A Search for Variables Predicting Cortisol Response to Low-Dose Corticotropin Stimulation Following Supraphysiological Doses of Glucocorticoids

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Objectives To determine which biological or clinical variables may predict cortisol response to low-dose adrenocorticotropic hormone (ACTH) stimulation following supraphysiological doses of glucocorticoids in children.

Study design This retrospective study included all patients who underwent ACTH testing (1 μg) between October 2008 and June 2010 at the Sainte-Justine University Hospital Center, Montreal, after supraphysiological doses of glucocorticoids.

Results Data from 103 patients (median age, 8.0 years; range, 0.6-18.5 years; 57 girls) were analyzed, revealing growth deceleration in 37% and excessive weight gain in 33%. Reasons for glucocorticoid treatment included asthma (n = 30) and hematologic (n = 22), dermatologic (n = 19), rheumatologic (n = 16), and miscellaneous (n = 16) disorders. The following information was recorded: duration of glucocorticoid treatment (median, 374 days; range, 5-4226 days); duration of physiological hydrocortisone replacement (median, 118 days; range, 0-1089 days); maximum daily (median, 200 mg/m^2/day; range, 12-3750 mg/m^2/day) and cumulative (median, 16 728 mg/m^2; range, 82-178 209 mg/m^2) doses, in hydrocortisone equivalents; and interval since the last dose (median, 43 days; range, 1-1584 days). Sixty-two patients (58%) exhibited a normal response (ie, peak cortisol >500 nmol/L) to ACTH stimulation. Peak cortisol level was not related to sex, prior morning cortisol level, duration of treatment, or cumulative glucocorticoid dose; 28% of the patients with normal baseline cortisol levels nevertheless demonstrated a subnormal response to ACTH.

Conclusion Given the absence of clinical or biological predictors of the cortisol response to ACTH after suppressive doses of glucocorticoids, physicians have only 2 options: (1) empirically advocate glucocorticoid stress coverage during 18 months after cessation of high-dose glucocorticoid treatment; or (2) perform serial ACTH testing in all such patients until a normal peak cortisol level is attained. *(J Pediatr 2013;163:484-8)*.

Secondary adrenal insufficiency may result from hypothalamopituitary malfunction or from administration of supraphysiological doses of glucocorticoids.[1] Iatrogenic suppression of the hypothalamic-pituitary-adrenal (HPA) axis occurs in 28%-100% of patients even after short-term exposure to glucocorticoids.[2-4] Adrenal insufficiency must be diagnosed and treated even in asymptomatic patients, given the nonspecific symptoms and possibly life-threatening nature of acute adrenal crisis.[5]

In some previous studies, morning cortisol level was reportedly correlated with the response to dynamic testing.[6,7] A baseline cutoff value predicting a normal response remains to be determined, however.[8] Currently, the insulin tolerance test (ITT) is the gold standard for diagnosing adrenocorticotropic hormone (ACTH)/cortisol insufficiency; however, the ITT is potentially dangerous, associated with seizures, hypokalemia, cardiac arrhythmias, and even death.[9] The widely used low-dose ACTH (corticotropin) stimulation test has proven to be as accurate as the high-dose (standard) ACTH test in adults[1,7,10] as well as in children, in whom low dose is defined as either 1 μg[3] regardless of size or 500 ng/m^2.[11] The aim of the present retrospective study was to assess whether pretest biological or clinical variables might predict peak cortisol response to low-dose ACTH stimulation in children and adolescents who had received supraphysiological doses of glucocorticoids.

Methods

This study was approved by the hospital's Head of Medical and Academic Affairs. The charts of 103 patients with suspected iatrogenic suppression of the HPA axis who had received a supraphysiological dose of glucocorticoids and had

ACTH	Adrenocorticotropic hormone
HPA	Hypothalamic-pituitary-adrenal
ITT	Insulin tolerance test

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undergone low-dose ACTH stimulation testing at our center between October 2008 and June 2010 were studied.

The weaning protocol from high-dose steroid therapy was as follows. The corticosteroid dose was decreased by 10%-15% every 3-7 days until the maintenance dose was reached (equivalent to 5-15 mg/m^2/day of hydrocortisone, with 20 mg hydrocortisone corresponding to 5 mg of prednisone and to 0.75 mg of dexamethasone). The decline could be faster or slower depending on the risk of recurrence of the underlying disease. Once the maintenance dose was achieved, the current corticosteroid was changed to hydrocortisone, given once or twice (split dose) daily at the maintenance dose. After 4 weeks, an 8:00 a.m. serum cortisol level was measured, with ACTH testing performed if the value exceeded 200 nmol/L. Otherwise, morning serum cortisol level was remeasured 1 month later.

Clinical variables recorded included age, sex, underlying chronic disease, presence of clinical signs suggesting glucocorticoid excess (ie, excessive weight gain [>1 SD] and deceleration of linear growth [>1 SD]) or hypoadrenalism, duration of treatment, total and maximum doses, duration of physiological hydrocortisone replacement therapy (routinely prescribed after discontinuation of longer-acting glucocorticoids), and timing since the last dose. All glucocorticoid doses were converted to hydrocortisone equivalents except inhaled steroids (physiological replacement dose defined as 5-16 mg/m^2/day).[12] The biological variables were morning serum cortisol level measured before scheduling the test (ie, prior cortisol), baseline cortisol, and peak cortisol on the day of ACTH stimulation.

Low-Dose ACTH Stimulation Test

The patient did not receive his or her scheduled doses of hydrocortisone the night before and the morning of the test. At 8:30 a.m., while on bed rest, the patient was given an intravenous bolus of 1 μg ACTH (Cortrosyn; Amphastar Pharmaceutical, Rancho Cucamonga, California). The Cortrosyn was diluted in 0.9% NaCl to a concentration of 1 μg/mL by our pharmacist, and the diluted ACTH was used within 1 hour of preparation. Blood samples for serum cortisol levels were drawn at 0 and 30 minutes, and measurements were performed by competitive immunoassay (Access; Beckman Coulter, Fullerton, California). Our laboratory's lower limit for an 8:00 a.m. serum cortisol value is 200 nmol/L. Normal peak cortisol level in children is ≥500 nmol/L.[11]

Statistical Analyses

All variables except stimulated peak cortisol were nonnormally distributed (assessed with the Shapiro-Wilk normality test). Data are expressed as median with range. The Wilcoxon signed-rank test with continuity correction was used to compare 2 sets of variables. To test for correlation between stimulated peak cortisol and other variables, univariate and multivariate linear regression analyses and the Spearman rank correlation test were used to assess the robustness of regression against an abnormal distribution of some variables. Differences were considered statistically significant at $P < .05$. Data analysis was performed using R version 2.12.0 (R Project for Statistical Computing, Vienna, Austria)[13] and SPSS version 19 (IBM, Armonk, New York).

Results

Testing was performed in 103 patients (57 girls; 55%), at a median age of 8.0 years (range, 0.6-18.5 years). Three patients required retesting because glucocorticoid treatment was reinstated. Clinical characteristics and response to ACTH for the different subgroups are indicated in **Table I**. Reasons for glucocorticoid treatment included asthma (n = 30) or hematologic (n = 22), dermatologic (n = 19), rheumatologic (n = 16), and miscellaneous (n = 16) disorders. Thirty-eight patients (37%) exhibited growth deceleration, 34 (33%) had excessive weight gain, and 14 had both (7 from the hematology group). Clinical signs of glucocorticoid excess or adrenal insufficiency were uncommon, but 2 patients complained of fatigue. None of the patients with asthma had received long-term oral prednisolone therapy, and none of the patients with a dermatologic disorder (the majority of whom had hemangiomas) had received topical steroids.

Characteristics of glucocorticoid treatment were as follows: median duration of pharmacologic glucocorticoid treatment, 374 days (range, 5-4226 days); median physiological hydrocortisone replacement, 118 days (range, 0-1089 days); median maximum daily and cumulative doses, in hydrocortisone equivalents, 200 mg/m^2/day (range, 12-3750 mg/m^2/day) and 16 728 mg/m^2 (range, 82-178 209 mg/m^2); median interval since last dose, 43 days (range, 1-1584 days). One patient with a hematologic disorder completed HPA axis evaluation only 1584 days after discontinuing glucocorticoid therapy. The patients with dermatologic disorders, mainly those treated for facial hemangiomas (89%), were younger than the rest of the study cohort (median 1.5 years [range, 0.6-14.0 years] vs 9.6 [range, 0.6-18.5 years]; $P < .05$).

Cortisol Response to ACTH

To evaluate whether response to ACTH stimulation can be predicted, we examined the relationship between peak cortisol level and various clinical and biological variables. **Table I** describes prior morning cortisol and cortisol response to the 1 μg ACTH test. The median peak stimulated cortisol level in all diagnosis subgroups was near or greater than 500 nmol/L, but individual responses varied widely.

Prior morning cortisol was correlated with baseline cortisol on the day of testing ($\rho = 0.29$; $P < .05$). Peak stimulated cortisol was not correlated with prior morning cortisol ($\rho = 0.10$, $P = .34$) (**Figure**), but was weakly related to baseline cortisol on the day of testing (adjusted R^2, 0.30; $\rho = 0.43$; $P < .05$). Testing was performed at a median of 72 days (range, 11-321 days) after blood sampling for prior morning cortisol, with intercurrent illnesses explaining the longer delays. The children in the dermatologic subgroup had a significantly higher peak cortisol compared with other subgroups (median peak cortisol, 683 nmol/L [range, 337-902 nmol/L]