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LESSON OF THE MONTH

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lesson of the month (2)

Cushing's syndrome with low levels of serum cortisol: the role of inhaled steroids

With the introduction of new drugs and new devices believed to have less potential for systemic effects, the propensity for potent inhaled glucocorticoids to cause potent hypothalamic–pituitary–adrenal axis suppression is still under recognised.

Lesson

In January 2010, a 22-year-old man presented to Barts and the London School of Medicine for investigation of apparent adrenal insufficiency but with a cushingoid habitus. Around one year earlier, he had complained to his GP of central weight gain and the appearance of purple striae on his upper body; the GP found, to his surprise, that the patient's random serum cortisol was <50 nmol/l on three occasions (normal range 200–600 nmol/l); on a short synacthen test (adrenocorticotropic hormone (ACTH) (1–24) 0.25 mg, intravenous (iv)) the basal cortisol of 28 nmol/l and only rose to 133 nmol/l 30 minutes after stimulation (normal, >550 nmol/l). His 0900 plasma ACTH was 22 ng/l (normal, 10–60 ng/l). Other markers of pituitary function were normal. A pituitary magnetic resonance image was reported as normal. In view of these results, interpreted as adrenal insufficiency, the patient was initiated on hydrocortisone replacement treatment 30 mg daily in divided doses. Over the following 11 months he continued to gain weight centrally and noticed the further development of his striae, and thus sought medical assistance.

On clinical examination the patient was markedly cushingoid, with a body mass index (BMI) of 26.4 kg/m^2, centrally distributed fat and broad purple striae over his shoulders and upper arms. His blood pressure was normal. He denied inadvertently taking oral corticosteroid medication, but on direct questioning admitted to be taking inhaled fluticasone propionate 250 micrograms plus salmeterol 50 micrograms per blister (Seretide250 Accuhaler®), two blisters twice daily, for four years, for asthma. It was hypothesised that he had iatrogenic Cushing's syndrome and adrenocortical suppression due to inhaled glucocorticoids (IGC), and he was advised to stop hydrocortisone and given a Steroid Card, a hydrocortisone emergency pack and a supply of hydrocortisone with education as to corticosteroid replacement during episodes of severe intercurrent illness, trauma or surgery.

Four months after stopping hydrocortisone the patient had noticed a drop in weight to a BMI of 25.4 kg/m^2 and a marked reduction of his purple striae. Twenty-four hours off inhaled glucocorticoids, basal and dynamic tests were performed. All baseline pituitary function tests were normal other than a suppressed serum cortisol of <20 nmol/l.

The patient had a long corticotropin (ACTH-Synacthen) test (1 mg intramuscular with sampling for 24 hours; Table 1). This showed a suppressed 0900 serum cortisol with an impaired response at 30 and 60 mins, confirming adrenocortical insufficiency; however, cortisol levels showed a delayed

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Table 1. Laboratory findings.

Long corticotropin (ACTH-synacthen) test

Time	Cortisol (nmol/l)
0 min	<20
30 min	39
60 min	58
90 min	63
120 min	75
4 hr	86
6 hr	109
8 hr	126
12 hr	187
24 hr	414

ACTH = adrenocorticotropic hormone.

rise during the test, achieving a subnormal response, but consistent with a supra-adrenal cause for his adrenal insufficiency. These results confirmed a diagnosis of adrenocortical suppression and features of glucocorticoid excess (weight gain and skin changes) secondary to IGC for asthma. After discussion with respiratory physicians, the patient was discharged with the Seretide® dose reduced to a half of that used previously.

After a further three months the patient was again reviewed; his asthma was well controlled so he was gradually weaned off the asthma medication entirely over two months. On a short admission, now being off all steroid medications for two weeks, all his cushingoid features had disappeared, his BMI was 23 kg/m^2, and he had an insulin tolerance test showing essentially normal function of the hypothalamo–pituitary–adrenal (HPA) axis (peak plasma cortisol of 535 nmol/l).

Discussion

Diseases such as asthma and chronic obstructive pulmonary disease are very common worldwide, and many millions of people take IGC to treat these conditions, principally because of their anti-inflammatory and immunologic actions.

IGC have considerably fewer systemic effects than oral corticosteroids, but nevertheless adverse effects have been reported. The ability of IGC to suppress the HPA axis and cause features of Cushing's syndrome has been known for several years.[1–5] Nevertheless, with the introduction of new drugs and new devices believed to have less potential for systemic effects, the propensity for potent IGC to cause potent HPA-axis suppression is still generally under-recognised. This is thought to be due to systemic absorption through the lungs rather than oral absorption via ingested corticosteroids after inhalation.

This case confirms that HPA-axis suppression with features of glucocorticoid excess occurs at commonly used, and licensed, doses of IGC. In view of the long-term sequelae of chronic glucocorticoid excess, decisions regarding treatment should be subject to constant review based on efficacy and side effects. Clinicians should be alert to the induction of a cushingoid phenotype by these agents with awareness for the possibility of adrenal crisis.

Finally, recovery from suppression may take several months. To avoid symptoms of glucocorticoid deficiency, such inhaled steroids should be cautiously withdrawn over a period of months and the function of the HPA axis assessed by appropriate testing. Physicians in general should be aware that the fact that corticosteroids are inhaled does not mean that they cannot be absorbed with all consequential adverse effects. Similar problems may arise from other forms of corticosteroids therapy not given orally.[6]

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