Low-Dose Adrenocorticotropin Test Reveals Impaired Adrenal Function in Patients Taking Inhaled Corticosteroids


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ABSTRACT

The aim of the present study was to examine the use of low-dose ACTH-(1–24) stimulation for assessment of adrenal function and the detection of mild adrenal insufficiency. The criteria for normal response to ACTH-(1–24) are a peak cortisol level of more than 500 nmol/L (18.1 µg/dL) and an increment of the cortisol level above the basal one of more than 200 nmol/L (7.2 µg/dL). These criteria were satisfied by 32 of 33 healthy children and adults subjected to an ACTH-(1–24) dose 500 times lower (0.5 µg/1.73 m²) than the dose of 250 µg in the standard test. At 20 min, the peak cortisol level was the same in the low-dose test [(627 ± 28 nmol/L) (22.5 ± 1.0 µg/dL)] as in the standard ACTH test [(654 ± 31 nmol/L) (23.7 ± 1.1 µg/dL)]. Of 46 asthmatic patients who had been treated with inhaled beclomethasone dipropionate (482 ± 42 µg/m²/day; n = 32) or budesonide (507 ± 62 µg/m²/day; n = 14) for over 6 months, 16 (35%) failed to reach a cortisol peak of more than 500 nmol/L (18.1 µg/dL) following stimulation with 0.5 µg ACTH-(1–24/1.73 m²). Of these, 11 (24%) showed a cortisol increment of less than 200 nmol/L (7.2 µg/dL). These 16 patients, showing insufficient response to low-dose ACTH-(1–24), also had a significantly lower (<0.01) mean 24-h urinary free cortisol excretion [(71 ± 10 nmol/m².24 h) (25.7 ± 3.6 µg/m².24 h)] than patients who responded normally [(118 ± 11 nmol/m².24 h) (42.8 ± 4.0 µg/m².24 h)]. Nonetheless, all but one of the poor responders to a 0.5 µg ACTH showed normal stimulation with the standard 250 µg ACTH test. Therefore, it appears that a low-dose ACTH test is capable of revealing mild adrenal insufficiency, which is not detected by the standard high-dose ACTH test. (J Clin Endocrinol Metab 80: 1243–1246, 1995)

For three decades, the iv injection of a pharmacological dose (250 µg/1.73 m²) of ACTH-(1–24) has been used as a standard test in the initial assessment of adrenal function (1–3). However, pharmacological ACTH tests provide information only about the ability of the adrenals to respond to unusual stimuli and may not reflect the daily cortisol secretion or the response to minor stresses, such as mild infectious disease. Studies in healthy volunteers demonstrated that low doses (0.5–1 µg/1.73 m²) of ACTH-(1–24) are sufficient to stimulate release of cortisol from the adrenal gland that will meet the standard criteria for a satisfactory ACTH test result (4, 5). It has been suggested that the low-dose ACTH test could be a sensitive method to detect subtle impairment in adrenal function that would be masked when the standard test is used (5).

Findings from studies on occurrence of adrenal suppression in asthmatic patients treated with inhaled corticosteroids have been controversial; some investigators reported that there were no effects (6–9), and others claimed to have adrenal suppression at high doses (10, 11) or even at conventional doses of steroids (12–15). Many of these studies have relied on the pharmacological standard-dose ACTH test or on stress tests, such as insulin-induced hypoglycemia. The purpose of this work was to study the role of the low-dose ACTH-(1–24) test in assessment of adrenal function in healthy children and young adults and to evaluate the possibility that it is a more sensitive method for detection of impaired adrenal function in asthmatic patients treated with inhaled corticosteroids.

Subjects and Methods

Subjects

Forty-six asthmatic patients comprised of 30 children (22 male, 8 female, aged 5–14 yr) and 16 adults (10 male, 6 female, aged 18–30 yr) took part in this study. Fifty-three children (12 male, 3 female, aged 5–14 yr) referred to our Pediatric Endocrinology Clinic for investigation of short stature and 18 medical students (12 male, 6 female, aged 22–26 yr) served as a control group. The children were matched for age, and the young adults were matched for age and sex. Thirty-two of the asthmatic patients were taking inhaled beclomethasone dipropionate, 148–198 µg/m² daily (mean 182 ± 42); 14 inhaled budesonide, 250–1050 µg/m² daily (mean 507 ± 62), divided into 2–3 doses per day for more than 6 months. All used metered-dose inhalers. Patients were excluded from the study if they had been treated with oral steroids during the 6 months preceding the study. The study protocol was approved by the ethical committee of the Tel Aviv Medical Center, and informed consent was obtained from the parents of each child as well as from adult participants.

Study protocol

The low-dose ACTH test was performed in all asthmatic patients and controls. A vial of 250 µg ACTH-(1–24) (Cortrosyn, Organon International Oss, The Netherlands) was diluted in sterile saline solution to a concentration of 0.5 µg/mL. The solution was used immediately. An
indwelling iv cannula was inserted into the forearm at 0900 h and heparinized. After a resting period of 60 min, 0.5 μg/1.73 m² ACTH-(1-24) was administered as a bolus injection iv, and blood samples were obtained at 0, 20, 30, and 45 min for measurement of serum cortisol concentration. A normal result of the ACTH test was defined as a peak serum cortisol concentration of at least 500 nmol/L and a rise of 200 nmol/L from the basal value after the ACTH-(1-24) injection (16, 17). On separate days, 11 asthmatic patients who failed to meet these criteria of a satisfactory ACTH test, as well as 15 controls who passed the low-dose ACTH test, underwent a standard 250 μg/1.73 m² test. The adrenal function in the asthmatic patients was also evaluated by measuring the excretion of free cortisol in 24-h urine samples, which was expressed in relation to body surface area (18). Urinary free cortisol excretion expressed in this way gives an excellent index of adrenocortical function during childhood, one that is independent of chronological age or stage of pubertal development.

Cortisol measurement

Serum and urinary cortisol concentrations were measured using a commercially available radioimmunoassay kit (Coat-A-Count, Diagnostic Products, Los Angeles, CA) with intraassay coefficients of variation of 3.2% and 6.9% for cortisol measurements in the serum and urine, respectively, and interassay coefficients of variation of 4.8% and 7.3%, respectively.

Statistical analysis

Data are expressed as the mean ± SEM. Results were analyzed using unpaired two-tailed Student's t test. Pearson's correlation coefficient and linear regression were used to evaluate the relationship between peak serum cortisol after injection of ACTH-(1-24) and 24-h urinary free cortisol.

Results

Low ACTH test in healthy untreated controls

The mean serum cortisol concentration attained in healthy controls 20 min after stimulation with 0.5 μg ACTH-(1-24)/1.73 m² [621 ± 28 nmol/L (22.5 ± 1.0 μg/dL)] was similar to that produced at the same time by the standard pharmacological dose of 250 μg [654 ± 31 nmol/L (23.7 ± 1.1 μg/dL)]. Serum cortisol levels continued to rise 45 min after stimulation with the high dose but fell 30 min after administration of the lower dose (Fig. 1). Although the mean peak serum cortisol response to 0.5 μg ACTH-(1-24)/1.73 m² [571 ± 23 nmol/L (20.7 ± 0.8 μg/dL)] and the incremental rise in cortisol [274 ± 17 nmol/L (9.9 ± 0.6 μg/dL)] were lower than those produced in response to the standard dose of 250 μg [698 ± 32] (25.3 ± 1.1) and 372 ± 20 nmol/L [13.5 ± 0.7 μg/dL], respectively, the results indicate that the lower dose is sufficient to stimulate release of cortisol from the adrenal gland, which meets the criteria for a satisfactory ACTH test. Indeed, in 32 of 33 controls, the peak cortisol response to the lower dose was more than equal to 500 nmol/L (18.1 μg/dL), and the rise in serum cortisol from basal values was more than equal to 200 nmol/L (7.2 μg/dL) in all controls.

Low-dose ACTH test in asthmatic patients taking inhaled corticosteroids

Mean serum cortisol responses at 20, 30, and 45 min to stimulation with 0.5 μg/1.73 m² ACTH-(1-24) were significantly lower in patients taking inhaled corticosteroids than in untreated controls (Fig. 1). In 16 of 46 patients (35%, 10 of 30 children and 6 of 16 young adults) peak serum cortisol levels following stimulation with the low dose of ACTH-(1-24) were less than 500 nmol/L (18.1 μg/dL) and, of these, 11 (24%, 7 of 30 children and 4 of 16 young adults) had also an incremental rise in cortisol of <200 nmol/L (7.2 μg/dL). In these 11 patients, a repeat ACTH stimulation test with the standard dose of 250 μg/1.73 m² gave a normal response in all but one case (Fig. 2).

Urinary free cortisol

There was a positive correlation between the peak cortisol response to 0.5 μg ACTH-(1-24) and the 24-h urinary cortisol excretion (r = 0.455, P < 0.002). Furthermore, those patients who failed to pass the low-dose ACTH test had lower 24-h urinary free cortisol concentration [71 ± 10 nmol/m²·24 h (25.7 ± 3.6 μg/m²·24 h)] than the patients who responded normally [118 ± 11 nmol/m²·24 h (42.8 ± 4.0 μg/m²·24 h)] (Fig. 3). No significant correlation was found between the daily dose of inhaled corticosteroids and the peak cortisol
response to low-dose ACTH stimulation or urinary free cortisol excretion.

Discussion

Inhaled corticosteroid therapy is based on the premise that the untoward systemic side effects will be minimized. However, there is still controversy in the literature as to the extent of adrenal suppression. Previous reports demonstrated adequate responsiveness to the standard pharmacological ACTH test in patients taking conventional doses of inhaled corticosteroids (6-8, 14). A poor cortisol response was usually not encountered at corticosteroid doses of less than 1800-2000 μg daily (10-12). In the present study, the use of the low-dose ACTH test has demonstrated reduced adrenal response in approximately one-quarter of patients treated with doses of corticosteroids within the conventional limits. Although 11 of 46 patients showed reduced adrenal reserve in the low-dose ACTH test, all but one case gave normal responses to the standard test (250 μg ACTH-(1-24)/1.73 m²) and in poor responders.

FIG. 3. Twenty-four h urinary free cortisol excretion in patients taking inhaled corticosteroids who reached a serum cortisol peak in excess of 500 nmol/L after injection of 0.5 μg ACTH-(1-24)/1.73 m² and in poor responders.

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References