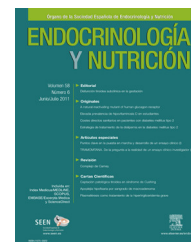


ENDOCRINOLOGÍA Y NUTRICIÓN

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SCIENTIFIC LETTER

Topical corticosteroids and secondary adrenal insufficiency: A relationship in the shade[☆]

Corticoides tópicos e insuficiencia suprarrenal secundaria: una relación en la sombra

Glucocorticoids have important anti-inflammatory and immunosuppressive activity. They are frequently used in a wide variety of diseases, especially dermatologic diseases, and in some cases they are given in excessive doses, both through topical and systemic administration. Treatment with glucocorticoids may suppress the normal functioning of the hypothalamic–pituitary–adrenal (HPA) axis, and quick or unexpected withdrawal is the most frequent cause of secondary adrenal insufficiency.

We present the case of a 77-year-old male who was admitted to the Internal Medicine ward for evaluation of dizziness and constitutional syndrome. He had a history of primary autoimmune hypothyroidism which was adequately treated with 50 µg/day of levothyroxine, mild Alzheimer's disease, chronic fatigue syndrome and constipation. He had lost around 13 kg over the previous year (his usual body weight was 70 kg) and he recalled suffering from dysphagia over the past couple of months. Additionally, he had experienced several episodes of acute dizziness in both the standing and sitting positions, sometimes even leading to a loss of consciousness, which was diagnosed as vasovagal syncope.

A physical examination revealed skin pallor and general cachexia. He weighed 57 kg (body mass index [BMI] 21.4 kg/m²), and his sitting blood pressure was 80/60 mmHg, which dropped to 60/40 mmHg when standing up, with a heart rate of 47 per minute.

Laboratory data revealed the following: fasting blood glucose 61 mg/dL, total proteins 5 g/dL, plasma sodium 133 mEq/L, plasma potassium 4.6 mEq/L, hemoglobin 10.3 g/dL and an erythrocyte sedimentation rate of 52 mm/h. The remaining biochemical results, thyroid hormone evaluation, Mantoux and HIV-serological markers

were normal. Basal serum cortisol levels were 1.1 mcg/dL [6.2–19.4] and basal ACTH was 5.3 pg/mL [8–46].

After a 250 mcg cosyntropin stimulation test (Synacthen®), cortisol levels were 3.2 mcg/dL, which supported the diagnosis of secondary adrenal insufficiency. Pituitary evaluation was subsequently completed: IGF-1 < 25 ng/mL [59–177], GH 1.3 ng/mL [0–0.8], free T4 1.11 ng/dL [0.89–1.8], TSH 4.29 mcU/mL [0.35–5.5], prolactin 8.3 ng/mL [2.2–17.7], FSH 6.9 U/L [2.8–55.5], LH 9.39 U/L [3.1–34.6], total testosterone 670.77 ng/dL [241–827]. Pituitary magnetic resonance imaging (MRI) was normal, and abdominal computed tomography (CT) revealed hypoplasia of both adrenal glands.

The patient repeatedly denied any past or recent use of glucocorticoids. However, we were not convinced, and we continued to ask the patient and his relatives if he had used some sort of cream or shampoo which might have contained glucocorticoids. His wife finally recalled that the patient had been using a topical treatment (Menaderm cream® [betamethasone dipropionate, 0.025%]) over the past 5 years due to facial dermatosis, which he had stopped several weeks before the beginning of the current episode.

The patient was diagnosed with secondary adrenal insufficiency due to the withdrawal of prolonged topical treatment with corticosteroids, and a significant improvement of symptoms was observed once substitution treatment with hydrocortisone was initiated. Eight weeks later, the patient had gained some weight (66.9 kg), his blood pressure was 134/74 mmHg, and he remained asymptomatic with no new syncope episodes. Basal ACTH levels were 8.5 pg/mL, and serum cortisol levels were still low (basal cortisol 1.2 mcg/dL and 4.5 mcg/dL after a 250 µg cosyntropin stimulation test), so hydrocortisone treatment was maintained. We are optimistic that the patient's HPA axis will eventually recover, and so allow the withdrawal of hydrocortisone treatment.

Before corticosteroid treatment can be stopped, several factors have to be taken into account: firstly, the possibility that the disease for which glucocorticoids had been prescribed may reappear; secondly, that secondary adrenal insufficiency may develop, even when physiologic doses are used; also, that the HPA axis may remain suppressed for prolonged periods of time; and finally, that there have even been cases described of psychological dependence.¹

The exogenous administration of glucocorticoids inhibits the synthesis and secretion of corticotropin hormone (CRH), leading to a decrease in the synthesis of proopiomelanocortin and, consequently, to a deterioration in ACTH

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secretion. This entails a reduction in the size and number of corticotroph pituitary cells, which, in turn, prompts the degeneration of the adrenal cortex (pars fascicularis and pars reticularis) and disturbs cortisol production.

The risk of suppressing the HPA axis can be classified as high, moderate or low, depending on the dose, activity and duration of the specific glucocorticoid used. Dosages equivalent to 20 mg of prednisone for a period of more than 3 weeks determine a high risk of axis suppression; 10–20 mg of prednisone for more than 3 weeks are associated with moderate risk; glucocorticoids that are not administered parenterally for less than 3 weeks and physiologic doses are associated with a low risk of suppression.

Sulberger and Witten, in 1952, were the first to use topical glucocorticoids. Subsequently, in 1955, Malkinson and Ferguson proved that percutaneous absorption could occur, and in 1962, Scoggins observed a decrease in urine free cortisol levels when topical steroids were used.

Despite the fact that the topical administration of glucocorticoids reduces the incidence of adverse effects, they cannot be overlooked. Several studies agree that the HPA axis may be affected when high-potency steroids are used at weekly doses of 50 g.^{2–4} Levina and Maibach reported that steroid absorption may be increased depending on several factors such as the area in which they are applied (from greater to less absorption: eye lids, intertriginous area, scrotum, forehead, scalp, face and forearm), the associated compound used (urea or salicylic acid), area occlusion, impaired skin integrity and younger age.^{2,3,5} It is worth noting that the prescription of glucocorticoids may not only be oral, transdermal or parenteral, but also ocular, inhaled or even rectal, and that they are sometimes included as one of the ingredients of certain herbal and cosmetic products. Therefore, a complete medical history in order to rule out their possible use is considered necessary.

Betamethasone dipropionate is known to have moderate–high glucocorticoid potency and is widely and routinely used because of its efficacy in controlling several types of dermatosis. However, it also entails a series of adverse effects when administered both orally or topically.^{2,3,5,6}

To our knowledge, there are few cases published up to date that describe adrenal insufficiency secondary to topical glucocorticoid use.^{4,7–10} The majority of them remark that the patient's medical history served as a clue for establishing the diagnosis, unlike in the case we present, in which previous steroid treatment was not initially recalled.

Some publications report that patients had suffered from Cushing-like adverse effects due to excessive glucocorticoid dose; on the contrary, other reports, describe well-tolerated prolonged treatments, as in the case presented here. Most of these patients had been using this topical approach for the treatment of dermatological diseases, although cases have

been reported of negro patients using it for the purpose of skin depigmentation.

In conclusion, we highlight the importance of obtaining a complete and truthful medical history when approaching secondary adrenal insufficiency. We should take particular care regarding the previous use of creams, shampoos or other apparently harmless products containing corticosteroids, because in many cases, the patients are usually unaware of the composition of the products they use.

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