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Evaluation of adrenocortical function in 3-7 aged asthmatic children treated with moderate doses of fluticasone propionate: reliability of dehydroepiandrosterone sulphate (dhea-s) as a screening test

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KEYWORDS

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Abstract

Background: Inhaled corticosteroids (ICS) are the first-line therapy in the treatment of persistent asthma. At medium to high doses and prolonged usage, ICS can suppress the hypothalamic-pituitary-adrenal axis. Dehydroepiandrosterone sulphate (DHEA-S) is a corticotropin-dependent adrenal androgen precursor that is suppressible in patients treated with ICS.

Objectives: To evaluate the adrenal axis in asthmatic children treated with moderate doses of fluticasone propionate and to evaluate the DHEA-S as a possible marker for adrenal axis in preadrenarchal children.

Methods: Twenty-eight children with persistent asthma with a mean age of 4.4 years (median 4.2; range 2.5-7.1) on long term treatment (mean 6.16; median 6; range 4.5-9 months) with moderate doses (mean 250; median 253; range 158-347 (g/m²/day) of inhaled fluticasone propionate were evaluated with low-dose ACTH stimulation test to assess adrenal function, and DHEA-S levels were compared with the results.

Results: One out of 28 patients (3.57%) demonstrated an abnormal cortisol response to low-dose ACTH test. There was no correlation between DHEA-S and peak cortisol, morning cortisol and fasting blood glucose levels. However, mean inhaled corticosteroid dosages were inversely correlated with the DHEA-S.

Conclusions: In most of the children with persistent asthma, mild to moderate fluticasone propionate doses suppress the hypothalamic-pituitary-adrenal axis rarely. Chronic moderate doses of ICS may suppress adrenal androgen levels without suppression of cortisol production. DHEA-S levels may be used as a practical method to follow adrenal functions and may be an earlier indicator of adrenal dysfunction in children.

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Introduction

Inhaled corticosteroids (ICS) are the first-line treatment in the management of persistent asthma.¹ Recently there have been reports of symptomatic adrenal insufficiency in children on chronic ICS treatment.²⁻⁴ Most of these children were treated with high doses of inhaled fluticasone. For most patients aged <12 years, the recommended dose of fluticasone propionate (FP) is classified as low (88-176 $\mu\text{g}/\text{day}$); medium (176-440 $\mu\text{g}/\text{day}$); or high (> 440 $\mu\text{g}/\text{day}$).¹ Fluticasone has the highest receptor binding affinity of any of the commercially available ICS.⁵ Use of FP has been reported to produce dose-related adrenal suppression greater than that of other commercially available ICS.⁶⁻⁸ Studies using low or medium doses of FP in adults with mild to moderate asthma have conflicting results.⁹⁻¹² Children may be even more susceptible to adrenal suppression than adults. The number of studies concerning the effects of FP on adrenal axis at low to medium doses in children is limited and results are also conflicting.¹³⁻¹⁶

For the evaluation of the hypothalamic-pituitary-adrenal (HPA) axis, insulin induced hypoglycaemia and metyrapone are considered the most sensitive tests but they are associated with unpleasant symptoms and significant potential complications.¹⁷ Recently, low dose cosyntropin has been found to be a sensitive test for determining adrenal suppression.¹⁸⁻²⁰ However, it is an invasive and time-consuming test and not reliable for screening purposes.

Dehydroepiandrosterone sulphate (DHEA-S) is an adrenal androgen precursor secreted by the zona reticularis, under the dominant regulation of corticotropin. Serum levels of DHEA-S are affected by several factors, the most important of which are age, gender, chronic illness and the prior use of glucocorticoids. DHEA-S has a long half-life (10-12 hours) and concentrations do not fluctuate throughout the day.²¹ There are some reports indicating that the adrenal androgen secretion is sensitive and suppressible with the exogenous glucocorticoids.²²⁻²⁴ However, data on the use of DHEA-S in the assessment of adrenal function, especially in preadrenarchal children, are limited.

In the present study, we evaluated the effect of moderate doses of FP on HPA axis in preadrenarchal children and compared the results with DHEA-S levels. Our aim was to document the effects of FP at moderate doses in HPA and determine whether there was a correlation between DHEA-S levels and HPA functions in preadrenarchal children.

Patients and methods

Twenty-eight children with persistent asthma and using moderate doses of fluticasone propionate between doses of 158-347 $\mu\text{g}/\text{m}^2/\text{day}$ and for at least 4 months were enrolled in the study. Patients were all at preadrenarchal ages and this was confirmed by a detailed physical examination. None of the children were exposed to systemic corticosteroids more than two courses (each of which at most 5 days and 1 mg/kg/day) within the last 6 months. Any patient with exposure of systemic or topical corticosteroids one month before the adrenal function testing or with a history of chronic illnesses other than asthma were excluded from the study. This study was approved by the ethics committee of

Dr Sami Ulus Children's Hospital numbered 0016/2007 and informed consent was obtained by the parents of each child who participated in the study.

Detailed clinical histories were obtained from the previous medical records, including length of time of exposure and dose of fluticasone propionate. Children were admitted to the Dr Sami Ulus Children's Hospital paediatric allergy and paediatric endocrinology out-patient units with a history of 12 hours fasting and they all stopped the ICS usage 24 hours prior to admission. First an experienced paediatric endocrinologist made a detailed physical examination and patients with the signs of adrenarche were excluded from the study. Half an hour after inserting an intravenous tube the baseline laboratory measures including morning cortisol (between 9:00 and 9:30 a.m.), fasting blood glucose and DHEA-S levels were taken. Then low-dose ACTH (0.5 $\mu\text{g}/\text{m}^2$ up to a maximum of 1 μg) was administered intravenously, and the cortisol levels were measured at the 10th, 20th, 30th, and 40th minutes. A cortisol level of 19.8 $\mu\text{g}/\text{dl}$ or greater was considered as passing the test.²⁵

DHEA-S levels were measured by means of chemiluminescence immunoassays using a commercial kit (DHEA-S radioimmunoassay; Diagnostic Systems Laboratories, Inc., Webster, TX, USA); and cortisol levels were measured by means of enzyme immunoassays using the ST AIA PACK CORT system (TOSOH Bioscience, San Francisco, CA, USA).

The data were analysed by using SPSS version 8.0 (SPSS Inc. Chicago, IL, USA). Pearson's correlation coefficient was used to analyse the relationship between DHEA-S and inhaled corticosteroid, morning cortisol, peak cortisol, and fasting blood glucose levels. The level of statistical significance was at 5%.

Results

The average age of the patients was 4.4 (median 4.2, range 2.5-7.1) and the male-female ratio was 17/11. Demographic data and the other characteristics of patients are shown in Table 1.

One out of 28 asthmatic children (3.57%) demonstrated biochemical adrenal suppression, that is he had a peak serum cortisol response to low-dose ACTH test <19.8 $\mu\text{g}/\text{dl}$. No patient presented symptoms suggestive of adrenal insufficiency. When Pearson's correlation coefficient test was performed no significant correlations were found between DHEA-S and fasting blood glucose levels ($r = 0.157$; $p = 0.424$); DHEA-S and morning cortisol levels ($r = 0.279$; $p = 0.150$) (Figure 1) and between DHEA-S and peak cortisol levels ($r = -0.006$; $p = 0.976$). There was no correlation between the mean inhaled corticosteroid dose and morning cortisol or peak cortisol levels either ($r = -0.140$; $p = 0.478$ and $r = -0.61$; $p = 0.759$ respectively). Mean inhaled corticosteroid dosage of the patients was 250 $\mu\text{g}/\text{m}^2/\text{day}$ (median 253, range 158 to 347) and there was an inverse correlation between the mean ICS dosages and DHEA-S levels of the patients ($r = -0.440$; $p = 0.019$) (Figure 2).

Discussion

Inhaled corticosteroids (ICS) are the first-line treatment in the management of persistent asthma.¹ There have been

Table 1 Demographic and other characteristics of the patients.

Characteristic	Mean \pm Standard deviation	Median, Range
Patients (n), Male/Female	28, 17/11	
Age, years	4.4 \pm 1.3	(4.1; 2.5 to 7.1)
ICS ^a dosage $\mu\text{g}/\text{m}^2/\text{day}$	250 \pm 44.8	(253; 158 to 347)
Duration of treatment months	6.16 \pm 1.1	(6; 4.5 to 9)
FBG ^b mg/dl	84.1 \pm 9.7	(85.5; 59 to 104)
Morning cortisol $\mu\text{g}/\text{dl}$	10.7 \pm 3.6	(10.6; 5.1 to 18.2)
Peak cortisol $\mu\text{g}/\text{dl}$	28.4 \pm 7.9	(26.1; 18.8 to 59.4)
DHEA-S $\mu\text{g}/\text{dl}$	15.4 \pm 9.3	(12.2; 3.3 to 42.4)

^aICS: Inhaled corticosteroids, ^bFBG: Fasting blood glucose.

reports of symptomatic adrenal insufficiency in children who were treated with high doses of inhaled fluticasone.²⁻⁴ In adolescent and adult asthmatics most of the therapeutic benefit of FP is achieved at doses of 100-250 $\mu\text{g}/\text{day}$ and the use of FP in doses up to 500 $\mu\text{g}/\text{day}$ rarely causes adrenal suppression.²⁶

In children, comparable dose response relation for FP has not been formally established for either efficacy or adrenal suppression. There have been reports of symptomatic adrenal insufficiency^{2,27,28} including acute adrenal crisis^{3,4,29} attributed to FP therapy at doses $>500 \mu\text{g}/\text{day}$ in asthmatic children. The presented data show that fluticasone propionate at medium doses $<400 \mu\text{g}/\text{m}^2/\text{day}$ (or nearly 200-250 $\mu\text{g}/\text{day}$ at studied age group) does not cause adrenal suppression in children. Only one out of 28 children (3.57%) showed biochemical suppression of HPA. No symptomatic adrenal insufficiency observed.

Eid et al. made an observational study of 62 children for 8 months and abnormal morning cortisol levels were found in

17% (1/6) of children receiving low-dose (176 $\mu\text{g}/\text{day}$), and in 43% (12/28) of children receiving high-dose ($>880 \mu\text{g}/\text{day}$) FP.³⁰ In the study of Peden et al., fluticasone doses up to 200 $\mu\text{g}/\text{day}$ did not change the 24-hour urinary cortisol levels.¹³ In another study Verona et al. showed that FP at 400 $\mu\text{g}/\text{day}$ caused adrenal suppression in a small but clinically significant proportion of children, compared with the 200 $\mu\text{g}/\text{day}$ dose.³¹ A similar result was found by Kanisto et al. in which 20% of the asthmatic children had an abnormal response at 500 $\mu\text{g}/\text{day}$.¹⁹ Taken together, these results suggest that fluticasone propionate is unlikely to cause adrenal suppression at 200 $\mu\text{g}/\text{day}$ and adrenal suppression occurring in some children at 400 to 500 $\mu\text{g}/\text{day}$.^{13,15,19,30}

Since ICS can cause adrenal suppression at high doses in asthmatic children, assessment of the adrenal functions during the treatment period is an important issue.²⁻⁴ For the evaluation of HPA axis, insulin-induced hypoglycaemia and metyrapone are considered the most sensitive tests but they are associated with significant potential

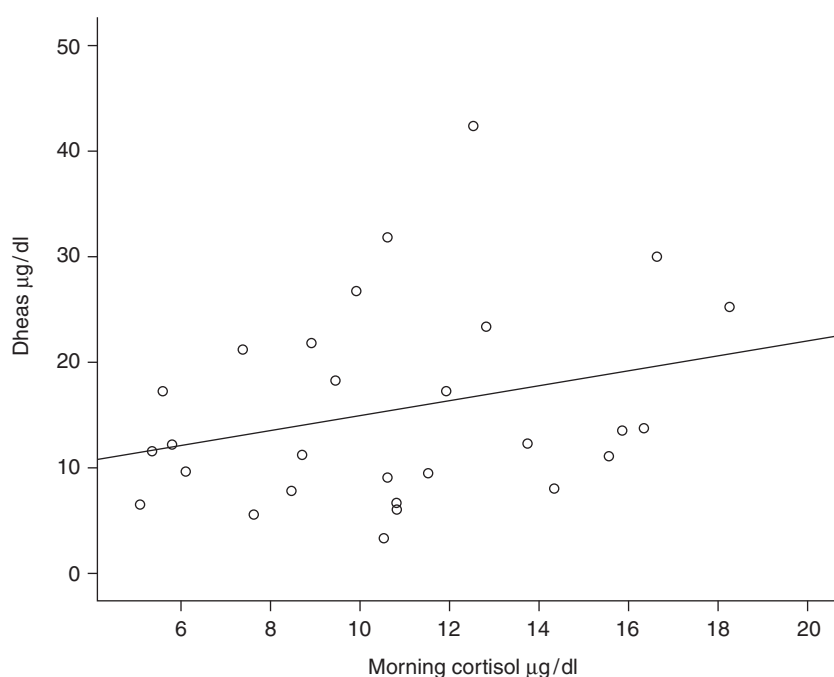


Figure 1 No correlation was found between dehydroepiandrosterone sulphate and morning cortisol levels (Pearson's correlation coefficient $r=0.279$; $p=0.150$).

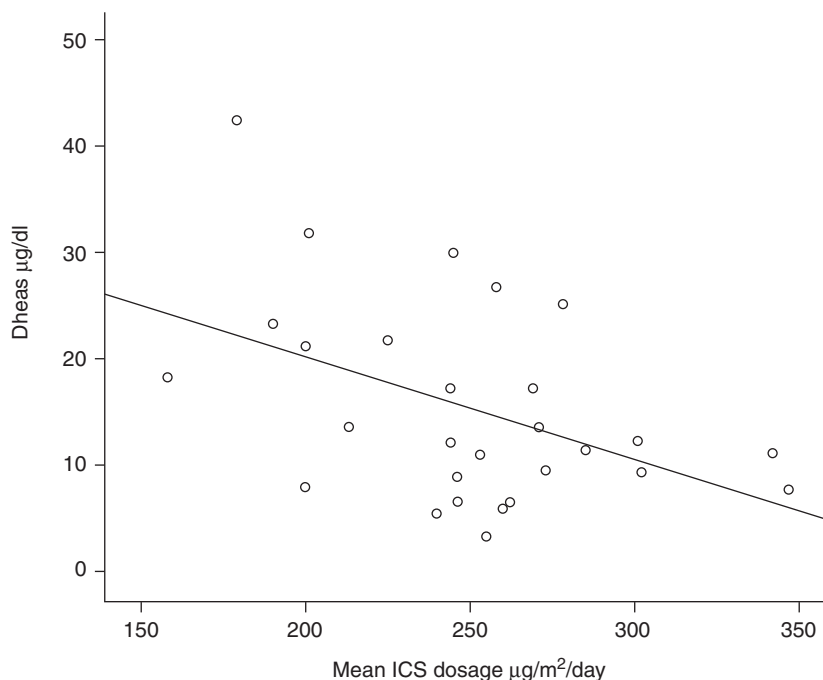


Figure 2 There was an inverse correlation between dehydroepiandrosterone sulphate levels and mean inhaled corticosteroid dosages used by patients (Pearson's correlation coefficient ($r = -0.440$; $p = 0.019$)).

complications.¹⁷ Low-dose cosyntropin has been found to be a sensitive test for determining adrenal suppression.^{18–20} However, it is an invasive test requiring intravenous cannula and repeated blood samples and not reliable for screening purposes.

Dehydroepiandrosterone sulphate (DHEA-S) is an adrenal androgen under the dominant regulation of corticotropin and has a longer half-life (10–12 hours) than cortisol (<2 hours). Thus, diurnal changes in serum DHEA-S concentrations are much lower than cortisol.²¹ Levels of DHEA-S have been shown to be decreased in asthmatic patients exposed to high ICS doses.^{22–24} In the present study, serum DHEA-S levels correlated inversely with the mean inhaled corticosteroid levels and a dose-dependent decrease was found in preadrenarchal asthmatic children. The same correlation was not found with the peak plasma cortisol levels and low-dose ACTH stimulation test revealed only one patient with the biochemical evidence of adrenal suppression. These findings support the studies of Cutler et al. and Rittmaster et al. who found that adrenal androgen secretion is more sensitive than cortisol production to the suppressive effect of glucocorticoid therapy.^{31,32} Kreitzer et al. did not find any decrease in DHEA-S levels in preadrenarchal children after a short one-week course of prednisone, even though the decrease in postadrenarchal children was significant.³³ In a preadrenarchal child there may also be alternative ACTH independent regulatory pathways of DHEA-S synthesis. However if the dosage or the duration of the corticosteroids increase as in the present study, DHEA-S levels decrease with the suppressive effects of ICS.

Hypoglycaemia was not found in any of the patients and there was not a correlation between DHEA-S levels and fasting blood glucose levels as expected. In adrenal axis suppression, hypoglycaemia is a result of loss of glucocorticoid

effect of cortisol and we found cortisol function loss in only one out of twenty-eight patients with low-dose ACTH test. That is why we could not find hypoglycaemia in the study group.

In the present study, morning cortisol levels were not correlated with the DHEA-S levels. A morning cortisol level may be practical to assess the adrenal functions. However, it has been shown to be an insensitive measure of adrenal function in different studies.^{24,34}

In conclusion, fluticasone propionate is unlikely to cause adrenal suppression at moderate doses (<400 µg/m²/day), and conventional doses of inhaled corticosteroids in preadrenarchal children may suppress DHEA-S production. The presence of low DHEA-S levels may be used as a screening test to identify the child who needs further evaluation of adrenal suppression.

Conflict of interest

The authors have no conflict of interest to declare.

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