

A woman with Cushing's syndrome after use of an Indonesian herb: a case report

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ABSTRACT

A 69-year-old woman developed Cushing's syndrome after long-term use of Sinatren[®], an Indonesian over-the-counter drug, which was pharmacologically analysed three times before the correct content was discovered. After discontinuation she developed adrenal insufficiency, for which she needed substitution of steroids. Physicians should be aware of the presence of corticosteroids in over-the-counter products, that are not mentioned on the instruction leaflet.

KEYWORDS

Cushing's syndrome, herbal drugs

INTRODUCTION

In the literature several reports have been published about the systemic effects of corticosteroid therapy applied by intra-articular injections,^{1,2} enemas,^{3,4} topical therapy,⁵ and inhalation.^{6,7} We present a case of a woman who developed a clear Cushing's syndrome after long-term use of an Indonesian mixture, Sinatren[®].

CASE REPORT

A 68-year-old woman was referred to our hospital because of progressive fatigue and dizziness for a few years. Her medical history revealed eczema of the face and extremities, hay fever, nonspecific chest pain for which she had a cardiac evaluation in 1988, and cerebral concussion after a collapse of unknown origin in 1999. On admission, she was on budesonide nasal spray, 200 µg per day, fexofenadine 120 mg once daily and diltiazem 180 mg

once daily. Previously, she had used a steroid-containing ointment as a local therapy for her eczema, but this had been discontinued for more than six months.

Her complaints consisted mainly of tiredness and she had developed full, reddish cheeks and neck region. She denied an increase in weight, but had noticed spontaneous bruising on her extremities and her skin had become thinner in the past few years. She had no chest pain or dyspnoea, but she did report emotional lability and easy agitation.

On physical examination clear signs of Cushing's syndrome were present. There was a centripetal obesity, especially in the face (so-called 'moon face') with plethora over the cheeks, in the neck, trunk and abdomen, with the extremities relatively spared and wasted. Enlarged fat pads filling the supraclavicular fossae were noted. The blood pressure was 115/70 mmHg, weight 57 kg and height 165 cm. There were no ecchymoses present, nor oedema.

Laboratory results were as follows (normal values in parentheses): haemoglobin 8.0 mmol/l (7.4 to 9.9), white cell count $7.6 \times 10^9 / l$ (3.5 to 11.0) with in the differentiation 67% neutrophils (50 to 70%) and 23% lymphocytes (25 to 40%), glucose 5.5 mmol/l (3.5 to 6), creatinine 59 µmol/l (-105), sodium 139 mmol/l (136 to 146), potassium 3.1 mmol/l (3.5 to 4.5), thyroid-stimulating hormone 0.5 µIU/ml (0.1 to 5), Ca²⁺ 1.28 mmol/l (1.13 to 1.30), alkaline phosphatase 78 IU/l (-100), lactate dehydrogenase 89 IU/l (-110), albumin 38 g/l (37-58), cortisol <0.02 µmol/l (9.00 am) (0.25 to 0.76), cortisol <0.02 µmol (04.00 pm), and ACTH 5 ng/l (10 to 20).

Budesonide nasal spray was discontinued. She was only taking fexofenadine and diltiazem as before, but no other medications or products. Cortisol levels were detectable within two weeks: 0.39 µmol/l (9.00 am), 0.28 µmol/l (04.00 pm); high-dose synacthen test (250 µg ACTH): t=0 cortisol 0.51 µmol/l, t=30 min cortisol 0.77 µmol/l.

At that time she felt better and showed no signs of adrenal insufficiency.

After three months she reported reappearance of her symptoms. She was no longer using nasal sprays. However, she mentioned that she had started using Sinatren[®], an Indonesian product which was claimed to contain only herbal constituents (figures 1 and 2). She purchased it at the local market in Indonesia for treatment of her eczema. She had used it on and off for years, but she did not know exactly what the product contained. Because we had previously discussed the possibility that the symptoms and biochemical results could be due to exogenous corticosteroids, she had approached her pharmacist for analysis of these Sinatren[®] sachets. UV spectrophotometrical and thin layer chromatographic analyses repeatedly reported acetaminophen being the only pharmacological constituent. Being satisfied with these results, she again started taking Sinatren[®] on a daily basis. At that time, the cortisol levels were again not detectable (cortisol <0.02 µmol/l), the result of ACTH being 3 ng/l. It was then assumed that the Sinatren[®] sachets had to be the source of the steroids, even though there was no direct evidence at that time. Sinatren[®] was stopped immediately. The sachets were therefore reanalysed in our own pharmacy.

After two weeks she developed signs of a relative adrenal insufficiency with flu-like muscle pain, nausea with a weight loss of 5 kg, and stiff hands. She also complained of acute low back pain. Her blood pressure was 95/70 mmHg.

Figure 1. Sachets of Sinatren[®] (see text for details)

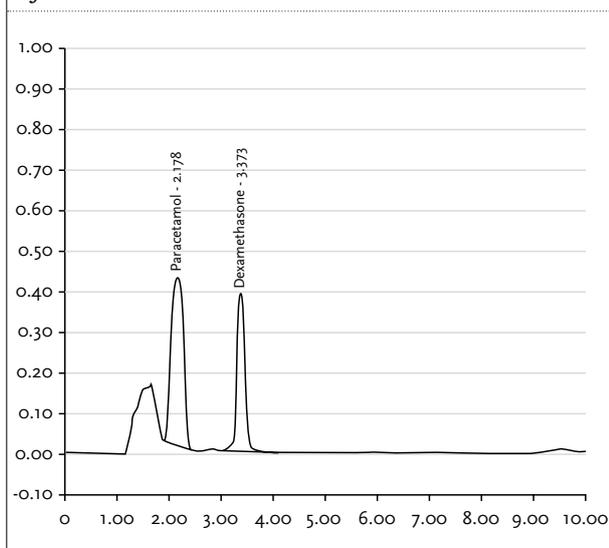


Figure 2. Sachets of Sinatren[®] (see text for details)



There were no signs of oedema. She was admitted to the hospital for clinical testing and analysis of her low back pain. Cortisol and ACTH values were 0.33 µmol/l and 14 ng/l respectively (9.00 am). Other laboratory values were as follows: creatinine 52 µmol/l, sodium 134, and potassium 3.6. Repeatedly measured cortisol values between 8.00 and 9.00 am were low (cortisol 0.22 and 0.29 µmol/l). In combination with the clinical presentation we assumed that she had signs of a relative adrenal insufficiency and therefore a synacthen test was not performed. Substitution therapy with hydrocortisone was started (10-5 mg). An X-ray of the lumbar spine was taken, revealing loss of height of several corpora (Th11, Th12, L1, and L2) and secondary thoracolumbar kyphosis. Bone densitometry showed low values of the bone mineral density for the lumbar region (T score -3.8, Z score -1.7) and both colla (T score -3.3, Z score -1.6) indicating osteoporosis. After a few days of bed rest and medication for the low back pain, she was able to resume daily activities again. She was also being treated with bisphosphonates and calcium supplements. At that time, the results of the Sinatren[®] analysis by our hospital pharmacy department became known. High-performance liquid chromatography (HPLC) revealed the presence of dexamethasone and acetaminophen (figure 3).

Figure 3. High-performance liquid chromatography of Sinatren®



DISCUSSION

This case illustrates how difficult it can be to prove the presence of corticosteroids in an innocent appearing drug. In this case the patient was not aware of the content of an Indonesian mixture, Sinatren®, presented and sold as a herbal drug, which led to Cushing's syndrome with suppression of the hypothalamic-pituitary axis.

It took a long time to prove the presence of corticosteroids in this product. Three analyses were needed before the evidence was found. The first examination was not conclusive. The Research Institute of Dutch Pharmacists (WINAP) performed the second examination. They analysed two different sachets of Sinatren® (LNA registration numbers: C1037, yellow sachet; C1038, brown sachet). After UV spectrophotometrical and thin layer chromatographic examinations they excluded the presence of steroids in the sachets. The brown sachets contained acetaminophen in a concentration of 200 mg/g.

Only after the third analysis with high-performance liquid chromatography (HPLC) in our own hospital was it shown that dexamethasone is present in Sinatren®: the yellow sachet contained approximately 0.6 mg dexamethasone per gram powder and 1 mg acetaminophen per gram powder, the brown sachet contained approximately 3.1 mg ibuprofen per gram powder and approximately 37 mg acetaminophen per gram powder. This again underlines the importance of the choice of a suitable method for analysing pharmacologically active products. Only HPLC proved to have a detection limit low enough to recognise the presence of a pharmacologically significant amount of dexamethasone.

Both UV analysis and thin layer chromatography had detection limits far above the pharmacologically relevant concentration and could not measure the lower quantity of dexamethasone present in this case. Interestingly, 'sinatren' is the Indonesian word for express train (phonetically it sounds in Dutch like 'sneltrain') suggesting a rapid action.

Some reports have been published about adrenal insufficiency after treatment with intra-articular steroid injection,^{1,2} enemas,^{3,4} and topical steroid therapy⁵ and after inhaled corticosteroids.^{6,7} However, literature about adrenal insufficiency after ingestion of herbal or alternative mixtures is very scarce. Only three reports have passed on this matter, one of them in the Chinese language.⁸⁻¹⁰ An excellent review on herbal remedies has been published¹¹ and is very much worth reading.

This case underscores the importance of taking a medical history carefully, with special interest to the use of regular and alternative (herbal) drugs. Physicians should be aware of potential, previously described or yet unknown, hazards related to these products. Even when products appear to be completely harmless, a thorough analysis with a method capable of producing clinically relevant results is warranted if no other source of exogenous steroids can be detected.

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