

EFFECTS OF CORTICOSTEROIDS ON ADRENAL FUNCTION IN CHILDREN WITH ASTHMA

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Undoubtedly Inhaled Corticosteroids (ICS) and, to a lesser extent, nasal steroids (NS) have revolutionised therapy and improved quality of life in a cost-effective way for every asthma patient. Prior to 1972, only oral corticosteroids (OCS), usually prednisone, were used to treat asthma whenever non-steroid therapy was ineffective. Prednisone, however, is four times as potent as hydrocortisone (HC) or its natural equivalent, cortisol (C) and therefore potentially more likely to suppress the hypothalamic-pituitary-adrenal axis (HPA). This was proven in a small study of 11 asthmatic children, who were given prednisone at 2 mg/kg/day in three divided doses for 5 days. Three days after the course was completed an insulin tolerance test (ITT) was performed which showed that all, but two, failed to have an adequate C response.¹ Ten days after termination of therapy the axis had recovered in all patients. In spite of its limitations, this study demonstrated how easily the HPA can be suppressed by supra-physiological doses of OCS within a relatively short time. Given a lapse of OCS therapy with an additional exposure to stress, such as infection or trauma, adrenal crisis may thus be a distinct possibility.

The introduction of ICS and NS made it possible to deliver these medications to where they are needed most, i.e., the lungs and the nose, hopefully affecting other organs, such as the adrenal glands, less than OCS. Although the dose of these CS is much lower, they are more potent. Budesonide (BUD), for example, is 12½ times more potent than HC. Yet, suppression of the HPA induced by these is regarded as a “benign physiological response”.² In a small published series of 5 asthma deaths, of which 3 were on unknown doses of inhaled beclomethasone dipropionate (BDP), adrenal atrophy was found in the four autopsies performed.³ This report was largely overlooked. However, adrenal crisis as a result of high doses of fluticasone propionate (FP) continued to be reported in several case series. Asthma cases with identified biochemical HPA suppression (HPAS) or presenting with clinical features of Cushing’s syndrome were also documented. In a landmark

UK survey published in 2002, 2% of all paediatricians and adult endocrinologists mailed, reported at least one case of adrenal crisis associated with ICS.⁴ Twenty-eight of the 33 cases identified were children. Most of these were on FP metered dose inhaler (MDI) with a spacer on very high doses of 500-2000 µg/day (12.5-50 mg HC equivalent/day). In another case series a dose of 400 µg BUD (5 mg HC equivalent), given with a MDI and a nebuliser for 1 year, was enough to cause symptomatic adrenal suppression. An asthmatic child treated with 200 µg BDP/day (2.5 mg HC equivalent) via a volumatic spacer was found to have severe, yet asymptomatic, HPAS. These cases indicate that ICS other than FP, even when given at physiological doses (equal to a C production rate of 3-10.6 mg/m²/day), can also cause HPAS.

PREVALENCE OF HPAS

Many reviews on the risks of ICS have been published. As far as the author could establish, the same does not apply for NS, topical steroids (TS) or OCS. The suppressive effects of OCS on the HPA are well documented. Reviews on the suppressive effects of ICS were, however, found to be conflicting. This is not surprising, as reviewers did not differentiate between studies using basal, gold standard (ITT and metyrapone test) or other dynamic adrenal function tests. NS are claimed to cause “minimal” suppression. TS have been found to precipitate HPAS only if very potent agents are being prescribed or multiple atopic diseases are treated by various CS via multiple routes. The author’s own systematic review, analysing studies that only utilised gold standard adrenal function tests, identified a cohort study in which all asthmatic children treated with a BDP MDI at a dose of 250-600 µg/m²/day (3.1-7.5 mg HC equivalent/m²/day) for 6-42 months developed HPAS.⁵ Utilising the overnight metyrapone test, a study has shown that two-thirds of children treated with corticosteroids in allergy units may have a degree of biochemical HPA dysfunction, while in one-third, central function recovered, but adrenal suppression persisted.⁶

THE DYNAMIC NATURE OF HPAS AND ITS CONSEQUENCES

The above-mentioned study confirmed the dynamic nature of the axis which is highly sensitive to changes in adherence, dose adjustment, technique, supplementary steroid use, as well as genetic and epigenetic factors. Thus the degree of HPAS may fluctuate, varying from time to time, situation to situation and person to person. This variability in suppression may partially explain the contradictory prevalence published in the literature. While partial biochemical dysfunction may not be of concern, suppression of both the hypothalamus-pituitary and adrenal (as occurred in about 16% of subjects), as well as frank hypocortisolaemia (in 6%) may well be, if suppression is not reversed. In the long term, adrenal glands may atrophy. This phenomenon may go unnoticed, as C is being replaced by exogenous steroids. During a stressful event however, such as an infection, injury, burn, surgery or even an asthma exacerbation (possibly coupled with a period of poor adherence following prolonged good adherence), demand for C may outstrip its exogenous supply. This could precipitate an adrenal crisis which may result in death, if not recognised and adequately treated.

DOSE-EFFECT RELATIONSHIP

Current teaching is that “systemic adverse effects” increase exponentially while the benefit is minimal at a

fluticasone propionate (FP) dose > 1000 µg [equivalent to a hydrocortisone (HC) dose > 25 mg] in adults.⁷ This statement is based on cortisol profiles, serum cortisol and urinary free cortisol (UFC). These tests, however, cannot predict whether the HPA can appropriately respond to stress. In children aged 8-14 years a FP dose > 400 µg (HC equivalent dose > 10 mg), given with a MDI through a large volume spacer, has been shown to have a more pronounced suppressive effect on 12 hourly UFC than at lower doses.⁸ The impression created by subsequent publications and texts is that “systemic adverse effects” are negligible below these cut-offs and ICS given at these doses are safe.

Our cross-sectional study has shown that hypothalamic-pituitary suppression may occur at doses equal to the daily C production rate (Figure 1).⁶ It also confirmed that a dose-effect relationship exists, but that this is weak and seems to be lost at supra-physiological doses [equating to > 10.6 mg HC equivalent/m²/day or 848 µg BUD equivalent/m²/day]. Thus, at high doses, the probability of developing hypothalamic-pituitary suppression is expected to be 50% irrespective of the exact dose. Physiologically this makes sense, since normal endogenous C production would inhibit ACTH production through a negative feed-back loop in a dose-related fashion. This would continue until the dose-effect reached a threshold where it plateaued. The findings of our cross-sectional study thus confirm previous work,

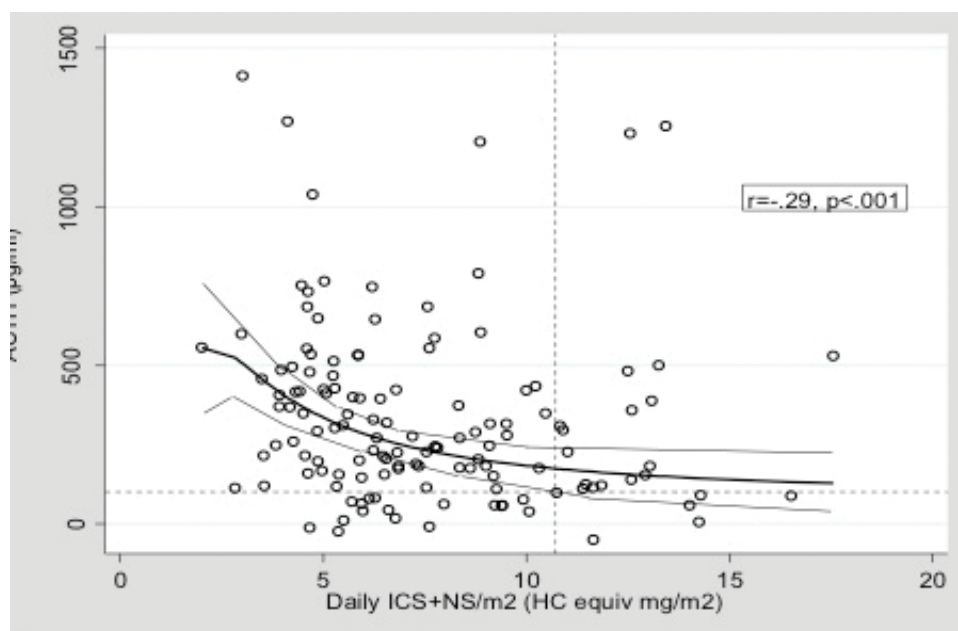


Figure 1. Scatter plot and quantile regression (median & CI) of post-metyrapone ACTH versus the daily ICS and NS dose, adjusted for BSA (ICS adherence as covariate). Horizontal dotted line = cut-off between adequate and inadequate response. Vertical dotted line = upper limit of normal cortisol production rate. Conversion factor for converting ACTH in pg/ml to pmol/l = 0.2202 (Reprinted from “Paediatrics” with permission from the American Academy of Paediatrics).

except that our threshold appears to be much lower (10.6 mg/m²/day versus 25 mg HC equivalent/day) and, most importantly, that HPAS is not uncommon at a dose below this threshold.

PREDICTORS OF HPAS

It appears that no serious attempts have been made by researchers to identify predictors of HPAS, other than height velocity. Current literature suggests that clinical criteria cannot be used to diagnose HPAS in asthmatic children on CS. The vague symptoms of anorexia, weakness, lassitude, fatigue and dizziness, as well as orthostatic hypotension, diminished height velocity and weight velocity are unhelpful in detecting HPAS.⁶ However, the log daily NS dose/m² was identified as a significant predictor of its development. A patient treated with an intranasal dose of 400 µg BDP per day was 3½ times more likely to present with HPAS compared to a child who was not on NS.⁶ Poor adherence to ICS and NS, as well as the BMI were found to be significant protective factors for an inadequate ACTH response (Table I). Based on the effect size, a child, who is only 50% adherent to his ICS treatment, can be expected to have a post-metyrapone (PMTP) ACTH level 125 pg/ml (27.5 pmol/l) higher than a child who is 100% adherent. Similarly, the PMTP ACTH level of a patient who misses half of his NS therapy would be 116 pg/ml (25.5 pmol/l) higher than the level of one who is fully compliant. Furthermore, the PMTP ACTH level of a child with a BMI Standard Deviation Score (SDS) of 2 (cut-off for obesity) would be 100 pg/ml (22 pmol/l) higher than the level of a child with a BMI SDS of 0. As a normal ACTH stress response should be at least 100 pg/ml (22 pmol/l), all the differences in ACTH release described above are thus clinically significant.

INTER-INDIVIDUAL RESPONSE OF THE HPA TO CORTICOSTEROIDS

When ICS and NS were given at physiological doses in our study, HPAS could be demonstrated in two patients after as little as 3 months of therapy, implying that these children may be more sensitive to CS than the others in the sample. Our data therefore, indicates that there may be an inter-individual variation in HPA function, as has been suggested by other authors.⁹ Conversely, the ACTH/C ratio has been shown to be stable within each individual. This led to the proposal of a unique set point which governs HPA reactivity of each person. It is programmed by genotype, but can be modified by epigenetic factors, such as maternal deprivation or stressful life events. Numerous gene variants coding for proteins at virtually every level of the HPA, and which influence HPA reactivity, have been identified. These naturally occurring common variants are single nucleotide polymorphisms (SNPs) that often cause subtle effects. The heterozygote state for the N363S polymorphism of the glucocorticoid receptor has been shown to cause relative "hypersensitivity" in 6% of elderly. Homozygotes for the SNPs rs 1876828 and rs 242941 in the corticotropin-releasing hormone receptor 1 gene, the T-2C variant in the promoter region of the melanocortin receptor 2 gene and *Bcl* heterozygote for restriction length polymorphism of the glucocorticoid receptor 1 gene have been identified to modify the response to ICS in Greek asthmatic children.¹⁰ The G894T SNP of eNOS gene was found to be a predictor of the response to an ICS-long acting beta agonist combination in asthmatic children.

Even the metabolism of CS is subject to variation. A crucial

Table I: Linear regression model of $\sqrt{\text{Post-metyrapone ACTH}}$ ($R^2 = 0.176$)
(Reprinted from "Paediatrics" with permission from the American Academy of Paediatrics)

Variable	Effect size	SE	p-value
Intercept	23.54	5.24	
Age	0.03	0.25	0.304
BMI (SDS)	1.16	0.58	0.048*
% ICS adherence (previous week)	- 0.07	0.03	<0.001*
% NS adherence (previous week)	- 0.06	0.02	0.002*
$\sqrt{\text{Daily ICS dose/m}^2}$ (HC equiv ²) mg/m ²)	0.51	1.32	0.797
Log daily NS dose/m ² (HC equiv mg/m ²)	- 1.67	1.62	0.307

¹) Per m² body surface area

²) Hydrocortisone equivalent

* Significant, p<0.05

element in the inactivation of CS is the 11 β -hydroxysteroid dehydrogenase (11 β -HSD) enzyme. It converts endogenous or synthetic CS to and from their inactive metabolites. Two isoforms exist: 11 β -HSD1 can function bi-directionally, but acts mainly to produce active CS; 11 β -HSD2 acts to produce inactive metabolites. Paradoxically 11 β -HSD2 may activate some synthetic CS. This enzyme has been found in lung epithelium, where it is thought to be responsible for sustaining activity of ICS. To the best of the author's knowledge, no SNP of this isoform has yet been described.

A multitude of genes potentially contribute to the inter-individual response of the HPA in asthmatics. Appropriate studies should thus be carried out to identify gene variants which could help predict either proneness or resistance to developing HPAS.

CONCLUSIONS

Contrary to common belief, a degree of biochemical HPA dysfunction may exist in about two-thirds of asthmatic children treated with various CS in an asthma clinic. By nature, HPAS is dynamic. A linear dose-effect relationship can be observed at physiological doses, while at supra-physiological doses this effect is lost. The use of NS, in addition to ICS therapy, is a significant predictor of HPAS. High BMI and poor adherence to ICS and NS treatment protect against HPAS. It is therefore recommended that

every child with a low or normal BMI, who is treated with both ICS and NS, and adheres to therapy, should have his or her HPA function assessed. Further research might identify genetic factors that predict or protect from HPAS. Until then, therapy should be modified to keep the total CS dose to a minimum.

DECLARATION OF CONFLICT OF INTEREST

The author declares no conflict of interest.

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