Iatrogenic Cushing's syndrome by an interaction between cobicistat and fluticasone: a case report

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SUMMARY
We report a case of iatrogenic Cushing's syndrome associated with an interaction between cobicistat and fluticasone in a seropositive woman treated with elvitegravir/cobicistat/emtricitabina/TAF (Genvoya®). This case highlights the importance to review interactions between antirretroviral therapy and other drugs, especially when antirretroviral scheme includes protease inhibitors enhanced with ritonavir or cobicistat. These enhancers interfere the cytochrome P-450 metabolic pathway. A large number of drugs are metabolized by cytochrome P-450 and may be altered by cobicistat or ritonavir.

Key Words: **HIV, cobicistat, fluticasone, Cushing´s syndrome.**

Síndrome de Cushing yatrogénico asociado a la interacción entre cobicistat y fluticasona: caso clínico

RESUMEN
Presentamos un caso de síndrome de Cushing asociado a la interacción entre cobicistat y fluticasona en una mujer seropositiva en tratamiento con elvitegravir/cobicistat/emtricitabina/TAF (Genvoya®). Este caso pone de manifiesto la importancia de la revisión de las interacciones entre el tratamiento antirretroviral y otros tratamientos concomitantes, especialmente cuando el esquema antirretroviral contiene inhibidores de proteasa potenciados con ritonavir o cobicistat. Esta potenciación afecta a la ruta metabólica mediada por el citocromo P450. Un elevado número de fármacos son metabolizados por el citocromo P450, y por tanto pueden verse afectados cuando se administran con ritonavir o cobicistat.

Palabras clave: **VIH, cobicistat, fluticasona, síndrome de Cushing.**

INTRODUCTION

Human inmunodeficiency virus (HIV) infection is one of the most important pandemic infections around the world. Since the discovery of the first antiretroviral drugs in the eighties, the patient management and its profile has changed significantly.

Recently, the introduction of new highly active antiretroviral regimens (HAART) has led to a major change in the natural history of the disease. New drugs have higher efficacy and fewer side effects. Nowadays, the treatment approach is not only directed towards the control of viral load but also to the control of different associated comorbidities and quality of life improvement of these patients. These comorbidities associated with age lead to an increase of pills number intake and can trigger clinically relevant interactions that, in some cases, may impact the efficacy and/or the safety of different treatments. Cobicistat and ritonavir are enhancers used in some antiretroviral treatment regimens. Cobicistat is a potent CYP3A4 complex inhibitor. CYP3A4 is a metabolic pathway shared by a large number of drugs, including glucocorticoids. Hence, the combination of cobicistat with certain corticosteroids such as fluticasone can cause the Cushing's syndrome by inhibiting its metabolism.

CASE REPORT

A 53 year-old woman, ex parenteral drug user, HIV positive since 1993, followed up by Infectious Diseases Unit since 2014. At that time, viral load (VL) was: 6,436 copies/mL and CD4 count: 182 cel/mL. Therefore, antiretroviral treatment was reintroduced with emtricitabine/tenofovir + efavirenz. After 4 months of treatment, a VL decrease (<37 copies/mL) and a CD4 count increase: 307 cel/mL were observed. Back then, poor treatment adherence due to bad tolerance led to the interruption of the therapy. In June 2016, the patient resumed her follow up by the Infectious Diseases Unit and her treatment was changed to emtricitabine /tenofovir/elvitegravir/cobicistat (Stribild®). In October 2016, the drug presentation was modified. The new scheme included TAF (Genvoya®) with the aim to prevent kidney damage.

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The patient also presented chronic obstructive pulmonary disease (COPD) and recurrent pneumonias, so she also restarted follow up by the Neumology Unit. Since disnea was not controlled with basal treatment, (salmeterol and ipratropium bromide), the treatment was modified and salmeterol/fluticasone and glycopyrronium bromide were introduced at the same time (June 2016).

In February 2017, the patient was admitted to emergency room with fever and dyspnea. Also, she reported an increase in facial and abdominal perimeter of several days of evolution.

On admission the parameters were: CD4 count: 381 cel/mL, CD4%: 14.67, CD8: 1,638 cells/mL, CD8% 63%, CD4/CD8 0.23. VL <37 copies/mL.

The Physical examination: blood pressure: 170/10 mm^3, heart rate: 112 bpm, basal saturation: 100%, tachypnea at 28-30 rpm with breathlessness, normocolored and perfused. Pre-auricular pain with bilateral local inflammation. Candidiasis in oropharynx. In the clinical tests performed during the admission, elevated levels of glucose and cholesterol (not previously known) were recorded, probably, as a result of the iatrogenic Cushing syndrome.

Completed drugs list: Genvoya® (1-0-0), salmeterol/fluticasone 50/500 mg (1-0-1), Tovanor® Breezehaler (glycopyrronium bromide) (1-0-0), alprazolam 2 mg (1-1-1), fluoxetine (1-0-0), omeprazole (1-0-0).

Taking into account the symptoms reported, the interaction between cobicistat and fluticasone was detected and the therapy was adjusted. Prednisone treatment was initiated in descending pattern. Salmeterol/fluticasone was discontinued and was replaced by nebulized ipratropium bromide + salbutamol. Regarding the antiretroviral treatment, Genvoya® was discontinued and replaced by Triumeq® (dolutegravir/abacavir/lamivudine). Since hypertension persisted during admission, amlodipine 5 mg (1-0-0) was prescribed; once the blood pressure was normalized it was retired. Due to the good patient evolution, she was discharged from hospital, without adding any new medication to her usual drug list.

DISCUSSION

The case reported is an example of clinically relevant interaction between cobicistat and fluticasone despite its use according to the daily regimen recommended by technical data sheets of both drugs[1,2].

In 2016 Elliot ER et al.[3] published a review of iatrogenic Cushing's reports related to the interaction between corticoids and ritonavir or cobicistat. Interactions between different corticosteroids administered by different routes were identified. Regarding the inhaled therapy, fluticasone causes a greater suppression of cortisol compared to other corticosteroids due to its longer half-life and its greater affinity for receptors. This, together with the fact that is metabolized exclusively by CYP3A4 pathway, when combined with a potent inhibitor such as cobicistat, makes the effect even greater. The article suggests the use of beclomethasone, because its metabolism is carried out through hydrolysis by esterases and the involvement of CYP3A4 in its metabolism is minimal.

Regarding the symptoms reported by the patient: hypertension, increase of abdominal and facial perimeter, dyslipidemia and hyperglycemia, are characteristics of Cushing's syndrome: however it should be noted that some of these findings may be side effects associated with antiretroviral treatment, so it is essential to perform a differential diagnosis when a patient shows this symptomatology.

In some published cases, a decrease in CD4 count has been described, however, in this case, the count remained stable the months prior to admission, maintaining around 380 cells/mL. The mechanism that causes this reduction is not known exactly, but it seems that the maintenance of high levels of cortisol in blood, activates the apoptosis of the T lymphocytes[4].

Regarding the therapeutic strategy for the management of these cases, the change of antiretroviral regimen can be proposed, as long as resistance tests allow it, to another scheme whose metabolism is not carried out through CYP3A4 pathway, or the use of other corticosteroids, which are not metabolized by this route such as beclomethasone.

Given the wide use of inhaled corticosteroids, it is essential to review the pharmacotherapeutic history of the patient's candidates for antiretroviral therapy on treatment with drugs that inhibit CYP3A4 complex, and consider possible interaction.

As for prevention strategies, it is critical to provide the information to the patients and to request them to notify to all health professionals any change in their usual treatment. Another key factor is the implementation of an optimal coordination between primary and specialized care to enable an updated pharmacotherapy history.

This case report has been communicated to the Spanish Pharmacovigilance System.

Conflicts of interest: The authors declare that they have no conflict of interest.

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