CASE REPORT

Budesonide-related adrenal insufficiency

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SUMMARY

Iatrogenic adrenal insufficiency is a potential harmful side effect of treatment with corticosteroids. It manifests itself when an insufficient cortisol response to biological stress leads to an Addisonian crisis: a life-threatening situation. We describe a case of a patient who developed an Addisonian crisis after inappropriate discontinuation of budesonide (a topical steroid used in Crohn's disease) treatment. Iatrogenic adrenal insufficiency due to budesonide use has been rarely reported. Prescribers should be aware of the resulting risk for an Addisonian crisis.

BACKGROUND

Iatrogenic adrenal insufficiency based on budesonide use has been rarely reported. In the current literature, few publications describe the possible side effects, and only one similar case is discussed.

CASE PRESENTATION

A 63-year-old patient with a medical history of hypertension, Crohn's disease and myocardial infarction, presented with extreme fatigue and anorexia. He had used oral budesonide capsules 6 mg/day for nearly 3 years. Two months earlier, his gastroenterologist had increased the patient's maintenance dose of budesonide to 9 mg in order to treat an exacerbation of his Crohn's disease. After remission of the symptoms, this medication was discontinued without further tapering.

Six days before admission to our department, the patient had undergone successful emergency angioplasty for a myocardial infarction. Subsequently, he had a type 1 allergic reaction to an intravenous contrast agent. After successful prednisolone treatment, he was discharged, his energy levels had increased and he generally felt better.

At presentation to our emergency department, he reported rapidly progressive weakness and pain in the whole body, especially the limbs. He also reported watery diarrhoea and near-collapse on standing up.

INVESTIGATIONS

Physical examination showed a moderately ill man with a Cushingoid habitus. His blood pressure was 114/70 mm Hg lying, and 94/70 mm Hg standing. Blood pressure measurements had earlier been 150/90 mm Hg. Pulse rate was 80 bpm and temperature was 38.7°C. Blood chemistry included sodium 136 mmol/L, potassium 3.6 mmol/L, creatinine 85 µmol/L and glucose 8.2 mmol/L. The cortisol level was 0.086 mmol/L (reference range 0.15–0.70 mmol/L). He was admitted and hydrocortisone 100 mg was administered intravenously with

NaCl 0.9%. A few days later, after short discontinuation of this treatment, his cortisol level was 0.028 mmol/L. The adrenocorticotrophic hormone (ACTH) was <5 ng/L (1–76 ng/L). All other pituitary investigations (basal hormones) were normal.

DIFFERENTIAL DIAGNOSIS

The patient had a low level of fasting cortisol combined with low concentration of ACTH. His recovery after treatment with steroids for an allergic reaction and after second admittance, in combination with the previously described clinical and laboratory findings, confirmed the diagnosis of iatrogenic adrenal insufficiency. Because other hormonal axes were intact and the patient used no other steroids, the insufficiency was most likely the result of exogenous corticosteroids, namely, budesonide maintenance therapy.

OUTCOME AND FOLLOW-UP

Iatrogenic adrenal insufficiency due to budesonide use has rarely been reported. Prescribers should be aware of the resulting risk for an Addisonian crisis. According to the guidelines, budesonide should only be prescribed for 1 year. However, exceptions to this rule have occurred, as in our index case. After such a prolonged treatment period, budesonide must be tapered, as should any form of long-term steroid treatment, and the patient must be warned that, in case of biologically stressful events or fever, corticosteroids should promptly be reintroduced.

After starting the patient on prednisolone maintenance, he quickly felt better. Currently, in outpatient follow-up 6 months later, his condition is stable and he is still being treated with a substitution prednisolone dose.

DISCUSSION

Our diagnosis was 'adrenal insufficiency' due to (untapered) discontinuation of budesonide therapy. An Addisonian crisis due to budesonide therapy has rarely been described; we found few descriptions of similar cases in the literature.^{1 2}

Pathogenesis

Iatrogenic adrenal insufficiency results from negative feedback of exogenous steroids in the pituitary and hypothalamus glands, which inhibits endogenous cortisol production. As a result, insufficient endogenous cortisol is produced in situations that require a stress response.

Symptomatology

Adrenocortical insufficiency is characterised by weakness, fatigue and anorexia. In addition,

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gastrointestinal symptoms such as nausea, vomiting, abdominal pain and diarrhoea often occur—these can resemble an ‘acute abdomen’. Orthostatic problems and arthralgias have also been described. On physical examination, 90% of cases present with hypotension (systolic blood pressure <110 mm Hg). Patients often have unexplained fever and hypoglycaemia, and, in advanced stages, become drowsy or even comatose. Shock symptoms are disproportionate to the seriousness of current illness.^{3–5} Blood chemistry may show hyponatraemia, hyperammonaemia, hypoglycaemia, hypercalcaemia and eosinophilia—this, however, is not always the case. Our patient presented similar symptoms. However, laboratory tests showed no abnormalities (ie, electrolyte disturbances or hypoglycaemia) except for low cortisol and ACTH.

Budesonide

Budesonide (Entocort) is a glucocorticoid with limited systemic effect because of a rapid first pass effect. The oral capsule has a time-dependent, targeted elimination of the drug in the ileum and ascending colon (sites often affected in Crohn’s disease). These features should limit systemic effects. There is controversy about the effectiveness of budesonide maintenance treatment. A Cochrane review in 2009 confirmed effectiveness only in short-term treatment. However, some studies show there are significantly less side effects using budesonide compared to placebo as longer maintenance therapy.¹ Despite this controversy, budesonide is still often prescribed. In American Gastroenterology guidelines, budesonide is indicated for 8 weeks in the acute phase, and for an additional 3 months for maintenance.⁶ In the Netherlands, budesonide 9 mg is officially registered for treatment up to 8 weeks, and may not be discontinued without tapering.⁷ In the case presented, however, the patient was exposed to budesonide for a much longer period. Doses of 3 and 6 mg daily are associated with aberrant ACTH-stimulation tests, suggesting iatrogenic adrenal insufficiency.¹ However, in a safety analysis from 2009, the authors concluded that adrenal function after 13 weeks and 1 year of treatment did not significantly differ in a budesonide-treated compared to control group.⁸

Treatment

In order to prevent iatrogenic adrenal insufficiency, it is necessary to avoid abrupt discontinuation of long-standing corticosteroid treatment. One should gradually taper the current steroid dosage. Furthermore, patients should raise current maintenance doses of steroids in times of physical illness, trauma or surgical stress. In case of any symptoms resembling Addisonian

crisis, vomiting included, patients should immediately attend hospital to receive parenteral corticosteroids and, if necessary, haemodynamic support.

Learning points

- ▶ An Addisonian crisis is a life-threatening situation in which only high-dose hydrocortisone and (if required) haemodynamic support can treat a patient successfully.
- ▶ Clinicians should be aware of the possibility of an Addisonian crisis in patients using budesonide treatment, since diagnosing adrenal insufficiency can be a serious challenge.
- ▶ Near-shock symptoms in an Addisonian crisis often resemble other life-threatening situations such as sepsis and an acute abdomen. This may cause treatment delay and may eventually lead to serious morbidity and mortality.

Contributors LvG wrote the majority of this case report. AA was the treating physician and assisted with writing the case report.

Competing interests None declared.

Patient consent Obtained.

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