# IATROGENIC ADRENAL CORTEX FAILURE IN PATIENTS WITH STEROID DEPENDENT ASTHMA IN RELATION TO DIFFERENT METHODS OF GLUCOCORTICOID TREATMENT

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**Objective.** To evaluate and compare the degree of adrenal cortex suppression in patients receiving long term treatment with different formulas and doses of glucocorticoids (GC) which is of considerable diagnostic and therapeutic importance.

**Methods.** A total of 97 subjects (51 women and 46 men) with bronchial asthma was divided into the groups subjected to different GC treatment (e.g. inhalation, oral and intramuscular GC). In all patients total blood serum and free salivary cortisol was estimated under basal conditions and after Synacthen stimulation as well as free cortisol and its metabolites in 24 hour urine.

**Results.** Reduced adrenal reserve was found in 58.33 % of patients chronically treated with systemic GC, in 21.05 % of patients periodically treated with systemic GC and in 9.09 % of patients treated with inhaled GC.

**Conclusions.** Inhaled GC caused a small degree of adrenal cortex suppression and thus should be preferred in the treatment of bronchial asthma. In addition, free salivary and urinary cortisol levels are a useful non-invasive method of evaluating adrenal cortex function in patients with bronchial asthma.

**Key words:** Glucocorticoid treatment – Adrenocortical function – Salivary cortisol – Serum cortisol – Urinary cortisol – Synacthen test – Bronchial asthma

One of the most important factors in the pathogenesis of bronchial asthma is the inflammation (Szefler 1991). There are important implications for the treatment with glucocorticoids (GC) which are thought to be the most effective anti-inflammatory drugs and are often used in large doses for long periods (International Consensus Report on Diagnosis and Treatment of Asthma 1992).

Long term treatment with adrenocortical hormones may cause the suppression of hypothalamic-pituitary-adrenal axis (HPA). The degree of adrenal suppression depends on the dose of GC, duration of treatment, frequency and time of the administration of the drug during the day and also on the route of administration (Scherman et al. 1982; Byron et al. 1983; Law et al. 1986; Altman et al. 1992).

In this study the frequency of iatrogenic adrenocortical failure in patients with bronchial asthma has been established with regard to different methods of GC treatment used, on the basis of free salivary cortisol levels (under basal conditions and during short Synacthen test), urinary free cortisol levels (24 hour excretion) and urinary 17-OHCS excretion.

## Subjects and Methods

**Patients.** A total of 97 subjects with bronchial asthma was investigated including 51 women aged 20 to 61 years (mean 39.9±3.5 years) and 46 men aged 21 to 60 years (mean 42.6±8.6 years).

The subjects with bronchial asthma were divided into the following groups depending on the degree

of severity of the asthma course according to International Consensus Report on Diagnosis and Treatment of Asthma (1992) and the treatment method used.

Group I consisted of 20 subjects: 11 women (26 to 50 years, mean 35.7±10.2) and 9 men (23 to 51 years, mean 33.6±4.0) with a mild form of asthma. The period of treatment ranged from 1 to 33 years. These subjects were never treated with GC.

Group II consisted of 36 subjects: 21 women (21 to 61 years, mean 41.2±12.1) and 15 men (31 to 60 years, mean 56.7±5.6) with severe asthma, who were chronically using GC for 1 to 17 years (mean 7 years). The period of the illness ranged between 3 to 35 years. They were treated with i.m. depot triamcinolone acetonide (Polcortolon 40) every 4-5 weeks and beclomethasone acetate and phosphate (Diprophos) every 2-4 weeks.

Subjects on oral steroid therapy received their last dose of medication 36 hours before the tests, those who were on depot medication were tested 2-3 weeks after the injection of the last dose.

Group III consisted of 19 subjects: 9 women (22 to 51 years, mean 45.0± 1.4) and 10 men (23 to 60 years, mean 39.2±15.5) with mild asthma, who received oral triamcinolone (Polcorton) 8-20 mg daily only during the exacerbation of their illness but no longer then 7 days a month. The period of illness in these subjects ranged from 8 to 22 years. The last medication was given 1-2 weeks before the collection of samples for tests.

Group IV included 22 subjects: 10 women (21 to 51 years, mean 39.7±9.6) and 12 men (33 to 60 years, mean 40.9±10.7) with moderate or severe asthma who received following inhalation GC formulas during the last year only: beclomethasone dipropionate (Beclocort) 1200-1600 µg daily or budesonide (Budesonide) 800-1200 µg daily.

The duration of illness was 3 to 18 years. The patients took the last dose of medication 12-24 hours before the beginning of tests.

**Control group** consisted of 31 healthy volunteers: 19 women (24 to 61 years, mean 36.0±5.2) and 12 men (23 to 51 years, mean 36.3± 6.6), who did not receive any medication.

**Evaluation of adrenocortical function.** On the day of testing the clinical status of all subjects was satisfactory. The evaluation of the adrenocortical function in all subjects was performed on the basis of: 1. total cortisol level (TF) in blood taken at 8.00 h; 2. salivary cortisol level (SF) in saliva obtained at the same time; 3. short Synacthen stimulatory test (SST: 0.25 mg Synacthen Ciba i.m.) followed by the estimation of TF and SF levels; 4. free cortisol and cortisol metabolites estimation in 24 hour urine on the day preceding the SST.

Blood and saliva were taken before the administration of Synacthen and then 30 and 60 min after that. Each subject was allowed to rest for 30 min before the SST, the washing of the oral cavity being performed one hour before the beginning of the test.

The saliva was collected in Salivette test-tubes (Sarsted). Blood serum and saliva were obtained by centrifugation and were frozen at -20 °C until the cortisol levels were measured. Urine was collected for 24 hours before the beginning of the SST and then was frozen at a temperature of -20 °C without preserving agents until the analysis was performed. All subjects had a normal serum creatinine levels.

Adrenal cortex function was considered normal according to Brown et al. (1991) when: 1. TF level at $8^{00}$ h was above 190 nmol/l,

2. urinary free cortisol (UFC) was above 80 nmol/24 h, 3. an increase of TF concentration was noted within 30 min after the administration of Synacthen by a value of not less than 200 nmol/l or TF level at 30 min after the Synacthen was above 500 nmol/l.

Suppression of the adrenal cortex was considered to be present when at least two of the three listed criteria were not fulfilled.

The range of normal salivary cortisol level for particular time points during the Synacthen test have been presented in previous study (Kos-Kudla et al. 1996).

**Methods.** Cortisol levels in serum, saliva and urine were measured by specific RIA using commercial kits (Orion Diagnostica, Finland) adapted for measurements in these biological materials. The sensitivity of the method was 4-7 nmol/l, intraassay variation was 2.1 % and interassay variation was 5.2 %.

Urinary 17-OHCS levels were measured according to Silber-Porter method (1954).

The above mentioned tests were approved by the Committee for the Control of Tests Conducted on Humans at the Silesian Medical School in Katowice.

**Table I**
**Evaluation of the adrenal cortex function in asthma patients under basal conditions and in Synacthen test**

| | | TF [nmol/l] | | | SF [nmol/l] | | | | |
|---|---|---|---|---|---|---|---|---|---|
| GROUP | n | 0' | 30' | 60' | 0' | 30' | 60' | UFC (nmol/l) | 17-0HCS (mg/24 hours) |
| I | 20 | 433.65 ±125.85 | 792.00 ±153.27 | 838 48 ±128.11 | 18.84 ±3.86 | 41.07 ±10.28 | 48.50 ±10.98 | 131.75 ±30.52 | 4.29 ±0.73 |
| II | 36 | 238.51* ±132.41 | 393.44* ±201.93 | 485.77* ±229.36 | 9.86* ±6.45 | 18.40* ±10.20 | 18.33* ± 9.82 | 62.96* ±39.35 | 2.58* ±1.19 |
| III | 19 | 363.52* ±111.09 | 673.58* ±197.02 | 732.45* ±160.32 | 15.75* ±6.61 | 31.91* ±11.17 | 38.23* ±7.92 | 87.01* ±23.31 | 3.86* ±0.92 |
| IV | 22 | 428.06 ±65.39 | 783.46 ±125.74 | 850.46 ±157.76 | 18.16 ±5.28 | 37.59 ±5.56 | 47.78 ±12.79 | 105.51 ±20.41 | 3.97* ±1.24 |
| V | 31 | 459.13 ±144.95 | 839.35 ±164.35 | 903.21 ±133.14 | 20.26 ±6.61 | 39.81 ±9.38 | 51.34 ±12.92 | 146.98 ±42.27 | 4.73 ±0.91 |

**I – patients without GC-treatment; II – patients with chronic GC-treatment; III – patients with periodic GC-treatment; IV – patients with inhaled GC-treatment; V – controls**
**TF – serum cortisol, SF – saliva cortisol, UFC –urinary cortisol,**
*** P < 0.05; n – number of patients**

**Statistical evaluation.** The Student's-test was used to determine the significance of mean values derived from different numbers of observations and with different standard deviations, of cortisol levels and 17-OHCS in the investigated groups as compared to the control group, considering $P < 0.05$ as the limit of significance. The values of cortisol levels as measured in different biological samples were compared using linear correlation.

## Results

Mean levels of cortisol under basal conditions and after the Synacthen stimulation in particular groups of subjects with bronchial asthma as compared to the control group are shown in Tab. 1.

As shown, in the subjects with bronchial asthma not treated with GC (Group I), no significant difference vs. control group was observed either in the basal or Synacthen stimulated cortisol level, urinary free cortisol and 17-OHCS excretion (Tab. 1).

In the patients with chronic GC treatment (Group II) significantly lower basal serum cortisol, urinary free cortisol and 24-h urinary 17-OHCS excretion were found as compared to the control group. In addition, significantly lower plasma cortisol levels were also found after the short Synacthen test.

In the patients subjected to periodic GC-treatment (Group III), significantly lower basal and Synacthen stimulated serum cortisol level vs. control group was demonstrated as well as significantly decreased excretion of free cortisol and 17-OHCS in 24-h urine.

In the subjects of Group IV (receiving inhaled GC preparation) no changes of cortisol levels in serum or urine either under basal conditions or during short Synacthen were found as compared to the control group. However, a significant decrease in 17-OHCS excretion in 24-h urine was observed.

From the levels of cortisol during the SST as well as from UFC and 17-OHCS excretion in 24-h urine the percentage of subjects disturbed GC function of adrenal cortex in individual tested groups was es-

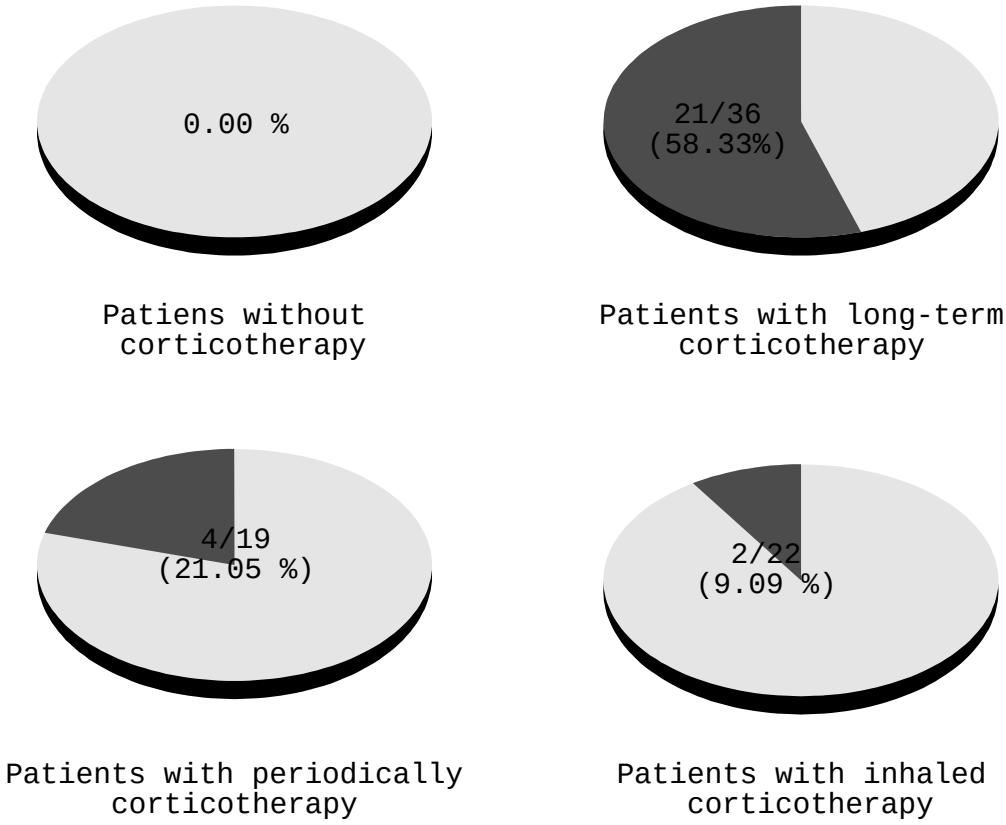


**Fig. 1 Number of asthma patients in who suppresion of the adrenal cortex was found (using modified Brown criteria)**
**Group I: patients not treated with glucocorticosteroids**
**Group II: patients treated chronically with glucocorticosteroids**
**Group III: patients treated periodically with glucocorticosteroids**
**Group IV: patients treated with inhaled glucocorticosteroids**

tablished. Thus, in Group I there was no reduced secretory function of the adrenal cortex in terms of cortisol secretion. However, in contrast to group II subjected to long-term treatment with depot glucocorticoid preparations and showing adrenal cortex suppression by Synacthen test in 21/36 subjects (58.33 %), in Group III (treated intermittently with peroral GC preparations) such suppression was found only in 3/19 subjects (15.78 %) and in Group IV (treated with inhaled preparations) only in 2/22 subjects (9.09 %).

Decreased UFC excretion vs. control group was noted in 19/36 subjects (52.77 %) of Group II, in 4/19 subjects (21.05 %) of Group III and only in 2/22 subjects of Group IV. Similar between group differences were also found in 24-h excretion of 17-OHCS, the values vs. control group being decrease in 16/36 subjects (44.0 %) of Group II, in 2/19 subjects (10.52 %) of Group III and in 3/22 subjects (13.63 %) of Group IV.

Taking into account the criteria by Brown et al. (1991), decreased adrenal reserve was found in 21/36 (58.33 %) subjects chronically receiving GC, in 4/19 (21.05 %) subjects periodically treated with GC and in 2/22 (9.09 %) subjects treated with inhaled GC (Fig. 1), while normal GC function of adrenal cortex was demonstrated in 20 subjects with bronchial asthma who were not treated with GC preparations.

Plasma and salivary cortisol levels during the Synacthen test are well illustrated in Fig. 2. Parallel secretion of serum and saliva levels of this hormone are demonstrated.

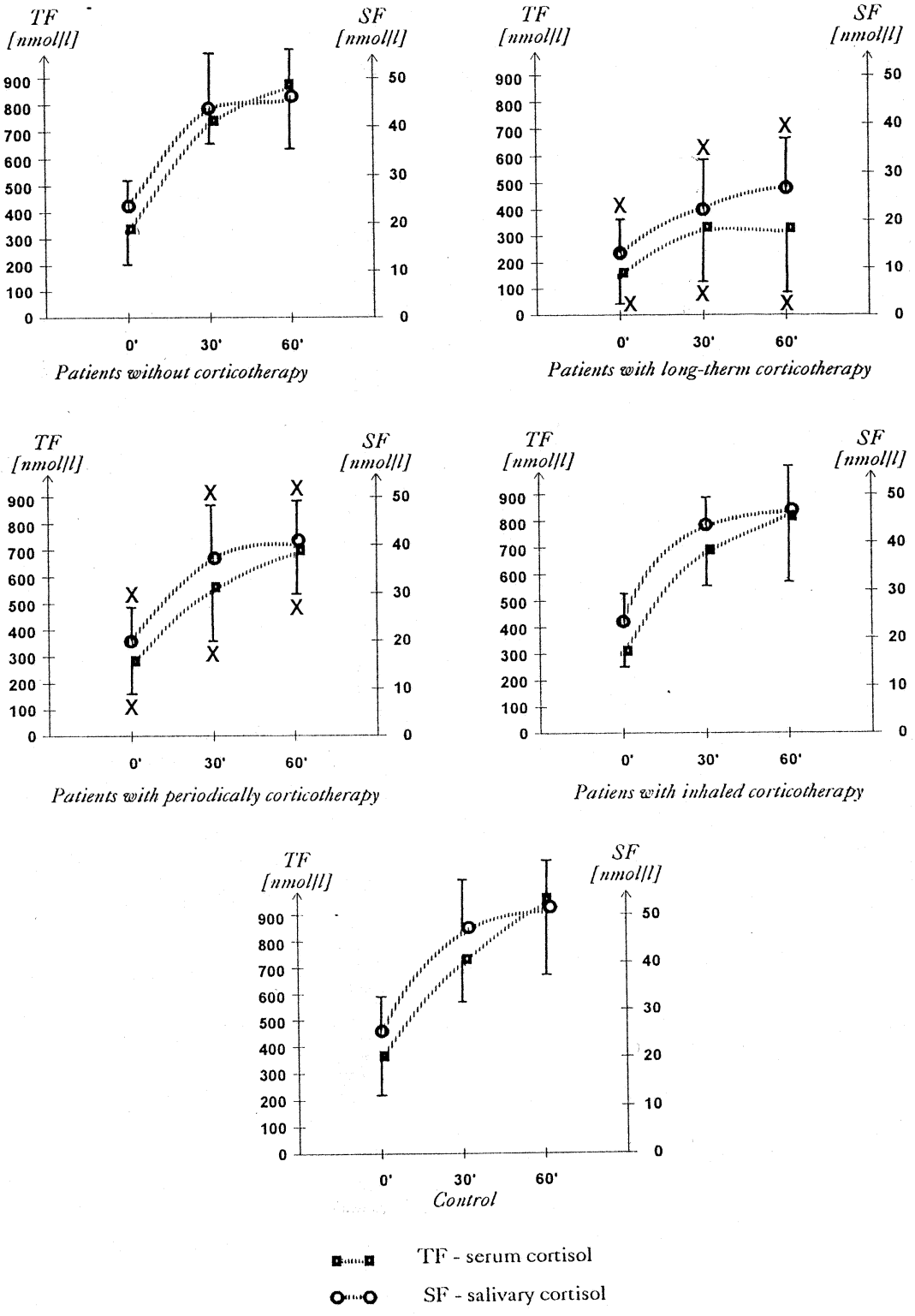


**Fig. 2. Serum and salivary cortisol level during adrenocortical stimulation test in asthma patients and in controls. (X – P ≤ 0.05 vs. control groups)**

## Discussion

The influence of various glucocorticoid preparations on the hypothalamus-pituitary-adrenal cortex (HPA) axis has been evaluated in many studies. However, the reported results appeared conflicting, since the patients studied were subjected to various treatment schedules concurrently, different periods of treatment and various tests were used to evaluate the changes of the HPA axis function.

Brown et al. (1991) proposed a method of evaluating the function of adrenal cortex for screening tests which seems to recognize all required parameters. Using this method it is possible to evaluate the basic glucocorticoid function of adrenal gland using the measurements of basal plasma cortisol level 24-h free urinary cortisol excretion as well as the adrenal reserve evaluation after Synacthen stimulation. We have proposed the modification of this method by use of salivary cortisol concentration.

In the patients with bronchial asthma not treated with GC there were no changes in mean cortisol levels as compared to the control group which directly confirmed the findings by others (Barnes 1980; Zimmermann and Nagel 1987). Haen et al. (1991), however, noted elevated values of basal cortisol concentrations, interpreting this as an endogenous protective reaction in this disease. Other authors (Mileva and Maleeva 1987) observed decreased basal cortisol concentrations, but did not present any information on the adrenal cortex function as evaluated by dynamic tests.

The results of tests obtained in our patients with bronchial asthma chronically treated with glucocorticoid preparations are comparable with the findings by Li and Zhong (1991) who showed adrenal cortex suppression in patients treated with triamcinolone acetonide in 53.2 % of subjects based on the estimations of basal serum cortisol level and in 45.6 % of these as based of the short Synacthen test. Different results were obtained by Droszcz et al. (1979) who found a decreased adrenal reserve in only 19 % of subjects chronically treated with similar dose of triamcinolone acetonide. An inappropriate response of adrenal cortex in 22 % of subjects treated with depot beclomethasone (Diprophos) has been demonstrated by short Synacthen test (Piotrowska et al. 1981) and also in 29 % of subjects treated with the same preparation (Salmeron et al. 1989). The differences in the results obtained by the quoted authors may originate from the different period of glucocorticoid treatment.

It has been shown that long term use of systemically acting glucocorticoids caused suppression of the adrenal cortex in a significant proportion of patients (in this study 58 % of subjects) which is associated with a serious complication of iatrogenic failure of this endocrine organ in the case of sudden termination of treatment, stress situations or worsening of the course of illness.

The patients with bronchial asthma who received oral triamcinolone only during the periods of worsening of disease symptoms, and for no longer than 7 days per month showed statistically significant decrease of F secretion.

None of the subjects who were tested two weeks after ceasing GC treatment showed a decreased response of the adrenal cortex to administered Synacthen or impaired basal cortisol secretion. Data from the literature confirm the opinion that after short treatment, i.e. not exceeding 1 week, with systemically acting oral GC the return of HPA axis function is fast and takes only several days (Milner 1982; Schleimer 1988).

Many authors are of the opinion that short term treatment with even large doses of GC (up to 60 mg/24 h of prednisone or equivalent dose) causes short term disturbance of adrenal glucocorticoid function (Zora et al. 1986; McFaden 1993; Schlaghecke et al. 1992). From the above observations it can be suggested that short term treetment with oral GC drugs (used for no longer then one week) leads to temporary disturbance of the adrenal cortex in only some patients and can be advised as a relatively safe treatment during the period of worsening of the illness.

Suppression of the adrenal cortex (according to the Brown's criteria) was demonstrated in 9.09 % of subjects treated solely with inhaled GC. The described changes were in subjects treated with beclomethasone dipropionate at a dose of 1200-1600 μg per day. One subject was treated with systematically acting oral GC for a period of 2 years before the beginning of treatment with inhaled GC and for this reason the observed adrenal cortex suppression may have been associated with the direct influence of in-

haled GC on the activity of this organ or the with persisting suppressive effect of previously used systemically acting GC.

The obtained results are also in agreement with the findings of TEELUCKSINGH et al. (1991) and MOLEMA et al. (1988) who showed that the use of small glucocorticoid doses (i.e. below 1000 µg/24 h) in adults may have an inhibitory impact on the adrenals. This effect was seen in a number of patients treated with inhaled GC at these doses.

The significant suppressive effect observed with basal and stimulated activity of the adrenals increases with increasing the of inhaled steroid above 1000 µg /24 h (BISGAARD et al. 1988; BROWN et al. 1992, 1993; GEDDES 1992; TABE et al. 1992). With the use of daily doses of about 1500 µg most authors found only few cases of adrenal cortex suppression, while such effect has been found in the majority of patients reeceiving the doses above 2000 µg/24 h (GORDON et al. 1987; SELROOS and HALME 1991; BARNES 1993; BROWN et al. 1992, 1993). PRAHL (1991) reported that the secretory function of adrenal cortex also depends on the individual qualities of tested subjects which may in consequence mean that some contradictory results of studies may be more related to biological characteristics of the patients than to administered dose of the drug. BROWN et al. (1991) proposed that every patient treated with inhaled GC at daily doses exceeding 1500 µg /24 hours should have screening tests of the adrenal cortex function performed. In the case of detection of adrenal suppression the patient should be protected from the consequences of decreased adreanocortical function by low substitution doses of oral GC for a short period. This view is supported by the observations of PHILIP et al. (1992) who found that a significant suppression of adrenal cortex may also arise after the use of conventional doses of inhaled GC on the basis of results from their tests.

The presented results confirm the relevance of using inhaled GC as a treatment of choice for patients with bronchial asthma. Their use is associated with a lower risk of adrenal cortex suppression than the use of other methods of GC therapy. The use of salivary and urinary free cortisol levels may be a useful, non-invasive method of evaluating the adrenal cortex function in patients with bronchial asthma.

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