

Adrenal insufficiency from steroid-containing complementary therapy: importance of detailed history

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Summary

A 62-year-old Asian British female presented with increasing tiredness. She had multiple co-morbidities and was prescribed steroid inhalers for asthma. She had also received short courses of oral prednisolone for acute asthma exacerbations in the last 2 years. Unfortunately, the frequency and dose of steroids for asthma was unclear from history. Her type 2 diabetes mellitus (DM) control had deteriorated over a short period of time (HbA1c: 48–85 mmol/mol). Blood tests revealed undetectable cortisol and ACTH (<28 mmol/L, <5.0 ng/L). Renin, electrolytes and thyroid function were within normal limits. A diagnosis of secondary adrenal insufficiency, likely due to long-term steroid inhaler and recurrent short courses of oral steroids for asthma exacerbations was made. Patient was commenced on hydrocortisone 10 mg, 5 mg and 5 mg regimen. Steroid inhaler was discontinued following consultation with respiratory physicians. Despite discontinuation of inhaled steroids, patient continued not to mount a response to Synacthen®. Upon further detailed history, patient admitted taking a 'herbal' preparation for chronic osteoarthritic knee pain. Toxicology analysis showed presence of dexamethasone, ciprofloxacin, paracetamol, diclofenac, ibuprofen and cimetidine in the herbal medication. Patient was advised to discontinue her herbal preparation. We believe the cause of secondary adrenal insufficiency in our patient was the herbal remedy containing dexamethasone, explaining persistent adrenal suppression despite discontinuation of all prescribed steroids, further possibly contributing to obesity, hypertension and suboptimal control of DM. In conclusion, a comprehensive drug history including herbal and over-the-counter preparations should be elucidated. Investigation for the presence of steroids in these preparations should be considered when patients persist to have secondary adrenal insufficiency despite discontinuation of prescribed steroid medications.

Learning points:

- The likelihood of complementary and alternative medicines (CAMs) in medication-induced secondary adrenal insufficiency should be considered in any patient presenting with potential symptoms of adrenal insufficiency.
- If the contents of CAM preparation cannot be ascertained, toxicology screening should be considered.
- Patients should be advised to stop taking CAM preparation when it contains steroids and hydrocortisone replacement therapy commenced, with periodic reassessment of adrenal function, and then if indicated weaned accordingly.
- Patients should be informed about the contents of CAM therapies, so they can make a truly informed choice regarding the risks and benefits.
- This case also highlights a need to increase regulatory processes over CAM therapies, given their propensity to contain a number of undisclosed medications and potent steroids.

Background

Complementary and alternative medicines (CAMs) and therapies are popular therapeutic option at the patients' discretion (1). CAM offers widespread treatments for a growing number of conditions including cancer and chronic pain, although the evidence base regarding safety and efficacy of these therapies is sparse (2, 3, 4). Several herbal remedies, including traditional Chinese medicines and Indian treatments, contain steroids, which has consequently resulted in adrenal insufficiency. Unfortunately, precise contents of CAM are often ambiguous and incomplete, hence misinforming patients and clinicians alike.

Case presentation

A 62-year-old Asian British female presented with increased tiredness to the Endocrinology Clinic. Past medical history included asthma, hypertension, chronic unexplained idiopathic vertigo, migraine, anxiety and depression, type 2 DM, osteoarthritis and total hysterectomy with bilateral salphingo-oophorectomy for fibroids. Current medication included cetirizine 10 mg once daily (OD), Seretide® inhaler, ramipril 10 mg OD, bendroflumethazide 2.5 mg OD, amlodipine 10 mg OD, aspirin 75 mg OD, topiramate 25 mg OD, paroxetine 50 mg OD, simvastatin 20 mg OD, metformin 500 mg twice daily (BD), pregabalin 50 mg BD and Adcal-D3® two tablets OD. She was a housewife. She had no known drug allergies, lifelong non-smoker, with no history of alcohol consumption or tobacco use.

On examination, there were no signs of abnormal skin pigmentation. She weighed 82 kg, BMI was 43 kg/m² and blood pressure was 155/78 mmHg. Heart rate was 87 beats per minute. Systemic examination was unremarkable. Other than being obese, there were no other physical signs of hypercortisolism.

Investigation

Blood tests revealed undetectable cortisol (<28 nmol/L), and did not respond to administration of tetracosactide as part of Short Synacthen® test (30 min post administration of 250 µg Synacthen® cortisol <28 nmol/L). Adrenocorticotrophic hormone (ACTH) was also suppressed (<5.0 ng/L), HbA1c – 85 mmol/mol. Other routine blood tests were within acceptable limits.



Figure 1
Complementary and alternative medicine our patient was taking.

Treatment

A diagnosis of secondary adrenal insufficiency, likely secondary to long-term steroid inhaler and recurrent short courses of oral steroids for asthma exacerbations was made. Patient was commenced on hydrocortisone 10 mg in the morning, 5 mg at lunch and 5 mg no later than 18:00h, with instruction of steroid adjustment during inter-current illness. She was issued with a blue steroid card and provided with an emergency hydrocortisone kit and training.

Following lung function testing, chest radiograph and respiratory team review, mild asthma was confirmed. Seretide® inhaler was discontinued with advice to consider less systemically absorbed steroid inhaler, such as ciclesonide, if she were to become symptomatic.

Outcome and follow-up

Despite discontinuation of steroid inhalers, the patient had persistent non-response to the Short Synacthen® test 7 months later. Upon obtaining a further detailed history, the patient admitted to taking a CAM for chronic



osteoarthritic knee pain (Fig. 1). Toxicological analysis of the preparation revealed the presence of dexamethasone, ciprofloxacin, paracetamol, diclofenac, ibuprofen and cimetidine (Fig. 2).

Toxicological analysis: The tablet was dissolved in 10 mL 50:50 methanol:water, mixed by gentle inversion for 60 min and placed in an ultrasonic bath for 15 min. 1 mL of the solution was removed and centrifuged to remove any debris. Suitable dilutions of the solution were analysed by high performance liquid chromatography with a diode-array detector (HPLC-DAD), gas chromatography–mass spectrometry (GC-MS) and high-resolution mass spectrometry (LC-QT of MS). Samples were compared to a library of compounds present on each instrument with positive findings based on matches of chromatographic retention times plus ultraviolet (UV) spectra (HPLC-DAD), MS spectra (GC-MS) or time of flight mass spectrometry (TOF MS) and tandem mass spectrometry (MS/MS) spectra (LC-QToF MS).

Patient was advised to discontinue the CAM. However, she remained adrenal insufficient on repeat testing. During her follow-up, the patient suffered a low trauma comminuted fracture of the distal third of the left radius. Bone densitometry scan revealed worsening osteopenia in the absence of any other risk factors (T score of -2.4 in 2018 vs -1.4 in 2013 at L1-L4 spine; T score of -0.7 in 2018 vs 0.1 in 2013 at femur). The patient is currently being followed up in our Endocrinology Clinic and will be reassessed at specified time intervals for potential recovery of her hypothalamic–pituitary–adrenal (HPA) axis in the near future.

Discussion

Adrenal insufficiency in our patient can be attributed to a combination of exogenous steroid treatment, including Seretide inhaler, short courses of oral steroids for asthma exacerbations and a CAM-containing dexamethasone. We believe the CAM had significant impact on suppressing the HPA axis due to their long half-life and potency. In addition to the secondary adrenal insufficiency, it was suspected that our patient's glycaemic control and blood pressure control had worsened since commencing the CAM. Long-term exogenous glucocorticoid intake suppresses endogenous glucocorticoid production through negative feedback of the HPA axis and suppression of ACTH (2). Rapid discontinuation of such exogenous steroids can precipitate an adrenal crisis. (5).

Numerous CAM alternative medicines have been implicated to adrenal insufficiency (6). Patell *et al.* reported

Sample B,17.3151050.Q (BLOOD) Collected 10 Oct 2017 Received 10 Oct 2017 14:00

Toxicology Screen

Toxicology Screen

Tablet analysis. Please see below for results.

Analysis of tablet on the above patient received in the laboratory on the 10.10.17. The tablet contained:
Ciprofloxacin, dexamethasone, paracetamol, diclofenac, ibuprofen and cimetidine.

Figure 2

Toxicology screen of the complementary and alternative medicine in our case.

a 50-year-old female with a cushingoid appearance presenting with bilateral hip fractures following a fall. Following surgery for bilateral hip replacement, she developed an adrenal crisis. Although there was no history of prescribed steroids, the patient had been taking a medication from her naturopath, which was shown to contain dexamethasone. Discontinuation of the alternative medication during her hospital stay and the stress of surgery led her into adrenal crisis. The authors commented that eliciting a detailed medication history including CAM medications might have prevented this crisis (6).

Gupta *et al.* found 38% of 120 herbal and Indian alternative remedies contained dexamethasone at various doses (4). Fung *et al.* reported the presence of steroids in various Chinese herbal medicines, although data were insufficient to elicit its clinical relevance and significance. Chong *et al.* in a case series of 65 patients using Chinese remedies showed that dexamethasone was a common component of these preparations, commonly inducing adrenal insufficiency and leading to one or more complications in 62% of cases, worryingly including mortality (3). Chen *et al.* reported failure to recover the HPA axis even after 1 year following discontinuation of herbal remedies (7). Thus, there is an important need to investigate and monitor such patients, especially if the alternative herbal medicines are used intermittently.

There are a few studies reporting steroid inhaler-induced adrenal insufficiency in children and adults (8, 9). However, a systematic review by Masoli *et al.* did not demonstrate a significant relationship between therapeutic doses of fluticasone and adrenal insufficiency. A caveat to this analysis, as reported by the authors, was the lack of long-term patient follow-up (10). That said, our patient had a persisted non-response to Synacthen® despite discontinuation of inhaled steroids making it an unlikely sole cause for her adrenal suppression.

Patient's perspective

The patient's increasing tiredness was significantly affecting her life and hence sought specialist advice. However, she initially did not believe that



her CAM was suppressing her natural hormone production when we reported this. After a detailed discussion of mechanism of action and pathway, the patient made an informed choice and reluctantly agreed to stop the CAM. She reported to feel initially worse off the CAM but quickly improved. She is grateful to have sought specialist input and being under regular review with our team.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this case report.

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Patient consent

Written informed consent has been obtained from the patient for publication of the submitted article and accompanying images.

Author contribution statement

All authors substantially contributed to the design of the work. P K, L S and L Q were involved in case management and preparation of initial draft. L S and S K performed all relevant endocrine tests. A B is the named physician for the patient, recommended all relevant investigations and supervised case management. All authors were involved in revision and approval of the final manuscript.

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