CLINICAL STUDY

Serum dehydroepiandrosterone sulfate concentration as an indicator of adrenocortical suppression during inhaled steroid therapy in adult asthmatic patients

Senja Kannisto, Anne Laatikainen¹, Antti Taivainen¹, Kari Savolainen², Hannu Tukiainen¹ and Raimo Voutilainen

Departments of Pediatrics, ¹Pulmonary Diseases and ²Clinical Chemistry, Kuopio University Hospital, Kuopio, Finland

(Correspondence should be addressed to R Voutilainen, Department of Pediatrics, Kuopio University Hospital, PO Box 1777, FIN-70211 Kuopio, Finland; Email: Raimo.Voutilainen@uku.fi)

Abstract

Objective: Supraphysiological doses of exogenous glucocorticosteroids cause adrenocortical suppression. Dehydroepiandrosterone sulfate (DHEA-S) is the most abundant adrenal androgen and estrogen precursor. We studied to what extent inhaled glucocorticosteroid therapy for asthma decreases serum DHEA-S concentrations.

Design and methods: We measured serum DHEA-S and cortisol concentrations in 101 adult patients with newly detected mild asthma before and after 2 and 12 weeks of treatment with inhaled glucocorticosteroids. The patients were randomized to receive budesonide 200 µg/day (low dose group, *n* = 50) or 800 µg/day (high dose group, *n* = 51) in two parallel groups double-blindly.

Results: In the low dose group, serum DHEA-S concentrations decreased from the baseline by a mean of 8 % (95 % confidence interval (CI), 3–13 %, *P* < 0.01) after 2 weeks of therapy, and by 2 % (95 % CI, 9 % decrease to 5 % increase, NS) after 12 weeks. In the high dose group, the respective decreases were 16 % (95 % CI, 10–21 %, *P* < 0.001) and 18 % (95 % CI, 12–24 %, *P* < 0.001). The difference between the treatment groups was significant at both 2 and 12 weeks. During the 12 week treatment period the baseline concentrations of serum cortisol did not decrease in the low dose group, while in the high dose group the decrease was significant at 12 weeks (*P* < 0.01), but not at 2 weeks. The forced expiratory volume in 1 s improved equally well in both groups.

Conclusions: Inhaled budesonide decreased serum DHEA-S concentrations, which may indicate adrenocortical suppression. Reduced adrenal production of androgen and estrogen precursors may increase the risk of osteoporosis especially in postmenopausal women.

European Journal of Endocrinology 150 687–690

Introduction

Inhaled steroids have been advocated as the first line treatment in newly detected asthma (1). When considering the efficacy of the therapy, most experts recommend starting the treatment with high doses of inhaled steroids, and then to step down (2, 3). However, there are also reports showing that an equal clinical response is attained whether the treatment is started with a high or low dose (4). On the other hand, the risk of side effects, such as adrenocortical suppression and osteoporosis, increases when high doses are used (5–7).

Serum dehydroepiandrosterone sulfate (DHEA-S) is quantitatively the most abundant steroid secreted by the adrenals. The vascular pool of DHEA-S is large, and it has a long (10–20 h) half-life. Thus the diurnal changes of serum DHEA-S concentrations are minor compared with those of cortisol. There is also evidence that adrenal androgen secretion is more sensitive than cortisol production to the suppressive effect of exogenous

glucocorticosteroids (8, 9), and in postmenopausal women high doses of inhaled steroids suppressed serum DHEA-S levels (10). Likewise, in asthmatics admitted to hospital for severe bronchospasm, serum DHEA-S levels were decreased if the patients had used inhaled or oral steroids (11).

In the present study, we compared the changes in DHEA-S concentrations in patients starting either low or high dose inhaled steroid treatment. Our aim was to evaluate the applicability of serum DHEA-S measurements for monitoring systemic effects of inhaled steroids in adult asthmatic patients.

Subjects and methods

Subjects and medication

One hundred and one adult patients (18–68 years old) with newly diagnosed mild asthma were randomized into a parallel group, double-blind study (3). Patients

with severe asthma were excluded. None of the patients had received oral or inhaled glucocorticosteroids or other regular pharmacological treatment for their asthma before the study; only a short-acting inhaled β_2 -agonist or anticholinergic was allowed. All patients fulfilled the asthma criteria of the American Thoracic Society (12), and only patients with bronchial hyper-reactivity (PC_{20} of < 8 mg/ml, provocative concentration of histamine causing a 20 % fall in forced expiratory volume in 1 s (FEV_1)) were accepted into the study. The patients were randomized by a computer program to receive inhaled budesonide (BUD) either 200 μ g/day ($n = 50$, low dose group) or 800 μ g/day ($n = 51$, high dose group). BUD was administered with a dry powder inhaler (Pulmicort Turbuhaler; Astra Draco, Lund, Sweden) by using two types of inhalers: one containing a BUD 100 μ g/dose and the other a 400 μ g/dose. All patients took one inhalation twice daily. Signed informed consent was obtained from all patients. The study was approved by the Research Ethics Committee of Kuopio University Hospital.

Clinical and laboratory assessments

The patients were examined before any steroid treatment and after 2 and 12 weeks (3 months) of treatment. Airway obstruction was examined by measuring FEV_1 by flow volume spirometry (Medikro 909 Spirometer; Medikro Ltd, Kuopio, Finland). The mean blood sampling time for serum cortisol and DHEA-S determinations was identical at all visits, at an average of 1000 h. The serum samples were stored at -20°C , and analyzed simultaneously. Serum DHEA-S was analyzed by a Coat-A-Count DHEA- SO_4 RIA (Diagnostic Products, Los Angeles, CA, USA). The sensitivity of the assay was 0.03 μ mol/l, and the intra-assay coefficient of variation was 3.8 % for low and 5.3 % for high values. The interassay coefficient of variation was 6.3 and 11 % for low and high values respectively. Serum cortisol was analyzed by a Cortisol ^{125}I RIA Kit (Orion Diagnostica, Espoo, Finland). The sensitivity of the assay was 20 nmol/l, and the intra- and interassay coefficients of variation were 3.0 and 5.8 % respectively, for the whole measuring range.

Statistical analyses

The data were analyzed by the Statistical Package for the Social Sciences, version 10 (SPSS, Inc., Chicago, IL, USA). For individual patients, the percentage changes of serum DHEA-S and cortisol values were calculated from the baseline (before treatment) values. The continuous variables were normally distributed (checked by using the histogram and Kolmogorov–Smirnov test). The statistical significance of the differences in the continuous variables was calculated using the *t*-test. Analysis of covariance was used for studying the effects of possible confounding factors between the

treatment groups. $P < 0.05$ was considered statistically significant.

Results

At the beginning of the study, the groups did not differ in respect of age, sex, atopy, smoking, FEV_1 , or serum DHEA-S and cortisol concentrations (Table 1). There was no difference between the study groups in the use of inhaled β_2 -agonists or anticholinergics either at the start or during the study period. During the treatment, FEV_1 improved significantly and equally well in both groups: mean change from 88.0 (% of predicted) to 89.7 in the low dose and from 86.7 to 88.3 in the high dose group. During the 3 month treatment period, the mean serum cortisol concentration did not change significantly in the low dose BUD group, while in the high dose BUD group it did (Fig. 1). In the low dose BUD group, the mean serum DHEA-S concentration decreased from the baseline by 8% (95% confidence interval (CI), 3–13%, $P < 0.01$) after 2 weeks, and by 2% (95% CI, 9% decrease to 5% increase, $P = \text{NS}$) after 3 months. The respective decreases in the high dose BUD group were 16% (95% CI, 10–21%, $P < 0.001$) and 18% (95% CI, 12–24%, $P < 0.001$) (Fig. 1). The mean percentage decrease in serum DHEA-S concentrations was significantly higher in the high dose than in the low dose BUD group at both 2 weeks and 3 months ($P < 0.05$ and $P = 0.001$ respectively), even when age or ventilatory obstruction (FEV_1 value) was taken into account as confounding factors.

Discussion

Inhaled steroid therapy caused a significant decrease in serum DHEA-S concentrations. BUD 800 μ g/day caused a constant decrease, while 200 μ g/day caused only a mild and temporary decrease in the mean serum DHEA-S concentrations. These results suggest that in the long term the higher 800 μ g/day dose has

Table 1 Characteristics of the patients at baseline. Values are expressed as means $\pm$ S.E.M. or mean (range).

Characteristic	BUD 200 μ g ($n = 50$)	BUD 800 μ g ($n = 51$)
Sex (male/female)	21/29	15/36
Age (years)	37.4 (18 – 68)	40.5 (19 – 62)
Smoking		
Never	23	28
Ex-smoker	13	10
Smoker	14	13
Atopy (yes/no)	32/18	36/15
FEV_1 (% of predicted)	88.0 $\pm$ 1.4	86.7 $\pm$ 1.4
Serum cortisol (nmol/l)	299 $\pm$ 18	279 $\pm$ 18
DHEA-S (μ mol/l)	5.9 $\pm$ 0.43	5.6 $\pm$ 0.53

Figure 1 Serum cortisol (upper panel) and DHEA-S (lower panel) concentrations (mean, 95% CI) in the two treatment groups at the beginning and after 2 and 12 weeks of inhaled BUD treatment. Compared with the baseline level, serum cortisol concentrations decreased significantly during the 3 month treatment period only in the high dose (800 μ g) BUD treatment group (** $P < 0.01$). Serum DHEA-S concentrations decreased in the high dose group significantly after both 2 and 12 weeks of treatment (*** $P < 0.001$), while in the low dose group they decreased only at the 2 week time point (* $P < 0.05$).

systemic effects, while the lower 200 μ g/day dose may be considered safe.

When starting the treatment of asthma, the same favorable clinical response can be obtained whether the dose of inhaled steroid is high or low (3, 4). Nevertheless, it has been suggested that quite high doses of inhaled steroids are needed to treat asthmatic inflammation and bronchial hyperresponsiveness (3, 13). However, after initial high dose treatment, the long-lasting control of asthma can be achieved by using quite low doses of inhaled steroids (14). Our data favor this kind of treatment policy, as the use of inappropriately high doses of inhaled steroids for a long time increases the risk of systemic side effects.

Some asthmatics, e.g. smokers, need high doses of inhaled steroids, and may therefore be at an increased risk of side effects (15). Some individuals, like perimenopausal women, may be exceptionally vulnerable to side effects (6). Therefore, a sensitive and simple

screening test to identify systemic side effects is still needed. As was seen also in the present study, determination of serum cortisol levels in the morning is a rather insensitive way to assess adrenocortical suppression. For example, Ferguson *et al.* (16) did not detect any changes in baseline cortisol levels in children treated with inhaled BUD 800 μ g/day or fluticasone propionate 400 μ g/day. In the case of stimulation tests, a standard dose adrenocorticotropin (ACTH) test (250 μ g) is insensitive in detecting mild adrenal suppression; up to 1000 μ g/day BUD or beclomethasone did not affect the standard dose ACTH test results (17). A low dose ACTH test, in which ACTH is used at small doses (causing physiological ACTH concentrations), has been suggested to be more sensitive than the standard test to reveal adrenocortical suppression (5, 17), but this may not be true if appropriate test specific cut-off cortisol levels are used (18). However, in clinical practice these tests are also somewhat cumbersome, because they require repeated blood samples. We recently found out that there was a dose dependent decrease in serum DHEA-S concentrations in children during inhaled steroid therapy (9). In the present study the same phenomenon was seen in adult asthmatics, showing that serum DHEA-S measurement can be used as a screening method for detecting systemic effects of inhaled steroids; clearly low or decreasing serum DHEA-S concentrations during inhaled corticosteroid therapy suggest adrenocortical suppression. However, a more definitive test, for example an ACTH test, is needed to verify suppression of cortisol secretion. Thus serum DHEA-S measurement can be used to screen for adrenocortical insufficiency in glucocorticoid treated patients in the same way as recently reported in ACTH deficiency for organic reasons (19). It must be emphasized that there are situations where adrenal androgen production decreases while cortisol secretion is maintained or even elevated. This steroid pattern can be seen in chronic inflammatory diseases and chronic stress situations (20, 21).

In the present study, serum DHEA-S concentrations decreased within 2 weeks, while cortisol levels were suppressed significantly only after 12 weeks of high dose therapy. Thus adrenal androgen production was more sensitive than cortisol production to the suppressive effect of inhaled glucocorticosteroids. This finding is consistent with the studies of Cutler *et al.* (22) and Rittmaster and colleagues (8, 23), who found that adrenal androgen secretion is more sensitive than cortisol production to the suppressive effect of glucocorticosteroid therapy. One explanation for this may be that during exogenous glucocorticoid therapy the intra-adrenal steroid concentrations alter in a manner that favors cortisol compared with androgen production (22, 24).

What should we do if we accept and confirm that low serum DHEA-S concentrations in asthmatic patients indicate a systemic effect of inhaled glucocorticosteroids? If the disease is under good control, the steroid

dose could be reduced or alternative treatment modalities could be considered. On the other hand, if the steroid dose cannot be reduced, DHEA treatment is a possibility to try to minimize at least some adverse effects of glucocorticosteroids (25).

In conclusion, serum DHEA-S concentrations decreased during inhaled steroid therapy. Clearly low or significantly decreasing serum DHEA-S concentrations during inhaled steroid therapy may indicate adrenocortical suppression and a risk of other systemic glucocorticoid side effects such as osteoporosis.

Acknowledgements

This work was supported by the Academy of Finland, Kuopio University Hospital, the Sigrid Juselius Foundation and the Jalmari and Rauha Ahokas Foundation.

References

- 1 Haahtela T, Järvinen M, Kava T, Kiviranta K, Koskinen S, Lehtonen K *et al.* Comparison of a beta 2-agonist, terbutaline, with an inhaled corticosteroid, budesonide, in newly detected asthma. *New England Journal of Medicine* 1991 **325** 388–392.
- 2 Keeley D & Rees J. New guidelines on asthma management. *British Medical Journal* 1997 **314** 315–316.
- 3 Tukiainen H, Taivainen A, Majander R, Poussa T, Svahn T, Puolijoki H *et al.* Comparison of high and low dose of the inhaled steroid, budesonide, as an initial treatment in newly detected asthma. *Respiratory Medicine* 2000 **94** 678–683.
- 4 van der Molen T, Meyboom-de Jong B, Mulder HH & Postma DS. Starting with a higher dose of inhaled corticosteroids in primary care asthma treatment. *American Journal of Respiratory and Critical Care Medicine* 1998 **158** 121–125.
- 5 Kannisto S, Korppi M, Remes K & Voutilainen R. Adrenal suppression, evaluated by a low dose adrenocorticotropin test, and growth in asthmatic children treated with inhaled steroids. *Journal of Clinical Endocrinology and Metabolism* 2000 **85** 652–657.
- 6 Laatikainen AK, Kroger HP, Tukiainen HO, Honkanen RJ & Saarikoski SV. Bone mineral density in perimenopausal women with asthma: a population-based cross-sectional study. *American Journal of Respiratory and Critical Care Medicine* 1999 **159** 1179–1185.
- 7 Richy F, Bousquet J, Ehrlich GE, Meunier PJ, Israel E, Morii H *et al.* Inhaled corticosteroids effects on bone in asthmatic and COPD patients: a quantitative systemic review. *Osteoporosis International* 2003 **14** 179–190.
- 8 Rittmaster RS & Givner ML. Effect of daily and alternate day low dose prednisone on serum cortisol and adrenal androgens in hirsute women. *Journal of Clinical Endocrinology and Metabolism* 1988 **67** 400–403.
- 9 Kannisto S, Korppi M, Remes K & Voutilainen R. Serum dehydroepiandrosterone sulfate concentration as an indicator of adrenocortical suppression in asthmatic children treated with inhaled steroids. *Journal of Clinical Endocrinology and Metabolism* 2001 **86** 4908–4912.
- 10 Smith BJ, Buxton JR, Dickeson J & Heller RE. Does beclomethasone dipropionate suppress dehydroepiandrosterone sulphate in postmenopausal women? *Australian and New Zealand Journal of Medicine* 1994 **24** 396–401.
- 11 Dunn PJ, Mahood CB, Speed JF & Jury DR. Dehydroepiandrosterone sulphate concentrations in asthmatic patients: pilot study. *New Zealand Medical Journal* 1984 **97** 805–808.
- 12 American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. *American Review of Respiratory Diseases* 1987 **136** 225–244.
- 13 Pedersen S & Hansen OR. Budesonide treatment of moderate and severe asthma in children: a dose–response study. *Journal of Allergy and Clinical Immunology* 1995 **95** 29–33.
- 14 Haahtela T, Järvinen M, Kava T, Kiviranta K, Koskinen S, Lehtonen K *et al.* Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma. *New England Journal of Medicine* 1994 **331** 700–705.
- 15 Pedersen B, Dahl R, Karlstrom R, Peterson CG & Venge P. Eosinophil and neutrophil activity in asthma in a one-year trial with inhaled budesonide. The impact of smoking. *American Review of Respiratory Diseases* 1996 **153** 1519–1529.
- 16 Ferguson AC, Spier S, Manjra A, Versteegh FG, Mark S & Zhang P. Efficacy and safety of high-dose inhaled steroids in children with asthma: a comparison of fluticasone propionate with budesonide. *Journal of Pediatrics* 1999 **134** 422–427.
- 17 Broide J, Soferman R, Kivity S, Golander A, Dickstein G, Spirer Z *et al.* Low-dose adrenocorticotropin test reveals impaired adrenal function in patients taking inhaled corticosteroids. *Journal of Clinical Endocrinology and Metabolism* 1995 **80** 1243–1246.
- 18 Mayenknecht J, Diederich S, Bähr V, Plöckinger U & Oelkers W. Comparison of low and high dose corticotropin stimulation tests in patients with pituitary disease. *Journal of Clinical Endocrinology and Metabolism* 1998 **83** 1558–1562.
- 19 Nasrallah MP & Arafah BM. The value of dehydroepiandrosterone sulfate measurements in the assessment of adrenal function. *Journal of Clinical Endocrinology and Metabolism* 2003 **88** 5293–5298.
- 20 Straub RH, Lehle K, Herfarth H, Weber M, Falk W, Preuner J *et al.* Dehydroepiandrosterone in relation to other adrenal hormones during an acute inflammatory stressful disease state compared with chronic inflammatory disease: role of interleukin-6 and tumour necrosis factor. *European Journal of Endocrinology* 2002 **146** 365–374.
- 21 Moriyama Y, Yasue H, Yoshimura M, Mizuno Y, Nishiyama K, Tsunoda R *et al.* The plasma levels of dehydroepiandrosterone sulfate are decreased in patients with chronic heart failure in proportion to the severity. *Journal of Clinical Endocrinology and Metabolism* 2000 **85** 1834–1840.
- 22 Cutler GB Jr, Davis SE, Johnsonbaugh RE & Loriaux DL. Dissociation of cortisol and adrenal androgen secretion in patients with secondary adrenal insufficiency. *Journal of Clinical Endocrinology and Metabolism* 1979 **49** 604–609.
- 23 Rittmaster RS, Loriaux DL & Cutler GB Jr. Sensitivity of cortisol and adrenal androgens to dexamethasone suppression in hirsute women. *Journal of Clinical Endocrinology and Metabolism* 1985 **61** 462–466.
- 24 Dickerman Z, Grant DR, Faiman C & Winter JS. Intraadrenal steroid concentrations in man: zonal differences and developmental changes. *Journal of Clinical Endocrinology and Metabolism* 1984 **59** 1031–1036.
- 25 Allolio B & Arlt W. DHEA treatment: myth or reality? *Trends in Endocrinology and Metabolism* 2002 **13** 288–294.

Received 12 September 2003

Accepted 12 February 2004