Herbal tea and hypoadrenalism

Adam Morton, Richard Ruddell, Oliver Treacy

CASE

A Vietnamese woman aged 64 years presented to her general practitioner with weight gain of 15 kg and lethargy over the previous 12 months. The patient's past history was significant for hypothyroidism, hyperlipidaemia and hypertension managed with thyroxine, atorvastatin and perindopril/amlodipine, respectively. On examination, facial fullness and thin skin were present, without easy bruising, proximal myopathy or truncal obesity. There was no history of hyperglycaemia or osteoporosis. The woman denied exposure to prescribed glucocorticoids. A dexamethasone suppression test to exclude Cushing's syndrome revealed an early morning basal serum cortisol of <50 nmol/L (reference range 150–500 nmol/L).

QUESTION 1

What are the most common causes of low serum cortisol? How would you differentiate between hypothalamic–pituitary–adrenal axis insufficiency (secondary adrenal insufficiency) and primary adrenal insufficiency?

ANSWER 1

Low serum cortisol may occur due to secondary adrenal insufficiency, primary adrenal disease or laboratory interference. Serum adrenocorticotropic hormone (ACTH) should allow differentiation between secondary adrenal insufficiency and primary adrenal insufficiency. In primary adrenal insufficiency serum ACTH will be elevated, whereas levels will be 'inappropriately' normal or low with secondary insufficiency. The most common cause of secondary adrenal insufficiency is exposure to exogenous glucocorticoids, including topical, aerosol, guttae and parenteral. Clinically exogenous glucocorticoid exposure should be sought as a cause of secondary adrenal insufficiency where signs of glucocorticoid excess are present with an unexpected low serum cortisol and ACTH. Secondary adrenal insufficiency may also occur with hypothalamic or pituitary surgery, radiotherapy, neoplasms or infiltrative disorders, or following head injury. Secondary adrenal insufficiency due to hypothalamic or pituitary disease may be associated with fatigue, weight loss, hypotension and hypoglycaemia, and symptoms and signs related to other pituitary hormone deficiencies and pituitary mass effect. Opioid use may lead to secondary adrenal insufficiency in 9–29% of long-term users.[1] Even short-term opioid use may result in adrenal insufficiency: a single dose of 30 mg slow-release morphine resulted in a 55% fall in serum cortisol in seven healthy volunteers, while a single dose of 20 mg methadone given by intravenous infusion resulted in suppression of cortisol in four individuals with depression.[2,3] Primary adrenal insufficiency most commonly occurs due to autoimmune destruction with Addison's disease. Primary adrenal insufficiency may also occur with metastatic disease, infectious adrenalitis and haemorrhagic infarction. Primary adrenal insufficiency is associated with glucocorticoid and mineralocorticoid deficiency and ACTH excess, with additional symptoms and signs of salt craving, postural tachycardia and hypotension, and hyperpigmentation. On rare occasions serum cortisol may be falsely low due to heterophile antibody interference with immunoassay.[4]

CASE CONTINUED

The patient's ACTH was low, confirming secondary adrenal insufficiency. The unexpected finding of a low serum cortisol and ACTH together with the woman's Cushingoid features was highly suggestive of exogenous glucocorticoid exposure. She disclosed use of herbal tea tablets obtained by mail from Vietnam, and a propolis spray her son had provided with the belief it could prevent COVID-19 infection. Analysis of the herbal tea tablets by liquid chromatography quadrupole mass Spectrometer revealed adulteration with significant amounts of dexamethasone (estimated 0.25 mg dose per tablet).

The patient was advised to cease the herbal tea tablets and was commenced

on replacement hydrocortisone (divided dose – total 0.25 mg/kg bodyweight per day). She was instructed to double her dose of hydrocortisone in the event of intercurrent illness and of the need for immediate parenteral replacement if she developed vomiting (Box 1). Early morning serum cortisol was checked monthly (having withheld the previous afternoon dose, and prior to the dose the morning of testing) to assess recovery of the hypothalamic–pituitary–adrenal axis. After four months, the patient's serum cortisol was >400 nmol/L and hydrocortisone was weaned over a period of one month and then ceased.

QUESTION 2

How common is complementary medicine use?

QUESTION 3

How common is adulteration of complementary therapies? What are the most common additives?

QUESTION 4

How can a specialist general practitioner test for adulteration of complementary medications?

Box 1. Sick-day advice for patients with adrenal insufficiency[12]

- Instruct patient/carers in use of parenteral hydrocortisone and supply with 100 mg dose
- Minor illness – double dose of glucocorticoid (to minimum total daily dose hydrocortisone 40 mg or prednisone 10 mg until well for 48 hours), then revert to usual
- Vomiting, diarrhoea or more severe illness – administer parenteral hydrocortisone 100 mg and seek medical attention immediately
- Wear MedicAlert bracelet (or equivalent) stating hydrocortisone treatment
- Provide letter for presentation to other health professionals in the event of acute illness
- Maintain adequate hydration in hot weather
- Seek advice regarding change in dose of glucocorticoid prior to any procedure, including dental work
- Ensure annual influenza vaccine

ANSWER 2

A cross-sectional online survey of Australian adults found that 47.8% used vitamin and/or mineral supplements.[5] A survey of 216 adult Vietnamese immigrants to the US reported the use of traditional Vietnamese medicine (TVM) herbal products in 32%, and the use of Eastern-influenced TVM herbal products in 16.7%.[6] Twenty-two per cent indicated willingness to discuss their TVM use with their health provider. A sensitive and supportive approach to enquiring about the use of complementary medicines is important, as a meta-analysis found a 33% disclosure rate to medical providers for biologically based complementary medicine.[7]

ANSWER 3

A Taiwanese study found that 23.7% of 2609 proprietary Chinese medicine samples were adulterated with synthetic drugs.[8] The most common categories of adulterants were non-steroidal anti-inflammatory drugs (17.7%), anorectics (15.3%), corticosteroids (13.8%), diuretics and laxatives (11.4%), sulphonylureas (10%) and erectile dysfunction drugs (6%). Dexamethasone was the most frequently detected corticosteroid. Adulteration of Asian herbal medicinal products with heavy metals, natural aflatoxins, banned drugs, drug analogues and animal thyroid tissue has also been reported. An analysis of 120 herbal and Indian alternative remedies found 38% contained dexamethasone in various doses.[9] An analysis of 49 analgesic and anti-inflammatory herbal preparations randomly sourced from pharmacies, health food stores, traditional herb retailers and online in Australian capital cities found 26 preparations (53%) were adulterated or contaminated with undeclared ingredients.[10] Of the 26 adulterated/contaminated herbal medicines, 19 (73%) were manufactured in Australia and seven (27%) were imported from other countries (including six from China). Six of the herbal medicine samples contained therapeutically relevant compounds including atropine, synephrine and ephedrine. Skin-lightening creams purchased over the counter at local African shops may be adulterated by highly potent glucocorticoids (eg clobetasol), mercury and hydroquinone,[11] which may pose significant risk to the user and to the fetus if the woman is pregnant.

ANSWER 4

Major public hospital and private pathology providers can perform testing for adulterants of complementary medications using mass spectrometry.

Key points

- Almost half of Australian adults report the use of complementary medicines.
- Complementary products may be adulterated with a wide variety of medications, heavy metals, and plant and animal substances.
- The risk of adulteration appears to be greatest in complementary or proprietary medicines imported from China and India, and skin-lightening creams from Africa.
- Health professionals need to be vigilant about the possibility that complementary medications may cause illness, particularly as individuals may be reluctant to disclose their use.

Authors

Adam Morton FRACP, Senior Staff Specialist, Endocrinology and Obstetric Medicine, Mater Health, Brisbane, Qld

Richard Ruddell FRCPA, Chemical Pathologist, New South Wales Health Pathology, John Hunter Hospital, Newcastle, NSW

Oliver Treacy FRCPA, Chemical Pathologist, Mater Health, Brisbane, Qld

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Correspondence to:
adam.morton@mater.org.au

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correspondence **ajgp@racgp.org.au**