Severe Adrenal Insufficiency Complicating Budesonide Therapy for Crohn's Disease

To the Editor:

Budesonide is effective for the short-term treatment of Crohn's disease.[1] Several studies have shown some benefits of budesonide as maintenance therapy of Crohn's disease (CD) by lowering Crohn's Disease Activity Index (CDAI) scores and increasing time to relapse.[2–7] Budesonide has also been studied as a maintenance therapy for CD during pregnancy.[8] As a topical steroid with rapid inactivation by the liver, budesonide minimizes systemic corticosteroid adverse effects, including suppression of the hypothalamic–pituitary–adrenal (HPA) axis. We describe a rare case of severe adrenal insufficiency complicating budesonide maintenance therapy for CD and emphasize the importance of its prompt recognition and treatment.

A 68-year-old male with a history of total proctocolectomy and ileostomy for intractable CD was placed on budesonide 9 mg per day plus infliximab for hemorrhagic ileal recurrence. After 2 months his budesonide dose was reduced to 6 mg per day and continued as maintenance therapy for the following 3 years. The patient then complained of extreme fatigue, ileostomy diarrhea, anorexia, and a 40-pound weight loss over a few months duration. His fatigue became progressive and severe and was associated with marked hypotension and renal insufficiency, prompting admission. Other medications included digoxin, warfarin, and citalopram. The past history was significant for aortic valve replacement. Physical examination revealed signs of hypovolemic shock with a blood pressure of 65/40 supine and postural hypotension of 50 systolic sitting. There was reduced tissue turgor and collapsed central veins. An abdominal examination was benign. An ileostomy was draining watery effluent, which was negative for occult blood. There was no stomal stricture palpated. Laboratory evaluation showed a normal blood count, sedimentation rate, C-reactive protein, and albumin. His BUN was elevated to 42 mg/dL, and creatinine 2.4 mg/dL (baseline 1.0 mg/dL). Sodium was 130 mEq/dL, potassium 5.1 mEq/dL, chloride 116 mEq/dL, and bicarbonate 20 mEq/dL. Thyroid function tests were normal. Blood pressure improved to 100 mm systolic with vigorous saline hydration, but remained below his baseline blood pressure. A morning cortisol was low at 1.0 μg/dL (normal 3–23 μg/dL). Similarly, evening cortisol level was low at 1.1 μg/dL. Adrenocorticotrophin hormone (ACTH) level was low at 3 pg/mL (normal 9–52 pg/mL). An ACTH stimulation test after receiving a dose of 250 μg of ACTH revealed a subnormal response with a cortisol level of 6.2 μg/dL at 30 minutes (normal >18 μg/dL). His cortisol level at 70 minutes was normal at 39 μg/dL. The low baseline cortisol level, followed by an early sluggish but ultimately normal response to ACTH stimulation, is typical of suppression of the HPA axis by chronic exogenous glucocorticoids. Thus, a diagnosis of adrenal insufficiency secondary to chronic budesonide therapy was made. Budesonide was discontinued. He was treated with replacement doses of hydrocortisone. This improved his blood pressure and postural hypotension. His renal function returned to baseline. His ileostomy diarrhea also returned to baseline. He regained his appetite and weight. His fatigue resolved and sense of well-being returned to normal. In order to exclude primary adrenal insufficiency (Addison's disease), his ACTH level was measured after holding several doses of hydrocortisone. His ACTH level remained low at 5 pg/mL. Since patients with Addison's disease would have elevated ACTH levels, this confirmed secondary adrenal insufficiency related to chronic budesonide therapy. Over the next several months his replacement dose of hydrocortisone was gradually tapered and discontinued.

Adrenal failure to the extent we described is rare after oral budesonide. Lichtenstein et al[7] noted two patients with adrenal insufficiency after oral budesonide: one after 12 months of 6 mg per day maintenance therapy, and another with corticosteroid withdrawal symptoms after 2 months of 9 mg per day. In contrast, acute adrenal crisis has been well described following inhaled topical corticosteroids for asthma, and to a lesser extent, allergic rhinitis.[9,10] The risk is greater for fluticasone, less with beclomethasone, and least with budesonide. This relates to the greater potency and longer half-life of fluticasone (14.4 hours) in comparison with budesonide (2.3 hours).

The effect of oral budesonide on the HPA axis has been studied. After 8 weeks of oral budesonide 9 mg per day, basal cortisol levels and response to ACTH was reduced compared to placebo in 69% and 50% of patients, respectively.[1] This, however, was not associated with clinically important symptoms. The effect of budesonide on the HPA axis was also studied after longer-term use of lower doses, 6 mg per day, used as maintenance therapy, either after 3 months or 1 year of treatment.[2–7] Adrenal function as assessed by basal cortisol levels and response to ACTH was reduced in three of five maintenance therapy trials.[2–7] Although adrenal function was depressed compared to placebo in some of these trials, the majority of patients had values within normal ranges and did not have any clinically relevant consequences. However, the potential for adrenal dysfunction was underscored in a review of 11 studies of budesonide for maintenance of remission in CD, in which abnormal ACTH stimulation tests were nearly three times more frequent in the budesonide-treated group.[6] Because of changes in adrenal function as noted, it is

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recommended to provide ''stress'' corticosteroid coverage for patients on budesonide who require surgery.

The systemic effect of chronic oral budesonide in our patient was able to suppress the HPA axis, but was not sufficient enough to provide adequate physiological cortisol replacement. Our patient did not have an acute stressor that precipitated his acute adrenal failure. Our patient was not on any medication known to significantly interact with budesonide, affect corticosteroid synthesis, or predispose to adrenal dysfunction (other than budesonide itself). Medications that inhibit cytochrome P450 (CYP) 3A4 delay the breakdown of budesonide and thereby increase the potential for HPA axis suppression. Our patient was on citalopram, but this medication has a negligible inhibitory effect on CYP 3A4. Our patient did not consume grapefruit juice, a known inhibitor of CYP 3A4. Since there is marked interindividual variability of CYP 3A4, it is possible that our patient had low expression and activity of CYP 3A4, leading to genetically slow clearance of budesonide, and greater vulnerability to HPA axis suppression.

Although a review of 11 studies on budesonide for maintenance of remission in CD found slight improvement in CDAI scores and increased time to relapse, the authors did not recommend budesonide for maintenance therapy of CD, since these benefits were offset by higher treatment related adverse events and more frequent adrenocorticoid suppression.[6]

In summary, we describe a rare case of severe adrenal insufficiency complicating budesonide maintenance therapy for CD. Gastroenterologists should be aware of this potential consequence of budesonide therapy, particularly when used for long-term maintenance. Prompt recognition and treatment are required to correct symptoms and prevent progression to life-threatening complications of acute adrenal failure.

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