

Review Article

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

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The evidence for hypothalamic-pituitary-adrenal axis (HPA) suppression by inhaled corticosteroids (ICS) was found to be conflicting.

Reviewers have not distinguished between gold standard and basal adrenal function tests. The utility of the latter is limited by physiological and pathological variability as well as by methodological concerns. The risk of HPA suppression in asthmatic children and adolescents treated with ICS, as determined by gold standard adrenal function tests, needs to be established. A systematic review of the literature from January 1973 to July 2005 was performed. The Medline and Cochrane databases were searched, the reference lists of retrieved articles were inspected and pharmaceutical companies were approached. Randomized-controlled trials, cohort and case-control studies designed to detect HPA suppression caused by ICS, diagnosed by the insulin tolerance test (ITT) or the metyrapone test, performed on asthmatics of all ages not on oral steroids, were included and assessed for methodological quality. Of the 22 identified studies only four met the criteria for inclusion. All of these were published before 1988 and only one was methodologically sound. The cohort study showed that the baseline risk for HPA suppression is 0% while the absolute risk is 100% in asthmatic children treated with a beclomethasone dipropionate metered dose inhaler at a dose of 250–600 $\mu\text{g}/\text{m}^2/\text{day}$ for 6–42 months. As suggested by other observations these results could be generalized to other ICS. They may be of clinical significance especially if children are subjected to stress. Further research is needed to establish the cumulative dose for all ICS at which HPA suppression will be precipitated. Guidelines for future trials are suggested.

Ekkehard Werner Zöllner

Endocrine & Diabetes Unit, Faculty of Health Sciences, Department of Paediatrics, University of Stellenbosch, Cape Town, South Africa

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Ekkehard Werner Zöllner, Endocrine & Diabetes Unit, Faculty of Health Sciences, Department of Paediatrics, PO Box 19063, 7505 Tygerberg, South Africa

Tel.: +27 21 938 9506

Fax: +27 21 938 9138

E-mail: zollner@sun.ac.za

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Many reviews on the benefits and risks of inhaled corticosteroids (ICS) have been published. Whilst the effectiveness of these agents cannot be disputed (1, 2), the evidence for hypothalamic-pituitary-adrenal axis (HPA) suppression was found to be conflicting (3–6). This is not surprising, as

reviewers did not differentiate between studies using basal and those using gold standard adrenal function tests. As shown previously (Part 1), the measurements of basal function tests (particularly urinary-free cortisol) are often unreliable and/or invalid, and unable to detect partial HPA

suppression. Their utility is limited by physiological and pathological variability and their diagnostic performance was either not or inadequately evaluated (7). Furthermore, the suppression of the cortisol rhythm does not measure the HPA's ability to respond to stress; hence it has little clinical significance. Its use is limited to demonstrating differences in systemic activity of various ICS and delivery devices. It is only gold standard adrenal function tests, i.e. the insulin tolerance test (ITT) and the metyrapone test, that can identify clinically relevant HPA suppression in asthmatic children on ICS. Its prevalence is, however, not known, as it has never been investigated. A systematic review of the literature was therefore performed to establish the risk for HPA suppression, as determined by gold standard adrenal function tests, in asthmatic children and adolescents treated with ICS. This systematic review does not attempt to answer any other question, be it the equi-systemic effects of various ICS or their efficacy.

Methods

The Medline and Cochrane databases were searched for articles published between January 1973 and July 2005, using the following Medical Subject Heading (MeSH) terms: 'pituitary-adrenal-function tests', 'adrenal insufficiency', 'steroids/adverse effects', 'asthma'. The titles and abstracts of the same databases were also searched using the terms 'insulin tolerance tests', 'insulin hypoglycaemia', 'metyrapone', 'adrenal suppression', 'asthma'. The reference lists of retrieved publications were inspected and pharmaceutical companies approached for additional studies. Randomized-controlled trials, cohort and case-control studies designed to detect HPA suppression caused by ICS, as diagnosed by the ITT or the metyrapone test, performed on asthmatics of all ages not on oral steroids, were

included. The articles were assessed for inclusion and methodological quality by the author. The quality was assessed by reviewing the protocol for endocrine tests, establishing whether patients were steroid naive or weaned off oral glucocorticoids for at least 1 yr prior to the respective study, ascertaining whether steroid use by other routes was excluded and compliance with ICS measured, and determining whether tests were performed at baseline and on control groups. Randomized-controlled trials were also assessed for quality of randomization, blinding, allocation concealment and description of withdrawals or dropouts.

Results

Twenty-two articles were identified. One Czech and one Japanese paper were excluded for language reasons. Of the 20 articles written in English, six were excluded, because the study groups were not homogenous, i.e. subjects were not all asthmatic, not every patient was tested with the gold standard adrenal function test or individuals were treated with more than one ICS during the study period. In nine papers oral steroids were weaned while ICS were introduced. One descriptive study was excluded leaving four articles eligible for quality assessment (Table 1).

Only four studies (8–11), which were all published before 1988 and were all performed on children and adolescents, met the inclusion criteria (Table 1). Because the included studies were quite old, missing data were not obtained from the authors. The study size of each was small, ranging from 10 to 22 patients. The HPA suppressive effects of beclomethasone dipropionate (BDP) and budesonide (BUD) given by chlorofluorocarbon (CFC) metered dose inhalers (MDIs) without spacers were assessed. The inhaled dose was the same for all patients in

Table 1. Papers eligible for quality assessment

Authors	Year of publication	Type of study (n)	Age group (yr)	ICS	Daily dose (μ g)	Daily dose per body size	Duration (months)	Device
Klein et al. (8)	1977	DBRCT* (22)	9–13	BDP† or placebo	400	/	1 each	MDI**
Vaz et al. (9)	1982	Cohort (16 cases, 48 controls)	6–15	BDP	300–500	250–600§	6–42	MDI
Goldstein and König (10)	1983	Cohort (15 cases; 11 controls)	7–16	BDP	250–800	4–28¶	3–30	MDI
Springer et al. (11)	1987	DBRCT (10)	9–15	BDP/BUD‡	400	/	1 each	MDI

*Double-blind randomized crossover trial.

†Beclomethasone dipropionate.

‡Budesonide.

§In μ g/m².

¶In μ g/kg.

**Metered dose inhaler.

Table 2. Quality assessment of eligible studies

Authors	Test	ACTH	Cut-off 11-DOC¶/cortisol** (nmol/l)	Steroid naive?	Off oral steroids for 1 yr?	Other steroids¶¶	Compliance assessed?	Analysed at baseline?	Control group analysed?
Klein et al. (8)	IV metyrapone*	No	173††	Yes	N/A‡‡	?	No	Yes	Yes
Vaz et al. (9)	ITT†	No	414	7 of 16	Yes	?	No	No	Yes
Goldstein and König (10)	ON‡ metyrapone	No	87- or 25-fold increase	No	No	?	Daily diaries***	No	No
Springer et al. (11)	ON metyrapone	Yes§	200	No	No	?	No	No	No†††

*Incorrect dose.

†Insulin tolerance test.

‡Overnight.

§Cut-off not given.

¶11-Desoxycortisol.

**Cortisol cut-off only applies to ITT.

††Individual results not shown.

‡‡Not applicable.

¶¶Nasal or topical.

***Compliance not correlated with metyrapone results.

†††Placebo group not analysed.

two studies (8, 11), but varied in the other two (9, 10). The dose was corrected for body size in the latter only. Only Goldstein and König (10) assessed compliance (Table 2).

Three studies used the metyrapone test while only Vaz et al. (9) employed the ITT as the gold standard test. Adrenocorticotrophic hormone (ACTH) levels were measured during the overnight (ON) metyrapone test by Springer et al. (11) only (Table 2). The measurement of ACTH during this test is essential, because the pick-up rate is doubled if ACTH levels rather than 11-desoxycortisol (11-DOC) levels are measured (12). A normal ACTH cut-off was, however, not indicated, making the results difficult to interpret. All three studies, using the metyrapone test, had different 11-DOC cut-off levels. Only Springer et al. (11) used the correct pass criterion of 200 nmol/l (13). Klein et al. (8) and Goldstein and König (10) did not indicate why they used a different pass criterion (Table 2). In only two studies (8, 10) were the subjects either steroid naive or off oral steroids sufficiently long as not to interfere with the HPA. In the study by Klein et al., steroid naive subjects were tested at the beginning of the study (8). However, an unconventional dose of metyrapone and a lower 11-DOC cut-off were used, making this result difficult to interpret. No significant differences were shown between control and treatment groups. On re-analysis of the data patients in both the treatment and control periods would have failed the metyrapone test had the correct pass criterion been used. Using Klein et al.'s (8) cut-off, some subjects in the control period and none in the treatment period would have passed the test. This fact was not explained. Furthermore, the

individual subjects' results were not shown, making it impossible to correlate the patients' results with the various periods of the study. For the two double-blind randomized crossover trials, methods of randomization, modes of concealment and withdrawals or dropouts were not described. Due to all the methodological limitations described, a meta-analysis is not possible.

The study by Vaz et al. (9) is the only included study that assessed the HPA by using the ITT. The authors followed the correct endocrine protocol and enrolled patients who were steroid naive or off oral steroids for at least 1 yr. Without giving an explanation, a peak cortisol of 414 nmol/l (15 µg/dl) rather than the conventional 550 nmol/l (20 µg/dl) was used as a cut-off (13). The data were therefore re-analysed by the author using the correct pass criterion. The baseline risk for non-asthmatic children to develop HPA suppression during the study was found to be 0%; the absolute risk for asthmatic children on BDP CFCMDI at a dose of 250–600 µg/m²/day for 6–42 months was 100% (computation of a 95% confidence level is not possible). Using Vaz et al.'s (9) unconventional cut-off the absolute risk is 31% (95% confidence interval: 11.0–58.7%).

Discussion

It is evident from the low number of identified studies that the HPA suppressive effect of ICS as detected by gold standard adrenal function tests has been inadequately researched. Of the included studies all but one had significant design flaws. All were published before 1988, indicating that allergologists and researchers have moved

away from gold standard tests in favour of the low-dose ACTH stimulation test and basal adrenal function assessment, notably urinary-free cortisol excretion (UFC) and plasma cortisol profiles. The latter are believed to be a 'very sensitive means of detecting any perturbation in the basal activity of the HPA (14)'. As discussed previously (Part 1), their use is limited, however, by physiological and pathological variations as well as by assay methodology. As far as the author could establish, their alleged 'sensitivity' remains unproven. The low-dose ACTH stimulation test does not test the integrity of the whole axis. Consequently, it will miss a number of patients whose HPA is suppressed by ICS. Furthermore, the testing protocol has not been standardized and the test is therefore best avoided (Part 1).

Although the methodology of the research on HPA suppression caused by ICS is not sound overall, the cohort study by Vaz et al. (9) is an exception and should not be ignored. Ideally asthmatics rather than patients investigated for short stature should have been used as controls, because it has been postulated that severe asthmatics may have relative adrenal insufficiency (15). As the axis needs 9 months to recover fully from the suppressive effects of oral steroids (16), it may have been acceptable to enrol patients who have been off oral steroids for more than 1 yr. The normal response of the HPA, however, should still have been documented at the commencement of the study. Nevertheless, the 100% absolute risk vs. 0% baseline risk represents the strongest possible association between cause and effect. Every single child in the cohort was proven to have HPA suppression on the ITT. This result becomes even more significant if one considers that compliance was not monitored during this study. Applied to everyday patient care, any paediatrician treating an asthmatic child with BDP CFCMDI without a spacer at a dose of 250–600 $\mu\text{g}/\text{m}^2/\text{day}$ can expect that child to develop HPA suppression in the course of 6–42 months.

Nowadays probably every clinician is likely to prescribe a spacer together with a MDI for every asthmatic child treated with ICS. Spacers are known to decrease the amount that is absorbed orally by filtering out large particles (17), but also increase lung deposition by up to 100% (18). The net effect will be greater systemic bioactivity, although technique, compliance, particle size, the state of the patient's asthma and the amount of the drug that undergoes first pass metabolism also plays a role (3). This was demonstrated when overnight urinary cortisol and 8 AM plasma cortisol levels were found to be twofold lower in

healthy adults taking 2 mg fluticasone propionate (FP) with a spacer as opposed to those using no spacer (19). It is therefore possible that HPA suppression could occur earlier and at lower doses if ICS are administered with a MDI and a spacer.

Another issue is whether the results of the one cohort study can be generalized to other ICS, hydrofluoroalkane (HFA) MDIs and other delivery devices. The excluded studies and other observations certainly suggest that this may be permissible. Nine of 18 children (whose compliance was not monitored) on a dose of 265–735 $\mu\text{g}/\text{m}^2/\text{day}$ of FP given by a MDI (presumably CFC) and a spacer over 5–16 wk had proven HPA suppression on the ITT (20). All 13 adult patients on flunisolide 2 mg MDI daily for 3 months had an inadequate response to metyrapone (individual results not shown; 21). Similarly all nine adult asthmatics treated with triamcinolone acetonide MDI at 800 $\mu\text{g}/\text{day}$ for 3 months failed the metyrapone test (22). In the asthma clinic setting, approximately a third of all asthmatic children treated with BUD CFC or HFA MDIs and spacers at various doses and nasal steroids can be expected to have HPA suppression (pilot study, data not shown). As far as the author could establish, no gold standard adrenal assessment of either mometasone furoate or ciclesonide has been carried out. The latter, however, contributed to adrenal insufficiency in at least one case (personal clinical experience).

Clinical adverse events which back up the described biochemical findings have been reported in the literature. Apart from case reports, one case series of eight patients and a questionnaire survey of paediatricians and endocrinologists have been published (23, 24). In the latter, adrenal crisis in 33 patients (28 of whom were children) has been reported. Nearly all of these were on FP doses of 500–2000 $\mu\text{g}/\text{day}$ given by various devices over approximately 1.7 yr (24). Most were precipitated by a stressful event or by a reduction/discontinuation of ICS. Adrenal crisis has also been documented following BUD and BDP (3, 23, 24). Three deaths of children treated with BDP inhalations of unknown dose for 5–6 months have been described (25). Adrenal atrophy was confirmed in two cases where the adrenal glands were examined at autopsy. All of these had an acute bout of dyspnoea prior to death. In both the questionnaire and the autopsy report oral steroids had been administered within the previous year, indicating that these may have contributed to the observed morbidity and mortality. Although the prevalence rate of adrenal crisis following ICS therapy is not known, the

above reports suggest that in rare cases this may occur especially if high doses are used. When it does occur, it is potentially fatal.

The signs of chronic adrenal insufficiency are subtle and non-specific and may occur without precipitating event (23). Frequently they will not be recognized or reported. Chronic adrenal insufficiency may also not be anticipated, because the dose of ICS may be lower than the dose causing adrenal crisis. A BUD dose of 400 μg /day given with a nebulizer for 1 yr was found to cause poor growth and frank hypocortisolaemia (23). Furthermore, asthmatic children may also not manifest any clinical symptoms if they are compliant with their inhaler therapy. Basal cortisol requirements would be provided for by both exogenous and endogenous glucocorticoids. A stressful event such as an asthma exacerbation may, however, precipitate acute adrenal insufficiency as the demand for cortisol may exceed the supply of exogenous steroids. In such a case rescue doses of steroids would be given. These, together with a higher maintenance dose of ICS and improved compliance may inadvertently mask the clinical features of acute adrenal insufficiency.

The clinical manifestation of HPA suppression will vary with the degree of stress the child is subjected to as well as with the degree and the rate of loss of adrenal function (26). Stress or the degree of stress can rarely be controlled or prevented. The degree of loss of adrenal function may depend on the systemic activity (27), the cumulative dose of the ICS and the compliance of the patient. The systemic activity is determined by various factors such as potency, receptor affinity, oral bioavailability, half-life, water solubility and dwell time in lung (27–29). The clinician may have limited control over pharmacokinetic factors, but can influence device and ICS choice, inhaler technique, dose and dosing schedule. Most authorities have already recommended that licensed or recommended doses of ICS should not be exceeded (24). Overdosing, however, may more easily occur in children, because the dose emitted from the device is fixed. Consequently, doses cannot be adjusted for body size which is crucial especially in younger children. Based on the limited evidence presented in this review, it would be safe to assume that, given the right dose and duration, probably all ICS would cause HPA suppression at least biochemically. It would be unwise and ethically questionable to wait for clinical features of adrenal insufficiency or crisis. The knowledge of the respective cumulative dose at which a particular ICS and

device would precipitate HPA suppression would help to determine at what stage other treatment modalities such as long-acting β -agonists or leukotriene receptor antagonists should be introduced.

Researchers and pharmacological companies should be encouraged to establish the cumulative doses causing HPA suppression for the various ICS on the market. Double-blind randomized-controlled trials with a parallel study design, comparing different doses of the same ICS or different ICS of the same dose for 3–6 months, are suggested. The primary outcome should be HPA suppression as measured by the ON metyrapone test. Trial patients should be a homogenous group of asthmatic children in terms of airway obstruction with ideally no co-existing rhinitis or eczema. All should be treated with the same device. If a MDI is used, a spacer should be prescribed. Preferably they should all be steroid naive or have a documented normal ON metyrapone test at baseline. ICS doses should be reported in absolute terms and corrected for body size (in $\mu\text{g}/\text{m}^2/\text{day}$). An adequate response of the axis should be determined by measuring ACTH and not 11-DOC (see Part 1). Testing should be repeated at monthly or two-monthly intervals until HPA suppression can be demonstrated. Compliance should be monitored and ensured at all times.

Conclusions

The suppressive effect of ICS has been inadequately researched. The best available evidence is a study by Vaz et al. (9) which has shown that the risk of HPA suppression in asthmatic children being treated with BDP CFC MDI at a dose of 250–600 $\mu\text{g}/\text{m}^2/\text{day}$ for 6–42 months is 100%. Other observations suggest that these results may be generalized to other ICS. These findings may be of clinical significance, causing chronic adrenal insufficiency in unstressed children, or adrenal crisis if children are stressed or a high dose of ICS is reduced. As other modalities to supplement ICS treatment are available, the cumulative dose of each ICS at which HPA suppression is precipitated should be determined in well designed clinical trials.

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Potential conflict of interest

None.

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