Adrenal Insufficiency after Chronic Swallowed Glucocorticoid Therapy for Eosinophilic Esophagitis

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Objective To establish the prevalence of adrenal insufficiency (AI) in children with eosinophilic esophagitis treated with swallowed fluticasone propionate (FP) or budesonide.

Study design Children treated with FP or budesonide for ≥6 months underwent a low-dose adrenocorticotropin stimulation test. Patients using systemic, inhaled, intranasal, or topical glucocorticoids were excluded. The primary outcome is AI, defined as peak serum cortisol <18 μg/dL (≤495 nmol/L).

Results Of 58 patients (81% male), 67% were on FP (median age 13.7 years [range 4.3-19.1], dose 1320 μg/d [440-1760], treatment duration 4.0 years [0.6-13.5]). Thirty-three percent were on budesonide (median age 10.7 years [range 3.2-17.2], dose 1000 μg/d [500-2000], treatment duration 3.4 years [0.6-7.7]). The overall prevalence of abnormal peak cortisol response (≤20 μg/dL) was 15% (95% CI 6%-25%) (indeterminate [18-20 μg/dL] 5% [n = 3] vs AI [<18 μg/dL] 10% [n = 6]). All patients on budesonide had a normal response vs only 77% of patients on FP (*P* = .02), all of whom were taking FP at a dose >440 μg/d.

Conclusions AI was present in 10% of children treated with swallowed glucocorticoids for ≥6 months and was found only in those treated with FP >440 μg/d. We recommend low-dose adrenocorticotropin stimulation testing in children treated long term with high dose FP to allow early detection of AI. *(J Pediatr 2016;170:240-5)*.

Eosinophilic esophagitis (EoE) is a chronic, immune, antigen-mediated esophageal disease that is increasingly recognized over the past decade in both adults and children. It is characterized by swallowing dysfunction and eosinophilic-predominant inflammation.[1,2] Treatment options for EoE include swallowed "topical" glucocorticoids and removal of food antigens that trigger esophagitis.[1]

Swallowed glucocorticoids, most commonly fluticasone propionate (FP) or budesonide, have been demonstrated to be effective for the treatment of EoE although there are no Food and Drug Administration-approved treatments for this indication at present.[3] FP comes as a multidose inhaler that is taken by puffs into the mouth during a breath hold and then swallowed. Budesonide aqueous (nebulizer) solution is mixed with 5 gm sucralose to make a viscous preparation that is then swallowed. Because swallowed glucocorticoids control but does not cure EoE, long-term therapy is required, and recurrence of inflammation is quite common upon discontinuation of therapy.[4] Swallowed glucocorticoids are considered safe, but long-term safety data on linear growth, bone mineral accretion, and adrenal insufficiency (AI) are not available.[1,5]

AI can result from prolonged exposure to exogenous glucocorticoids (systemic, inhaled) and is due to suppression of the hypothalamic-pituitary-adrenal (H-P-A) axis. It is important to diagnose AI correctly because its presentation can be subtle, and failure of sufficient cortisol secretion during periods of acute stress may result in life-threatening adrenal crisis.[6,7]

Various methods are used to diagnose H-P-A axis insufficiency. Insulin-induced hypoglycemia and metyrapone testing are the gold standard tests but requires inpatient stay for close supervision. A single morning cortisol is easy to measure, but it has limited sensitivity. Dynamic tests, such as the standard-dose (250 μg) adrenocorticotropin stimulation test and the low-dose stimulation test (LDST, 1 μg) are, therefore, frequently used. In contrast to the standard-dose stimulation test, the LDST provides better assessment of adrenal response to physiologic stress, and, as such, provides greater assurance that normal endogenous glucocorticoid secretion occurs when a normal cortisol response is found.[8-10] When compared with the gold standard tests, the sensitivity of LDST is 92%-100%.[9,10]

A prior study among patients with EoE reported normal morning serum cortisol in all patients after 2 months of budesonide therapy.[11] In contrast, a recent study reported an AI prevalence of 43% among children using budeso-

ACTH	Adrenocorticotropin hormone
AI	Adrenal insufficiency
BMI	Body mass index
EoE	Eosinophilic esophagitis
FP	Fluticasone propionate
H-P-A	Hypothalamic-pituitary-adrenal
LDST	Low-dose stimulation test

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nide, screened using LDST.[12] These studies were limited by small study population, use of morning serum cortisol level,[11] and inclusion of subjects concurrently taking inhaled glucocorticoids.[12] To date, there is no large prospective study that includes both FP- and budesonide-treated children.

Our study aims to establish the prevalence of AI among children treated with long-term swallowed FP or budesonide for EoE, using LDST, and to provide information on recovery from AI from subsequent clinical follow-up of patients.

Methods

We prospectively recruited patients aged 2-20 years from the Cincinnati Center for Eosinophilic Disorders clinics between January and September 2014. We included patients with EoE treated with swallowed FP or budesonide who had been on a stable treatment regimen for at least 6 months prior to enrollment. We excluded patients with: (1) prior diagnosis of AI; (2) any systemic or inhaled glucocorticoids use over the past 6 months; and (3) intranasal glucocorticoid use for >2 consecutive weeks or transdermal glucocorticoid use for >3 consecutive weeks over the past 3 months. Glucocorticoid therapy history was obtained by review of clinical records; and current glucocorticoid regimen was confirmed with the parents upon recruitment. Pathology reports from esophageal biopsies obtained within 1 year of the study visit were reviewed. Active EoE was defined as >15 eosinophils per high power field. The study protocol was approved by the Institutional Review Board at Cincinnati Children's Hospital Medical Center. Informed consent was obtained from all parents and assent from children >8 years old.

Low-Dose Adrenocorticotropin Hormone Stimulation Test

Patients had one study visit at the Clinical Translational Research Center. The patients did not take their dose of either FP or budesonide on the morning of the study visit. The protocol was carried out by research nurses. The synthetic adrenocorticotropin hormone (ACTH) solution (Cortrosyn; Amphastar Pharmaceutical Inc, Rancho Cucamonga, California) was prepared fresh for each test day. A vial of Cortrosyn 250 μg was reconstituted to a 250 mL bag of normal saline to provide 1 μg:1 mL. One μg of Cortrosyn was given over 2 minutes as an intravenous push directly into the saline lock. One mL of blood was drawn at baseline, and 3 mL was drawn at 20 minutes (2 mL waste, 1 mL for serum cortisol) after ACTH administration. Serum cortisol was measured by competitive immunoenzymatic assay (Access; Beckman Coulter, Fullerton, California), in which samples can be measured within the analytic range of the lower limit of detection and the highest calibrator value (0.4-60 μg/dL; 11-1655 nmol/L) (coefficient of variation of <7%).

Outcome Analysis

Adrenal function was determined by the peak cortisol response (at 20 minutes after ACTH administration). Adrenal function was categorized as normal if peak cortisol was >20 μg/dL (>550 nmol/L), or abnormal if peak cortisol was ≤20 μg/dL (≤550 nmol/L). Abnormal responses were further categorized as indeterminate if peak cortisol was 18-20 μg/dL (496-550 nmol/L) or AI if peak cortisol was <18 μg/dL (≤495 nmol/L). Based on daily glucocorticoid dose over the past 6 months, the patients' glucocorticoid regimen was categorized into the following (dosage) groups: FP 1 (≤440 μg/d), FP 2 (441-880 μg/d), FP 3 (≥881 μg/d), budesonide 1 (≤1000 μg/d), and budesonide 2 (>1000 μg/d).

Data were exported from REDCap (Research Electronic Data Capture hosted at University of Cincinnati, Cincinnati, Ohio) and analyzed using SAS v 9.3 (SAS Institute, Cary, North Carolina). Body mass index (BMI) z-scores and height-for-age z-scores were calculated using the SAS program developed by the Centers for Disease Control and Prevention based on the year 2000 growth standards.[13,14] Two cortisol values were reported as below the limit of detection; therefore, the values used for analysis purposes were the limit of detection value divided by the square root of 2.[15] Because of the sample sizes and the distribution of the variables, continuous variables were presented as medians. Nonparametric Wilcoxon rank sum test and exact Wilcoxon test were used to compare characteristics between groups. For categorical data, Fisher exact tests were used for comparisons. Statistical significance was set a priori at $\alpha = 0.05$.

Clinical Follow-Up

Patients with abnormal cortisol responses were notified to provide timely clinical care. Patients who were followed in our institution were scheduled for immediate clinical evaluation. The patient and caregivers were educated about glucocorticoid stress dosing. Assessment of adrenal function was recommended every 3-4 months. In selected patients, serum ACTH, and random urine fluticasone 17-β carboxylic acid concentration were obtained (Mayo Medical Laboratories, Rochester, Minnesota).

Results

There were 58 study participants; 47 were male (81%), 53 were non-Hispanic Caucasian (91%), with a median age of 12.9 years (range 3.2-19.1). The median BMI z-score and height-for-age z-score were 0.17 (range −2.8 to 2.4) and −0.22 (range −3.5 to 2.0), respectively. The median age of EoE diagnosis was 6.0 years (range 1.2-18.1), and duration of glucocorticoid therapy was 3.7 years (range 0.6-13.5). Sixty-five percent reported use of proton-pump inhibitors. Baseline characteristics for both FP and budesonide groups are presented in **Table I**. The budesonide group was significantly younger ($P = .02$) with a lower body surface area ($P = .01$).

The overall prevalence of abnormal peak cortisol response was 15% (95% CI 6%-25%) (indeterminate was 5% [n = 3], AI was 10% [n = 6]). Abnormal compared with normal adrenal function significantly differed by treatment type: