

Adrenal Suppression in Children Treated With Oral Viscous Budesonide for Eosinophilic Esophagitis

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See “Adrenal Suppression in EoE Treated With Budesonide” by LeLeiko and Quintos on page 155.

ABSTRACT

We sought to determine the prevalence of adrenal suppression (AS) in children with eosinophilic esophagitis treated with oral viscous budesonide (OVB). This was a retrospective review of a quality assurance initiative, whereby all children in our center treated with OVB for ≥ 3 months were referred over an 18-month time frame for endocrine assessment including 1 μg adrenocorticotropic hormone stimulation test. Fourteen of 19 children complied with the referral; of these 14 children, 6 (43%) had suboptimal stimulated cortisol (range 343–497 nmol/L, mean $[\pm\text{SD}]$ 424.7 nmol/L $[\pm 52.4]$, normal ≥ 500 nmol/L). There was no significant association to treatment duration, dose, or concomitant use of inhaled/nasal corticosteroids. This study suggests that children treated with OVB may be at risk for AS.

Key Words: adrenal suppression, budesonide, eosinophilic esophagitis

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Eosinophilic esophagitis (EoE) is a chronic, immune/antigen-mediated, esophageal disease (1). It has emerged during the last decade as a major cause of gastrointestinal morbidity. The prevalence of EoE in children varies by geographic region, with reported rates reaching 43 per 100,000 children in the United States (2). Clinical manifestations are nonspecific and vary by age, with the most significant complication being esophageal stricture formation (3,4). EoE in children is often present in association with other atopic manifestations, such as asthma, eczema, rhinitis, and food/environmental allergies (4,5).

Topical corticosteroids (CS) are one of the major treatment options for EoE and are considered first-line agents in many cases (6). Before 2005, fluticasone was primarily used. Since then, oral viscous budesonide (OVB) has also been shown to be highly effective (7–9). Moreover, there is some evidence that OVB can

What Is Known

- Topical corticosteroids, including oral viscous budesonide, are one of the major treatment options for eosinophilic esophagitis.
- Oral viscous budesonide is considered to have a favorable safety profile because of high hepatic inactivation.
- Safety data regarding the risk of adrenal suppression, a life-threatening complication of corticosteroid therapy, are lacking for oral viscous budesonide treatment.

What Is New

- In this pilot study, 43% of our cohort demonstrated biochemical evidence of adrenal suppression, implying that systemic exposure of oral viscous budesonide may be higher than previously recognized.
- Clinicians should be aware of the risk for adrenal suppression when managing these children, especially in times of severe illness or stress.

reverse esophageal fibrosis (10). In regard to its safety profile, budesonide is considered a nonsystemic CS because of its high hepatic metabolism via cytochrome P450 3A (CYP3A) to inactive metabolites, resulting in an approximately 10% systemic bioavailability (11,12). Therefore, it is perceived to have a favorable safety profile. Recent literature on adults, however, indicates that active EoE may be associated with reduced elimination of budesonide by CYP3A in the liver, suggesting that there may be higher systemic exposure than anticipated (13).

One of the concerns with systemic absorption of CS is the risk of adrenal suppression (AS). This is a proven, yet underrecognized, complication of most forms of CS therapy (14,15). CS-induced AS can be asymptomatic or present with nonspecific symptoms until exposure to stress precipitates an adrenal crisis, resulting from the acquired inability to acutely increase cortisol production. Possible stressors include infection, trauma, surgery, and procedures requiring anesthesia such as endoscopy, the latter frequently occurring in this population. Unrecognized AS in an individual subjected to stress can lead to an adrenal crisis, characterized by hypotension, hypoglycemia, seizures, coma, and death (16).

Other formulations of budesonide are used in children for different indications, mainly asthma, allergic rhinitis, and small bowel Crohn disease. In asthma, high daily doses of inhaled budesonide (>1 – 1.5 mg) have been shown to result in biochemical AS in up to 46% of children (17,18), and practice guidelines exist for screening and monitoring for AS in patients using inhaled CS

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(19). Because OVB is a relatively new medication, safety data regarding AS in EoE are limited to 2 small studies, which both showed no effect on first morning cortisol following OVB treatment (8,9). There are presently no guidelines for screening these patients for AS.

The rationale for this study was the incidental identification of asymptomatic AS in 2 children with EoE on OVB at our center in 2010. Both children were referred solely because of longstanding (>3 months) treatment with OVB. The primary aim was to describe the prevalence of AS in children with EoE, who are treated with OVB for ≥ 3 months duration. Our secondary aim was to explore risk factors for AS in this population.

METHODS

The study was performed at British Columbia Children's Hospital (BCCH), a tertiary care center that is a pediatric referral center for all of British Columbia. We retrospectively reviewed a quality assurance (QA) initiative that took place between June 1, 2012, and November 30, 2013. The EoE clinic at the time included a total of 80 patients, of which 19 were treated with OVB, 12 with fluticasone/another inhaled CS, 23 with dietary therapy, 18 with proton pump inhibitors and 8 with no treatment. Consensus was reached between key stakeholders in the EoE clinic and the endocrinology division that, as a part of a QA initiative, all of the children who were being treated with a stable dose of OVB for ≥ 3 months should be referred for assessment of AS. As part of the initiative, relevant patients were identified, and during routine follow-up care, the gastroenterology physician discussed the potential risk of AS, using a specific handout (20), and referred to endocrinology. The endocrine assessment included a clinic consult and a 1- μ g adrenocorticotrophic hormone (ACTH) test, which is considered the test of choice for diagnosis of secondary AS in children (21,22). This test involves the intravenous administration of 1 μ g of ACTH followed by the measurement of serum cortisol levels at baseline, 20 and 30 minutes to assess the function of the hypothalamic-pituitary-adrenal axis. To diagnose AS, we used the commonly accepted cutoff value of <500 nmol/L as employed in most studies, with both a sensitivity and specificity of approximately 90% (22–24). Cortisol levels were performed at the BCCH laboratory and measured by chemiluminescent immunoassay (Beckman Coulter Access 2 System, Fullerton, CA).

Following the QA initiative, we reviewed the charts for the following parameters from the endocrine consult: demographic and anthropometric data, medical problems, and medication history, including use of topical and systemic CS, as well as for nonspecific symptoms suggestive of AS (eg, fatigue, orthostatic complaints, and prolonged recovery time from illnesses/procedures). We documented endoscopic and histological findings, if available within 3 months of the ACTH test. Active EoE was defined by the presence of ≥ 15 eosinophils/high power field at any esophageal biopsy site (1). We recorded the results of the ACTH test, treatment for AS, and clinical follow-up.

This retrospective chart review was approved by the Children's and Women's Hospital Research Review Committee and the University of British Columbia Clinical Research Ethics Boards.

Statistical Analysis

The prevalence of children with EoE who have AS was estimated by calculating the proportion of patients with an abnormal ACTH stimulation test over the total number of study participants. Descriptive data were reported as mean and 95% confidence intervals for continuous variables, and as frequencies and percentages for categorical variables. Data were compared across patient

groups (with and without AS) using the χ^2 and Fisher exact tests for categorical variables, and the Kruskal-Wallis test for continuous variables. All of the analyses were performed on SPSS version 21 (IBM Corp, NY). A *P* value of <0.05 was considered statistically significant.

RESULTS

All of the 19 children in our center treated with OVB were referred to endocrinology between June 1, 2012, and November 30, 2013. Of them, 14 were clinically assessed by an endocrinologist and underwent an ACTH stimulation test. The remaining 5 were not evaluated, because of scheduling difficulties, refusal to undergo testing, or needle phobia. Of those 14 patients, 13 were boys and 1 was a girl, mean age was 10.6 years (age range 3–17 years), dose of OVB ranged from 0.5 to 2 mg/day, and the mean duration of treatment was 19 months (range 4–52 months). Ten patients had comorbid allergic conditions. Four patients reported chronic fatigue. Five patients received inhaled CS, with treatment duration >3 months in all of the cases. None received systemic CS or any medications known to interfere with the elimination of budesonide through CYP3A metabolism in the 3 months before testing (eg, fluconazole, cyclosporine, or antiretroviral drugs).

Of the 14 patients, 6 (43%) had suboptimal stimulated cortisol (range 343–497 nmol/L, mean [$\pm$ SD] 424.7 nmol/L [$\pm$ 52.4], normal ≥ 500 nmol/L), consistent with AS (Tables 1 and 2). We found no significant association between suboptimal cortisol and fatigue, OVB dose (mg/kg or mg/body surface area [BSA]), frequency of OVB per day (daily versus twice a day dosing), duration of treatment or use of concomitant topical CS (Table 3).

All of the children (and their caregivers) identified as having suboptimal cortisol responses to ACTH, with the exception of an individual with a borderline cortisol of 497 nmol/L, received education about AS from an endocrine nurse clinician, and were prescribed treatment with hydrocortisone, 30 to 50 mg $\cdot$ m $^{-2}$ $\cdot$ day $^{-1}$, to be taken in the event of severe illness and for procedures involving anesthesia, including endoscopies. No adverse events, in terms of adrenal crisis, had been seen to date with the patients who were found to have suboptimal stimulated cortisol. In 2 cases, despite histological remission, parents requested to discontinue

TABLE 1. ACTH test results of all of the patients (N = 14)

Patient no.	Cortisol (nmol/L)		
	Baseline	20 min	30 min
1	85	310	343
2	109	364	403
3	80	411	432
4	125	379	497
5	148	441	459
6	218	362	414
7	234	594	653
8	201	523	558
9	316	627	671
10	343	532	568
11	93	407	520
12	184	556	538
13	459	610	647
14	280	733	838

Normal response defined as cortisol level ≥ 500 nmol/L at 20 or 30 minutes. Patients with suboptimal response are marked in bold. ACTH = adrenocorticotrophic hormone.

TABLE 2. Characteristics of patients with suboptimal stimulated cortisol (N = 6)

No.	Age, y	OVB duration, mo	OVB dose	Total OVB to BSA ratio, mg/m ²	Other topical CS	Fatigue	Peak cortisol, nmol/L
1	13.8	20	1 mg twice daily	1.55	—	—	343
2	14.1	24	0.5 mg once daily	0.31	Yes*	Yes	403
3	14.2	4	0.5 mg twice daily	0.58	—	—	432
4	3.7	10	0.5 mg twice daily	1.54	—	—	497
5	14.6	17.5	1 mg twice daily	1.42	Yes†	Yes	459
6	9.6	22	0.5 mg twice daily	1.08	Yes‡	—	414

BSA = body surface area; CS = corticosteroid; OVB = oral viscous budesonide.

* Mometasone furoate/formoterol inhaler 100 µg, 2 puffs twice daily; fluticasone furoate nasal spray 27.5 µg twice daily.

† Budesonide/formoterol inhaler 200 µg, 2 inhalations twice daily.

‡ Mometasone furoate inhaler 200 µg, 1 inhalation once daily; hydrocortisone 2.5% cream, used diffusely daily.

OVB treatment following suboptimal ACTH stimulation test results and went on to try dietary elimination therapy. ACTH stimulation test, repeated after discontinuing OVB for 6 months (patient number 1) and for 2 months (patient number 2), revealed that stimulated cortisol levels had improved but were still suboptimal (498 and 441 nmol/L, respectively).

DISCUSSION

This is the first study to demonstrate that children with EoE, treated with maintenance OVB at standard recommended doses (1), may develop AS, a potentially serious and life-threatening condition. Notably, almost half (43%) of our cohort was documented to have a suboptimal stimulated cortisol level following 4 to 24 months of OVB treatment. These data would suggest that systemic exposure of OVB is higher than previously recognized in some individuals and emphasizes the need for clinicians to be aware of the risk for AS when managing these children during illness and before procedures requiring anesthesia.

It is important to consider that the frequency of AS may not be solely attributable to OVB treatment but may also be related to other parameters, such as the use of additional CS (ie, topical, nasal and inhaled) in this atopic population. The combination of OVB with other CS may cause a cumulative systemic effect related to absorption of several different CS. Notably, there were 2 patients treated with OVB for a long duration (20 and 24 months, respectively) who continued to have a suboptimal cortisol response several months after stopping OVB (6 and 2 months, respectively).

Although recovery from AS may take up to 12 months following prolonged CS treatment (25), there may be other, as yet undefined, predisposing factors inherent in a subgroup of patients with EoE that lead to a prolonged suboptimal response to ACTH.

Another previously studied parameter (13) is EoE histological activity level, with active EoE shown to result in decreased elimination of budesonide by CYP3A enzymes, relative to healthy controls. This may be related to high disease activity but also possibly to inherently altered CYP3A function in the EoE population. Our pilot study does not support the former concept, with normal cortisol levels found more often in patients with active inflammation than in histological remission. The sample size, however, is inadequate to be conclusive about associated risk factors for AS in this population.

Another point to emphasize is that the lack of clinical events of AS in our patients does not undermine the fact that these patients are at risk. The same cortisol level cutoff for diagnosing AS is supported in guidelines for patients with asthma using inhaled CS (19).

A major strength of our study is the use of the highly sensitive and specific 1-µg ACTH stimulation test as a diagnostic tool, in contrast to previous studies (8,9) that used an early morning cortisol level as their end point. An early morning (08:00 AM) cortisol measurement is often more practical and is used for screening, but the sensitivity is quite poor (~60%) when a low cutoff value is used (26).

This study should be interpreted within the context of its limitations. First, because of the retrospective cross-sectional design, we could not perform ACTH tests before and after starting

TABLE 3. Analysis of potential risk factors for suboptimal stimulated cortisol

Variable	Cortisol <500 nmol/L (N = 6)	Cortisol ≥500 nmol/L (N = 8)
Age, y, mean (SD)	11.7 (4.3)	9.9 (3.5)
Fatigue, n (%)	2 (33.3)	2 (25.0)
Other topical CS, n (%)	3 (50.0)	2 (25.0)
OVB duration, mo, mean (SD)	16.3 (7.7)	21.2 (17.5)
OVB dose to weight, mg/kg, mean (SD)	0.038 (0.02)	0.044 (0.03)
OVB dose to BSA, mg/m ² , mean (SD)	1.1 (0.5)	1.2 (0.8)
OVB frequency, n (%)		
Once daily	1 (16.7)	3 (37.5)
Twice daily	5 (83.3)	5 (62.5)
Histological evidence of active inflammation (>15 eos/hpf), n (%)*	1/3 (33)	4/7 (57)

No significant association found. Chi-square and Fisher exact tests were used to compare categorical variables, and Kruskal-Wallis test for continuous variables. BSA = body surface area; CS = corticosteroid; hpf = high power field; OVB = oral viscous budesonide.

* Partial sample; histological data were included only if available within 3 months of ACTH test.

treatment with OVB nor directly assess adherence. Second, the sample size was small; however, this is related to the frequency of EoE in the population and to the fact that OVB is not the only treatment modality. Future studies should focus on improving on the shortcomings highlighted above and also study whether AS is found in EoE patients taking swallowed fluticasone, another frequently prescribed topical CS.

In conclusion, this pilot study suggests that some children with EoE treated with OVB for ≥ 3 months duration may be at risk for AS. These data highlight the need for clinicians to have a low threshold for assessment of AS and for providing stress dosing for severe intercurrent illness and anesthesia related to endoscopies or other procedures in these patients. Further research is needed to confirm these findings and to understand which children are at risk for this complication. A multicenter study design is likely required to obtain a sufficient sample size to answer these important research questions.

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