Iatrogenic Cushing's syndrome due to nasal betamethasone: a problem not to be sniffed at!

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Summary

Nasal steroid drops for the treatment of allergic rhinitis can cause iatrogenic Cushing's syndrome and care should be taken with their use in clinical practice.

Keywords: Cushing's syndrome, nasal steroids

Introduction

Topical steroids are widely used in the treatment of allergic rhinitis and have recently become available as an over-the-counter product (Beconase nasal spray). They are considered safe since it is believed that they are not absorbed in large enough quantities to have systemic effects. Reports of adverse effects relating to their use are rare.¹ We report a case of iatrogenic Cushing's syndrome resulting from the use of Betnesol (0.1% w/v) nasal drops.

Case report

A 28-year-old woman was referred from her general practitioner with a one year history of weight gain (11 kg confirmed from hospital records), facial swelling, and striae on her lower abdomen and legs. She had a long history of patchy alopecia involving her scalp which had been treated with two intradermal injections of methylprednisolone (0.5 ml each, 40 mg/ml solution) one year before presentation. Allergic rhinitis had been diagnosed two years earlier and had initially responded to Beconase nasal spray. However, her symptoms worsened after three months and she was prescribed betamethasone nasal drops (Betnesol 0.1% w/v) which she had been using for a year. She claimed to be using only one or two drops per nostril per day. Her only other medication was fluoxetine which had been prescribed by her general practitioner for depression. There was no other past medical history. She drank approximately 28 units per week but did not take recreational drugs.

On examination she was overweight (body mass index 31 kg/m², normal range 20–25) with facial swelling and livid striae on her thighs and arms (figure). Her blood pressure was 130/90 mmHg. She had no evidence of proximal myopathy, bruising, or atrophy of her skin. A clinical diagnosis of Cushing's syndrome was made and she was admitted for further assessment.

Figure Livid striae over both thighs

Serum urea and electrolytes and random blood glucose were normal. Surprisingly, twenty-four hour urine free cortisol concentrations were unmeasurable (<20 nmol/l) and measurements over the next two months remained low (range <20–58 nmol/l; normal range <270 nmol/l). Baseline 09.00 hour plasma cortisol measurements were also undetectable (<30 nmol/l; normal range 200–700 nmol/l) and remained so over a three-month period. This indicated an exogenous source of steroids as the cause of her Cushing's syndrome. Adrenal androgens were also low (dehydroepiandrosterone <1.0 µmol/l, androstenedione 4.2 nmol/l, range 4–10 nmol/l). Adrenal CT scan was normal.

Despite repeated enquiries she denied using more than the recommended dose of Betnesol and was convinced that her symptoms were the result of the two intradermal steroid injections. However, her general practitioner had supplied the Betnesol nose drops by repeat prescription and his computerised records showed that she had received 48 bottles (10 ml of 1 mg/ml solution) of Betnesol nasal solution in 1992. A diagnosis of iatrogenic Cushing's syndrome was made.

Reduction in Betnesol usage (16 bottles in 1993, 4 bottles in 1994) has resulted in partial recovery of adrenocortical function (short synacthen test 1994; baseline cortisol 370 nmol/l, 30 min cortisol 510 nmol/l; normal >550 nmol/l) and some improvement in her striae. A long synacthen test² (basal cortisol 100 nmol/l, day 3 concentration 670 nmol/l) confirmed some continuing suppression of adrenal function and it is planned to repeat this six months after transferring to Flixonase nasal spray and stopping Betnesol completely. Until

adrenocortical function fully recovers she has been given a supply of hydrocortisone for emergency use in the event of severe intercurrent illness.

Discussion

Assuming all the nasal solution was used, we calculate that this patient administered the equivalent of 10 mg prednisolone per day for two years. This is sufficient to cause adrenal suppression in normal subjects.³ The only other source of exogenous steroids were the intradermal methylprednisolone injections. These are equivalent to 50 mg prednisolone and, since the half-life of methylprednisolone is 2.3 h, we believe this is unlikely to have contributed to her clinical course. It is unfortunate that there is no method of measuring synthetic exogenous steroids in the blood, as this would be the 'obvious' diagnostic test for patients with Cushing's syndrome and undetectable serum cortisol levels.

There have been previous reports of Cushing's syndrome following the use of intra-nasal steroids. Long-acting dexamethasone preparations were reported to cause adrenal suppression in 1967⁴ and were withdrawn. Only two cases have been reported complicating the intra-nasal use of betamethasone.^{5,6} In each case therapy was started at hospital out-patients and continued by repeat prescription from general practitioners.

In both cases, as in the case described here, the patients used intra-nasal drops rather than aerosol spray. Both had used the drops incorrectly, squirting them into the nostrils. It is likely that significant amounts of the betamethasone were swallowed and absorbed through the gastrointestinal tract. As betamethasone has negligible first-pass metabolism,⁷ large quantities could enter the systemic circulation. Newer, locally inactivated, preparations may reduce the risk of

Learning points

- nasal steroid drops may produce iatrogenic Cushing's syndrome if recommended dose is exceeded
- synthetic steroids are not directly measurable in the blood. Therefore a careful drug history is essential in patients with Cushing's syndrome and an unmeasurable cortisol level

adrenal suppression following misuse of these compounds; this is particularly important as they are now available over the counter.

Mood disturbance in Cushing's syndrome is well recognised.⁸ In our case, the patient was depressed, and it is interesting that her depression has improved following withdrawal of the nasal steroid drops. She is no longer taking antidepressants.

The adrenal suppression which was very marked at presentation has shown a significant degree of recovery. We would expect her adrenal function to return to normal eventually, although the length of recovery is unpredictable.³ This could be monitored with serial short synacthen tests. In the mean time we have advised her to take hydrocortisone if she becomes unwell, to avoid hypoadrenal crises during intercurrent illness.

This case suggests that the excessive use of potent, long-acting, topical steroids for allergic rhinitis may cause iatrogenic Cushing's syndrome. Patients should be advised of the importance of not exceeding maximum recommended doses. General practitioners should be careful with repeat prescription of topical steroids, which are not without risk.

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