

Budesonide-Related Iatrogenic Cushing's Syndrome in Microscopic Colitis

Kartikeya Tripathi, MD¹, and Thomas Dunzendorfer, MD²

¹Department of Gastroenterology and Hepatology, Johns Hopkins Medical Institutions, Baltimore, MD

²Department of Gastroenterology, Berkshire Medical Center, Pittsfield, MA

ABSTRACT

Budesonide is the treatment of choice for microscopic colitis because of its excellent risk to benefit ratio. It is a potent, well-absorbed corticosteroid, but because of a high rate of first-pass metabolism in the liver, its systemic bioavailability is low. It has fewer corticosteroid-related adverse effects than prednisone, and adrenal suppression is considered to be rare. We present a middle-aged woman with lymphocytic colitis whose symptoms responded to budesonide but developed budesonide-related iatrogenic Cushing's syndrome. Withdrawal of budesonide led to restoration of normal pituitary-adrenal responsiveness but at the price of recurrent diarrhea due to re-emergence of lymphocytic colitis.

INTRODUCTION

Suppression of the hypothalamic-pituitary-adrenal axis by budesonide is mentioned as a possible complication in the package insert, and it has been described in case reports. All reported cases, however, had budesonide combined with other drugs that affect the hepatic cytochrome P450 system.^{1,2} The only systematic study on potential suppression of the hypothalamic pituitary adrenal axis in patients treated with budesonide was published only in abstract form.³ Lichtenstein et al. found that the mean morning cortisol levels at baseline and at 12 months of treatment were no different between patients treated with placebo versus budesonide.³ Adrenocorticotropic hormone (ACTH) stimulation tests at 12 months were abnormal in 30% of budesonide-treated patients but also in 18% of placebo patients. Of note, there was no difference in potential glucocorticoid side effects in these patients.

CASE REPORT

A 57-year-old woman presented in 2007 with a multiple-year history of severe intermittent diarrhea with fecal incontinence. Initial laboratory evaluation for infectious, inflammatory, and malabsorptive conditions was negative. Colonoscopy with mucosal biopsy was performed, leading to a diagnosis of lymphocytic colitis.

A treatment attempt with standard-dose mesalamine was unsuccessful, but treatment with budesonide restored her digestive health. She was maintained on 9 mg daily, but efforts to lower the dose were unsuccessful. In 2010 she underwent a laparoscopic adjustable gastric band placement and lost approximately 13.5 kg in weight. In 2013 she started gaining weight, noticed easy bruising of her forearms, and developed muscle cramps, lightheadedness, and fatigue. In September 2014 it was thought that she might have iatrogenic Cushing's syndrome, and budesonide was decreased to 3 mg daily. This resulted in prompt recurrence of 30-40 Bristol type 6-7 stool evacuations per week with several episodes of extreme urgency and fecal incontinence.

In 2015, her medications were 3 mg budesonide daily, cyclobenzaprine and hydrocodone for back pain, and fluoxetine for depression. Her family history was negative. She had a body mass index of 33 kg/m², several small ecchymoses on her forearms, and a suggestion of a "buffalo hump." Physical examination was otherwise unremarkable.

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Correspondence: Thomas Dunzendorfer, Berkshire Gastroenterology, 24 Charles St, Pittsfield, MA 01201 (tdunzendorfer@berkshireregastro.com).



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A colonoscopy in 2007 showed typical histologic findings of lymphocytic colitis. A second colonoscopy in 2012, while she was asymptomatic and maintained on 9 mg budesonide, revealed normal random mucosal biopsies. Celiac disease serology was negative. In September 2014 she had normal complete blood count, chemistry, and thyroid and liver function tests. Endocrine testing after budesonide had been decreased to 3 mg daily revealed that her pituitary ACTH and adrenal cortisol secretion were suppressed. Her morning cortisol, ACTH, and 24-hour urinary cortisol were undetectable.

We stopped budesonide and treated symptomatically with cholestyramine and loperamide with reasonably good symptomatic improvement, although the patient continued to have more than 3 Bristol type 5-7 stools per day. Initially she complained of fatigue and malaise but developed no symptoms of adrenal crisis. In November 2014, 2 months after budesonide had been stopped, she felt "like a new person." Her body mass index had decreased to 30 kg/m², she had no further ecchymoses or petechiae, and the buffalo hump had disappeared. Endocrine testing showed early recovery of the pituitary-adrenal axis. Morning cortisol was 7 µg/dL and ACTH was 9.3 pg/mL. In January 2015 an ACTH stimulation test revealed that her adrenal responsiveness had recovered. Her morning cortisol was 6 µg/dL and rose after ACTH stimulation to 20 µg/dL (normal >20 µg/dL).

In March 2015, 6 months after budesonide had been stopped, her diarrhea recurred despite continued cholestyramine and loperamide. She had at least 7 Bristol type 6-7 stools per day with rectal urgency and occasional fecal incontinence. She reported that she felt better overall than when she had normal bowel habits on budesonide. We tried adding balsalazide and other mesalamine products as well as Pepto-Bismol without benefit. Immunosuppressants and antibiotics, specifically rifaximin, were considered; upon hearing about the potential side effects, however, she declined. Repeat colonoscopy showed acute and chronic inflammatory cells within the lamina propria, mucus depletion, and nuclear irregularity, diagnostic of lymphocytic colitis.

At her last encounter in February 2016, she remained on cholestyramine monotherapy and generally had 4-5 Bristol type 5 stools per day, although, at least once weekly she had watery stool with rectal urgency. Despite this, she continued to feel better overall when compared to the time on budesonide.

DISCUSSION

Our case demonstrates the natural history of lymphocytic colitis. A middle-aged woman had a long history of unexplained watery diarrhea that was eventually diagnosed with

colonoscopic mucosal biopsy. Her symptoms resolved and mucosal healing was documented with budesonide, but, as is commonly the case, dose reduction resulted in recurrent symptoms requiring maintenance treatment.⁴ In this situation, the management became difficult because of the lack of an equivalent alternative.

An American Gastroenterological Association Institute guideline on microscopic colitis, published in 2016, states that in symptomatic patients for whom budesonide therapy is not feasible, treatment with mesalamine, bismuth salicylate, or prednisolone is recommended to induce clinical remission.⁵ It recommends against a combination of cholestyramine with mesalamine, although there was only low-quality evidence for that latter recommendation. Other options include immunosuppressants⁶ and tumor necrosis factor antibodies,^{7,8} but they have not been studied extensively.

While treatment with budesonide was apparently well tolerated for several years, eventually the patient developed signs and symptoms of iatrogenic Cushing's syndrome. Iatrogenic Cushing's syndrome is not expected with budesonide because a "first pass effect" removes the drug from the circulation. Budesonide has the potential to reduce the response of the hypothalamus-pituitary-adrenal axis to stress, albeit to a lesser extent than conventional glucocorticoids.^{9,10} Theoretically, cytochrome P450 inhibition by fluoxetine could affect budesonide activity, but this has not been demonstrated to be of clinical importance.¹¹

Our patient had developed classic iatrogenic Cushing's syndrome with adrenal unresponsiveness to endogenous ACTH, and this put her at risk for adrenal crisis in case of significant stress. Generally, patients treated with glucocorticoids rarely present with adrenal crisis, although sudden withdrawal of glucocorticoids can result in exacerbation of the disorder for which they were given the medication (e.g., inflammatory disease, etc.), symptoms of glucocorticoid deficiency, or hypotension. As a result, one has to remain alert that glucocorticoid "stress coverage" may be required in patients taking budesonide who undergo surgery or other stress situations. Likewise, budesonide removal may result in signs and symptoms of adrenal insufficiency and a tapered withdrawal is advisable.

DISCLOSURES

Author contributions: Both authors contributed equally to the creation of the manuscript. T. Dunsendorfer is the article guarantor.

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