic pituitary suppression as established by postmetypapone ACTH.

^c Adrenal suppression as established by postmetypapone, 11DOC, and 11DOC + C.

^d ACTH <106 pg/mL (23.3 pmol/L) and 11DOC <208 nmol/L and 11DOC + C <400 nmol/L.

^e Basal C <83 nmol/L or ACTH <106 pg/mL (23.3 pmol/L) or 11DOC <208 nmol/L or 11DOC + C <400 nmol/L.

^f Denominator varies because not all children had all investigations for various reasons.

TABLE 3 Spearman Correlations Between Postmetypapone ACTH, 11DOC, 11DOC + Cortisol, and Patient Variables

Variable ^a	ACTH, r ($n = 133$)	11DOC, r ($n = 135$)	11DOC + Cortisol, r ($n = 133$)
Age	0.08	−0.01	−0.22*
BSA	0.15	0.03	−0.23*
Daily ICS/m ²	−0.20*	−0.17*	−0.03
Daily NS/m ²	−0.25* (114)	−0.24* (116)	−0.19* (114)
Cumulative NS/m ² (previous year)	−0.29*	−0.32*	−0.27*
Monthly TS/m ²	−0.11 (131)	−0.10 (133)	0.01 (131)
% ICS adherence	−0.23*	−0.11	−0.15
% NS adherence	−0.36* (114)	−0.20* (116)	−0.15 (114)
Asthma score (no lung functions) ^b	0.00	0.09	0.24*
FEV ₁ (%)	−0.03 (132)	0.04 (134)	0.15* (132)

^a Only selected variables listed.

^b As published by E. Juniper.

* $P < .05$.

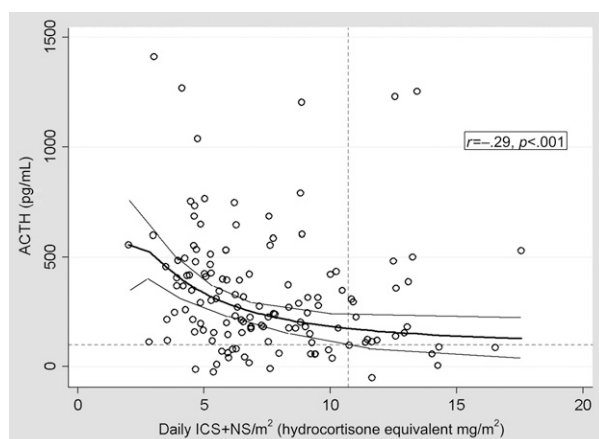


FIGURE 1

Scatter plot and quantile regression (median and CI) of postmetyrapone ACTH versus the daily ICS and NS dose, adjusted for BSA (ICS adherence as covariate). Horizontal dotted line = cutoff between adequate and inadequate response. Vertical dotted line = upper limit of normal cortisol production rate. Conversion factor for converting ACTH in pg/mL to pmol/L = 0.2202.

TABLE 4 Linear Regression Model of $\sqrt{\text{Postmetyrapone ACTH}}$ ($R^2 = .176$)

Variable	Effect Size	SE	P
Intercept	23.54	5.24	
Age	0.03	0.25	.304
BMI (SDS)	1.16	0.58	.048*
% ICS adherence (previous week)	−0.07	0.03	<.001*
% NS adherence (previous week)	−0.06	0.02	.002*
$\sqrt{\text{Daily ICS dose/m}^2}$ ^a (HC equiv mg/m ²)	0.51	1.32	.797
Log daily NS dose/m ² (HC equiv mg/m ²)	−1.67	1.62	.307

HC equiv, hydrocortisone equivalent.

^a Per m² body surface area.

* Significant, $P < .05$.

ACTH level of a patient who misses half of his NS therapy would be 116 pg/mL (25.5 pmol/L) higher compared with the level of one who is fully compliant. Furthermore, the postmetyrapone ACTH level of a child with a BMI SDS of 2 would be 100 pg/mL (22 pmol/L) higher compared with one with a BMI SDS of 0.

A logistic regression model for HPAS identified percent ICS adherence and the log daily NS dose/m² as significant predictors of its development (Table 5). A patient treated with a dose of 400 μg BDP per day is 3 1/2 times more likely to present with HPAS compared with a child who is not on NSs.

Lung Functions and Asthma Control

FEV₁/FVC was the only lung function that was found to be significantly associated with HPAS (Table 6). This was independent of the cumulative ICS + NS dose, the percent ICS and NS adherence, and the asthma score. A child with a FEV₁/FVC <80% was found to have a 4 times greater chance to develop HPAS than a child who had a FEV₁/FVC >80%.

The prevalence of HPAS in well-controlled children (asthma score <0.75) was found to be 20% (95% CI: 5.7–43.7), whereas the prevalence of HPAS in poorly controlled children (score >1.5) was 55% (95% CI: 31.5–76.9). The prevalence of HPAS thus did not change significantly with the level of asthma control. In the 8 children who presented with hypocortisolemia, the difference was accentuated yet not significant (14% [95% CI: 0.4–57.9] for good control versus 43% [95% CI: 9.9–81.6] for poor control).

DISCUSSION

The 22% prevalence of HPS confirmed the findings of our recently published pilot study.¹⁰ The larger sample size allows for generalization of our results to other study populations. Provided

the same methodology is used, 15% to 30% of children attending allergy units may mount an inadequate ACTH response to stress. This, in itself, may not be clinically relevant. Severe or prolonged HPS may, however, cause the adrenal glands to atrophy and become less responsive to ACTH. An adrenal crisis may be precipitated if the child is exposed to stress, especially if coupled with cessation or inadequate dosing of exogenous corticosteroids. In practice, however, adrenal crisis is rarely seen. Our study may explain why.

The most appropriate cutoff for an adequate ACTH response after an ONMTPT is open to debate. Levels ranging from as low as 64 (14.1 pmol/L)²² to as high as 200 pg/mL (44 pmol/L)¹⁸ have been proposed. The 106 pg/mL (23.3 pmol/L) cutoff, used in this study, was based on the only published trial comparing the ACTH response of the insulin tolerance test to that of the ONMTPT in adults with normal pituitary function. It was found that no subject in either group mounted an ACTH response below 100 pg/mL (22 pmol/L).¹⁸ Though not the largest study on this topic, it is still the best comparison of the ONMTPT to hypoglycemia. Over- or underdiagnosis is kept to a minimum by setting the decision level between the suggested extremes (ie, at 106 pg/mL [23.3 pmol/L]). One can only assume that the established cutoff for adults also applies to children.

Twice the number of asthmatic children who had HPS was found to have AS. Both 11DOC and the 11DOC + cortisol decision levels should apply, indicating appropriate inhibition of the 11 β -hydroxylase by metyrapone to produce 11DOC with consequently decreased production of cortisol.²⁰ The higher number of children with AS suggests that the axis is already in the process of recovery in these children. Their central structures have fully recovered, but their adrenal gland function is still impaired. Suppression of the axis is thus not an all or

none phenomenon. It is in fact in a state of constant flux determined by adherence, dose adjustment, technique, and supplementary steroid use, as well as genetic and epigenetic factors.^{23,24}

As shown previously¹⁰ and confirmed in this study, adrenal insufficiency, though present biochemically, is not usually clinically apparent. If exposed to stress coupled with the abrupt discontinuation of corticosteroid therapy, frank adrenal crisis may still be likely. HPAS may thus be dynamic, presenting on a spectrum from mild and unapparent to severe and clinically obvious. Presumably, this reversible dynamism is lost when the glands have atrophied, potentially resulting in death, if cortisol is not adequately replaced by pharmacological corticosteroids.

Our study suggests that 65% of patients attending pediatric allergy units may suffer steroid suppressive effects, necessitating a good screening test to detect HPAS. To this end, we have recently proposed the early-morning serum ACTH.²⁵ It may, however, be premature to

recommend this for universal use, which is why we have attempted to identify predictors for HPAS.

The univariate logistic regression analysis identified the daily ICS + NS/m² as a significant predictor for HPAS. However, when plotting postmetyrapone ACTH against ICS + NS/m² (Fig 1), it is evident that the inverse dose-effect relationship is weak. Furthermore, at supraphysiologic doses, this effect is lost, making it impossible to predict HPAS at high doses. Confirmation in a larger study is necessary because the number of patients at these doses is small.

The linear regression model of $\sqrt{\text{postmetyrapone ACTH}}$ (Table 4) identifies the BMI and percent adherence to ICS and NS as useful predictors. A normal ACTH stress response should be at least 100 pg/mL (22 pmol/L). The 100 pg/mL (22 pmol/L) difference in ACTH release between a normal and an obese child is thus clinically significant. The potential for a thin child to develop HPAS could be even higher.

By halving the adherence to ICSs or NSs, an ACTH rise of 125 to 116 pg/mL (27.5–25.5 pmol/L) may be expected to occur during stress. Poor adherence, therefore, also exerts a protective effect on HPAS development. ICS compliance, ascertained by using electronic measuring devices, ranges between 63% and 92%,²⁶ similar to the findings in our study (79%), employing nondirective questioning. Because self-reporting of adherence is usually an overestimate, actual adherence may be even lower.

The logistic regression model for HPAS (Table 5) clearly identifies log daily NS dose/m² as the most significant predictor. This concurs with the finding of our pilot study.¹⁰ NSs bypass the lungs and enter the systemic circulation directly through absorption via the nasal mucosa and may thus have a greater systemic effect than ICSs, which enter the pulmonary circulation first. The systemic effect may also be mediated by direct inhibition of adrenal cortisol production by NS through a short feedback loop.²⁷ AS, without previous suppression at HP level, may therefore be more likely.

Limited documentation made it difficult to determine the monthly TS dose accurately. This is a well-recognized limitation in dermatological studies.²⁸ Moreover, categorization of TSs into the different potency groups by their skin blanching ability is problematic because this assessment is subjective. Furthermore, potency as determined by vasoconstriction does not equate potency as determined on a weight-for-weight basis. This explains the lack of correlation between the monthly TS/m² and the postmetyrapone outcomes. Evidence from the literature suggests that TSs rarely precipitate HPAS, unless highly potent agents are used to treat a significant percent of BSA or various corticosteroids are given via multiple routes.²⁸

Combined ICS and OCS exposure has been shown to increase HPAS risk.²⁹ The lack of correlation with the cumulative OCS/m² was thus unexpected. This may reflect treatment and adherence practice. OCS courses are often prescribed in anticipation of an exacerbation but, in the absence of an attack, may never be administered, or the course may be shortened. Corticosteroid load is thus reduced, making suppression less likely.

A child with a FEV₁/FVC <80% had a significantly higher probability of

TABLE 5 Logistic Regression Model for HPAS

Variable	OR (95% CI)
Age	0.9 (0.8–1.2)
BMI (SDS)	0.9 (0.5–1.4)
$\sqrt{\text{Asthma score}}$ (no lung functions)	1.2 (0.4–3.7)
% ICS adherence	1.0 (1.0–1.1)*
% NS adherence	1.0 (1.0–1.0)
Log daily NS dose/m ²	3.7 (1.1–13.6)*
Cumulative ICS dose/ m ² (previous year)	1.0 (1.0–1.0)

Postmetyrapone ACTH <106 p/mL (23.3 pmol/L) and 11DOC <208 nmol/L and 11DOC + cortisol <400 nmol/L.

* Significant, $P < .05$.

TABLE 6 A Comparison of Lung Functions of Children With HPAS to Those Without HPAS

Lung Function	n With HPAS (%)	P	OR (95% CI)
FEV ₁ ≥ 80%	11/84 (13.1)	.30	1.8 (0.6–5.3)
<80%	9/42 (21.4)		
Peak expiratory flow rate ≥ 80%	11/58 (20.0)	.47	0.6 (0.2–1.9)
<80%	9/69 (13.0)		
FEV ₁ /FVC ≥ 80%	14/110 (12.7)	.02*	4.1 (1.0–14.8)*
<80%	6/16 (37.5)		

OR, odds ratio.

* Significant, $P < .05$.

developing HPAS than a child with a $FEV_1/FVC \geq 80\%$. There was also a trend for children with a high asthma score to have a higher prevalence of HPAS. Both findings were unexpected because good control is associated with higher suppressive corticosteroid doses. It was thought previously that relative adrenal insufficiency in asthmatic children might contribute to the development of more severe asthma.³⁰ An alternative suggestion has been that asthma itself down-regulates HPA activity by inhibiting corticotrophin-releasing hormone release, possibly through mediation by interleukin-6 and tumor necrosis factor- α .^{7,31} A large interindividual variation in adrenal response to ACTH, reduced bioavailability of glucocorticoids, and altered signal transduction mechanisms have also been described.^{23,24,32}

CONCLUSIONS

Two-thirds of children treated with corticosteroids in allergy units may have a degree HPA dysfunction. HPS may occur at doses equal to the daily cortisol production rate. The use of NSs, in addition to ICSs, is a significant predictor of HPAS. Cumulative corticosteroid doses are not predictive. High BMI and poor adherence to ICSs and NSs protect against HPAS. Low FEV_1/FVC may be predictive of HPAS independently of the corticosteroid suppressive effect.

We, therefore, recommend that every asthmatic child with a low BMI, who is treated with both ICSs and NSs, and is adherent to therapy, should have his or her HPA function assessed. Although desirable, an assessment before commencement of treatment is not feasible because the primary physician would

invariably start ICS therapy on presentation. Every effort, however, should be made to determine the level of adherence to corticosteroids. Further research is needed to identify genetic factors that might predict or protect from HPAS.

ACKNOWLEDGMENTS

We thank Sisters Hill, Poggenpoel, Pontac, and Steyn, and their superiors (for allowing them to participate), as well as all pediatricians and medical officers at the various centers for recruitment of patients. We are grateful to Professor E. Juniper for supplying the asthma control questionnaire, and we are grateful for the laboratory support provided by B. Fenemore and the laboratories of Groote Schuur and Tygerberg Hospitals and the Bioanalytic Research Corporation.

REFERENCES

1. Dluhy RG. Clinical relevance of inhaled corticosteroids and HPA axis suppression. *J Allergy Clin Immunol*. 1998;101(4 pt 2):S447–S450
2. Russel G. Commentary: Symptomatic adrenal insufficiency during inhaled corticosteroid treatment. *Arch Dis Child*. 2001;85(4):333–334
3. Bisgaard H, Pedersen S. Safety of treatment. *Eur Respir J Suppl*. 1996;21(suppl 21):28s–34s
4. Sizonenko P. Effects of inhaled or nasal glucocorticosteroids on adrenal function and growth. *J Pediatr Endocrinol Metab*. 2002;15(1):5–26
5. Boner AL. Effects of intranasal corticosteroids on the hypothalamic-pituitary-adrenal axis in children. *J Allergy Clin Immunol*. 2001;108(suppl 1):S32–S39
6. Bruni FM, De Luca G, Venturoli V, Boner AL. Intranasal corticosteroids and adrenal suppression. *Neuroimmunomodulation*. 2009;16(5):353–362
7. Zöllner EW. Hypothalamic-pituitary-adrenal axis suppression in asthmatic children on inhaled corticosteroids: part 1. Which test should be used? *Pediatr Allergy Immunol*. 2007;18(5):401–409
8. Zöllner EW. Hypothalamic-pituitary-adrenal axis suppression in asthmatic children on inhaled corticosteroids (Part 2)—the risk as determined by gold standard adrenal function tests: a systematic review. *Pediatr Allergy Immunol*. 2007;18(6):469–474
9. Vaz R, Senior B, Morris M, Binkiewicz A. Adrenal effects of beclomethasone inhalation therapy in asthmatic children. *J Pediatr*. 1982;100(4):660–662
10. Zöllner EW, Lombard C, Galal U, Hough S, Irusen E, Weinberg E. Hypothalamic-pituitary-adrenal axis suppression in asthmatic children on inhaled and nasal corticosteroids—more common than expected? *J Pediatr Endocrinol Metab*. 2011;24(7–8):529–534
11. Graber AL, Ney RL, Nicholson WE, Island DP, Liddle GW. Natural history of pituitary-adrenal recovery following long-term suppression with corticosteroids. *J Clin Endocrinol Metab*. 1965;25:11–16
12. Dolman LI, Nolan G, Jubiz W. Metyrapone test with adrenocorticotrophic levels. Separating primary from secondary adrenal insufficiency. *JAMA*. 1979;241(12):1251–1253
13. Steiner H, Bähr V, Exner P, Oelkers PW. Pituitary function tests: comparison of ACTH and 11-deoxy-cortisol responses in the metyrapone test and with the insulin hypoglycemia test. *Exp Clin Endocrinol*. 1994;102(1):33–38
14. Johansson S-A, Andersson KE, Brattsand R, Gruvstad E, Hedner P. Topical and systemic glucocorticoid potencies of budesonide, beclomethasone dipropionate and prednisolone in man. *Eur J Respir Dis Suppl*. 1982;122:74–82
15. Rossiter D, ed. *South African Medicines Formulary*. Rondebosch, South Africa: Health and Medical Publishing Group of the South African Medical Association; 2010:258
16. Brazzini B, Pimpinelli N. New and established topical corticosteroids in dermatology: clinical pharmacology and therapeutic use. *Am J Clin Dermatol*. 2002;3(1):47–58
17. Juniper EF, Bousquet J, Abetz L, Bateman ED; GOAL Committee. Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. *Respir Med*. 2006;100(4):616–621
18. Staub JJ, Noelp B, Girard J, Baumann JB, Graf S, Ratcliffe JG. The short metyrapone test: comparison of the plasma ACTH response to metyrapone and insulin-induced hypoglycaemia. *Clin Endocrinol (Oxf)*. 1979;10(6):595–601
19. Fiad TM, Kirby JM, Cunningham SK, McKenna TJ. The overnight single-dose metyrapone test is a simple and reliable index of the hypothalamic-pituitary-adrenal

- axis. *Clin Endocrinol (Oxf)*. 1994;40(5):603–609
20. Berneis K, Staub JJ, Gessler A, Meier C, Girard J, Müller B. Combined stimulation of adrenocorticotropin and compound-S by single dose metyrapone test as an outpatient procedure to assess hypothalamic-pituitary-adrenal function. *J Clin Endocrinol Metab*. 2002;87(12):5470–5475
 21. Linder BL, Esteban NV, Yergey AL, Winterer JC, Loriaux DL, Cassorla F. Cortisol production rate in childhood and adolescence. *J Pediatr*. 1990;117(6):892–896
 22. Endert E, Ouweland A, Fliers E, Prummel MF, Wiersinga WM. Establishment of reference values for endocrine tests. Part IV: Adrenal insufficiency. *Neth J Med*. 2005;63(11):435–443
 23. Mormede P, Foury A, Barat P, et al. Molecular genetics of hypothalamic-pituitary-adrenal axis activity and function. *Ann N Y Acad Sci*. 2011;1220:127–136
 24. Derijk RH. Single nucleotide polymorphisms related to HPA axis reactivity. *Neuroimmunomodulation*. 2009;16(5):340–352
 25. Zöllner EW, Lombard C, Galal U, Hough S, Irusen E, Weinberg E. Hypothalamic-pituitary-adrenal axis suppression in asthmatic children on inhaled and nasal corticosteroids: is the early-morning serum adrenocorticotrophic hormone (ACTH) a useful screening test? *Pediatr Allergy Immunol*. 2011;22(6):614–620
 26. Cochrane MG, Bala MV, Downs KE, Maukopf J, Ben-Joseph RH. Inhaled corticosteroids for asthma therapy: patient compliance, devices, and inhalation technique. *Chest*. 2000;117(2):542–550
 27. Saito E, Ichikawa Y, Homma M. Direct inhibitory effect of dexamethasone on steroidogenesis of human adrenal in vivo. *J Clin Endocrinol Metab*. 1979;48(5):861–863
 28. Ellison JA, Patel L, Ray DW, David TJ, Clayton PE. Hypothalamic-pituitary-adrenal function and glucocorticoid sensitivity in atopic dermatitis. *Pediatrics*. 2000;105(4 pt 1):794–799
 29. Mortimer KJ, Tata LJ, Smith CJP, et al. Oral and inhaled corticosteroids and adrenal insufficiency: a case-control study. *Thorax*. 2006;61(5):405–408
 30. Barr J, Rapoport MJ, Tauber T, Hertzianu I, Cafri Y, Bistrizer T. The relation between adrenal function and the severity of bronchial hyperresponsiveness in children as measured by the methacholine provocation test. *J Pediatr Endocrinol Metab*. 2002;15(3):307–312
 31. Chrousos GP. Stress and disorders of the stress system. *Nat Rev Endocrinol*. 2009;5(7):374–381
 32. Bertagna X, Coste J, Raux-Demay MC, Letrait M, Strauch G. The combined corticotropin-releasing hormone/lysine vasopressin test discloses a corticotroph phenotype. *J Clin Endocrinol Metab*. 1994;79(2):390–394

(Continued from first page)

Dr Zöllner has made substantial contributions to the conception and design and acquisition of data. He also made a contribution to the analysis and interpretation of data. He drafted the article and revised it. He gave his approval for this version of the article to be published. Dr Lombard was involved in the design of the study. He also made a contribution to the analysis and interpretation of data. He reviewed the article. He gave his approval for this version of the article to be published. Dr Galal has performed the data analysis and contributed to the interpretation of the data. She has revised the article, and she gave her approval for this version of the article to be published. Dr Hough made a fundamental intellectual contribution to this article and approves publication of the version to be published. Dr Irusen has made a contribution to the conception and design of the study. He also made a contribution to analysis, interpretation, and discussion of the data. He gave his approval for this version of the article to be published. Dr Weinberg has had intellectual input in this article. He gave his approval for this version of the article to be published.

Dr Zöllner's former affiliation is Endocrine Unit, Red Cross Children's Hospital, University of Cape Town, Cape Town, South Africa.

www.pediatrics.org/cgi/doi/10.1542/peds.2012-1147

doi:10.1542/peds.2012-1147

Accepted for publication Jul 24, 2012

Address correspondence to Ekkehard Werner Zöllner, MB ChB, MMed (Paed), DCH, DTM&H, DPH, Endocrine and Diabetes Unit, Faculty of Health Sciences, Department of Paediatrics, PO Box 19063, 7505 Tygerberg, South Africa. E-mail: zollner@sun.ac.za

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2012 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Supported by the Medical Research Council, the University of Stellenbosch, the SA Thoracic Society, the Harry Crossley Foundation, and Red Cross Children's Hospital.

Hypothalamic-Pituitary-Adrenal Axis Suppression in Asthmatic School Children

Ekkehard Werner Zöllner, Carl J. Lombard, Ushma Galal, F. Stephen Hough, Elvis M. Irusen and Eugene Weinberg

Pediatrics; originally published online November 12, 2012;

DOI: 10.1542/peds.2012-1147

Updated Information & Services

including high resolution figures, can be found at:
<http://pediatrics.aappublications.org/content/early/2012/11/06/peds.2012-1147>

Subspecialty Collections

This article, along with others on similar topics, appears in the following collection(s):

Respiratory Tract

http://pediatrics.aappublications.org/cgi/collection/respiratory_tract

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
<http://pediatrics.aappublications.org/site/misc/Permissions.xhtml>

Reprints

Information about ordering reprints can be found online:
<http://pediatrics.aappublications.org/site/misc/reprints.xhtml>

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2012 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

