Case Report

Exogenous Cushing's syndrome as a result of ritonavir–budesonide interaction – A case report

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A B S T R A C T

Ritonavir is currently a commonly prescribed protease inhibitor for human immunodeficiency virus (HIV) infection. Its potent inhibition of hepatic cytochrome P450 3A4 isoenzyme may increase systemic glucocorticoids concentrations, leading to potential suppression of the hypothalamic pituitary adrenal axis (HPA) and iatrogenic Cushing’s syndrome (CS).

We describe a case of a 43-year-old woman with HIV infection that presented with a clinical overt CS resulting from the interaction between ritonavir and intranasal budesonide at low doses. Similar cases have been described with long-term concomitant use of many glucocorticoids with ritonavir but very few concerning inhaled or intranasal budesonide.

This case reinforces the importance of physicians to be aware of this interaction, promoting its early recognition and providing a careful assessment of potentially serious drug–drug interactions, especially when ritonavir is prescribed to a HIV-patient with bronchial hyperresponsiveness or rhinitis.

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1. Introduction

Ritonavir is an inhibitor of the human immunodeficiency virus type 1 (HIV-1) protease with potent antiretroviral activity. It is also responsible for a potent inhibition of cytochrome P450 fraction 3A4 (CYP450 3A4) activity, involved in systemic metabolism and clearance of a great number of drugs [1,2]. This pharmacological characteristic is commonly used to enhance plasma concentrations of other protease inhibitors (PI), reducing the pill burden, facilitating treatment compliance and preventing resistance emergence and treatment failures [3,4]. Despite this advantage, co-administration of ritonavir with other drugs sharing the same hepatic metabolic pathway may result in harmful side effects, even at low doses of both drugs [5]. Inhaled or intranasal synthetic corticosteroids, such as fluticasone or budesonide, are often prescribed in HIV-infected patients with bronchial hyperresponsiveness or rhinitis [6]. The CYP450 3A4 enzymic inhibition caused by ritonavir may result in impaired steroid catabolism, with increased bioavailability and suppression of the hypothalamic pituitary adrenal axis (HPA) with Cushing’s syndrome (CS) [4,7]. Although more frequently described with fluticasone propionate, due to its lipophilic features and long half-life, budesonide has also been implicated in few cases of exogenous hypercortisolism in HIV-patients treated with ritonavir [8].

We report one case of a HIV-patient treated with intranasal budesonide at low doses that developed clinical CS when ritonavir was added to his antiretroviral regimen.

2. Case report

A 43-year-old Caucasian woman was diagnosed with HIV-hepatitis C virus (HCV) co-infection in 1993. She had received multiple antiretroviral combinations with ritonavir–boosted therapy since 2004, due to multidrug resistances. She also had a medical history of allergic rhinitis controlled with intranasal budesonide for more than 10 years without notable side effects. Current medications included rescue antiretroviral therapy (lamivudine, raltegravir and ritonavir-boosted darunavir; 3TC + RAL + DRV/r), sporadic topical betamethasone and intranasal budesonide 200 μg bid. Her daily dose of ritonavir was of 100 mg qd and she has not received any oral or parenteral corticosteroids. She had good virologic and immunologic response to antiretroviral treatment (the last CD4+ T cells count was of 893/mm3 and the HIV-1 RNA load was undetectable).

In 2014, two years after symptoms onset, she was evaluated at the Endocrinology outpatient clinic for suspected CS. She reported...
progressive asthenia, sleeplessness and proximal muscle weakness, thinning and fragile skin, moon facies and increased fatty tissue deposits (particularly around the midsection and upper back, in the face, supraclavicular region and between the shoulders), and purple skin striae over the abdomen. On physical examination, she presented: facio-troncular obesity (BMI 31 kg/m²), facial plethora, buffalo hump and marked abdominal purple striae (Fig. 1A and B). She had no clinical, laboratory or radiologic signs of osteoporosis, glucose intolerance/diabetes mellitus or uncontrolled hypertension. CS was suspected and topic betamethasone administration was permanently stopped.

On laboratory investigation, subnormal 24 h urinary free cortisol of 4.9 μg (normal range: 36–137 μg/24 h) with low early morning serum cortisol level (0.4 μg/dL; normal range: 2.3–11.9 μg/dL), and a suppressed ACTH level (ACTH <5 pg/mL; normal range: 9–52 pg/mL) was found. Conventional 250 μg tetracosactide stimulation test confirmed impaired adrenal function (serum cortisol levels of 0.3 μg/dL and 3.2 μg/dL at 0 and 60 min, respectively). An interaction between ritonavir and budesonide was suspected. Ritonavir therapy was discontinued and replaced by unboosted atazanavir (400 mg qd) (chosen due to the patient tolerance) and glucocorticoid substitutive therapy was started (prednisolone 2.5 mg qd). Intranasal corticosteroid low-dose therapy with budesonide was tapered down but could not be interrupted due to worsening nasal symptoms. At last follow-up, after 4 months without ritonavir, clinical features gradually improved, but were still evident. There was a symptomatic improvement and regression of purple abdominal striae, facial plethora and fatty tissue deposits. HPA was still impaired and low dose glucocorticoid therapy was maintained.

3. Discussion

This case illustrates some of the potential severe systemic effects resulting of co-prescription of ritonavir and intranasal corticosteroids routinely used for the treatment of common conditions such as rhinitis or asthma. Despite the efficacy of PI in reducing HIV-viral load and morbidity, a variety of metabolic complications have been associated with ritonavir administration, particularly dyslipidemia, insulin resistance and lipodystrophy syndromes [9,10]. More recently, cases of overt iatrogenic CS have been reported in patients receiving either inhaled or intranasal corticosteroid with concomitant ritonavir therapy [11–13]. This adverse interaction results from the CYP3A4 and P-glycoprotein (PGP) inhibition by ritonavir with consequent increased serum concentrations of many of its substrates including corticosteroids [14]. Budesonide is metabolized by hepatic CYP3A4 and the PGP export pump. In patients treated with ritonavir, inhaled budesonide pharmacokinetics profile is impaired and Cushing’s clinical syndrome is established even with below standard doses.

Clinical diagnosis of CS in antiretroviral treated HIV-infected individuals poses some difficulties, mainly because of the overlapping phenotype between cortisol excess and some lipodystrophy syndromes. Clinical signs, such as typical moon face, rapid increase of body weight, cutaneous changes, proximal myopathy and clinical evidence of hyperandrogenism occur mainly in CS and could help differentiate between these two entities [10,15–17].

Mostly importantly, physicians treating HIV patients must be aware of the potential interaction between ritonavir and many other drugs. Alternative drugs regimens should be prescribed when facing a patient under chronic steroid therapy (oral or inhaled).

As a result of prolonged adrenal suppression, HPA recovery may vary from days to months after therapy cessation. In our case, we have chosen to keep the low dose intranasal budesonide and suspend the potent CYP3A4 inhibitory drug. Our aim was to avoid its abrupt cessation and consequent potential adrenal crisis and to control rhinitis symptoms. Substitutive therapy with steroids is usually needed as long as the response to adrenal stimulation test has not demonstrated normal response. The recovery delay observed in this case may be explained by its long-term co-administration of ritonavir and intranasal corticosteroid and probably to the also described moderate inhibition of the CYP3A4 by atazanavir [18].

The most widely established evidence in respect to exogenous CS in HIV patients involves co-administration of PI and inhaled fluticasone. This report seems to be, to the best of our knowledge, the fourth published case of CS induced by simultaneous intake of inhaled budesonide and ritonavir in HIV-infected adult patients. Inhaled budesonide is about 300 times less lipophilic and has a shorter half-life of binding to glucocorticoid receptor and a lower volume of distribution when compared with fluticasone [19]. These factors may contribute to the more frequent suppression of HPA axis of fluticasone when compared with other inhaled corticosteroids. Some authors have addressed this possible budesonide–ritonavir interaction. Kedem et al. reported a case of a 37-year-old woman treated with ritonavir-boosted PI treatment, with reemerged iatrogenic CS after discontinuation of fluticasone and initiation of recommended doses of inhaled budesonide (160 μg bid) [20]. In 2012, Yoganathan et al., also described a 48-year old woman with iatrogenic CS and adrenocortical suppression while on ritonavir for the past three years and inhaled budesonide, but at higher dose (1600 μg/day) for the past 18 months [13]. More recently, Blondin et al. reported a case of a 46-year-old female patient co-treated with inhaled budesonide 800 μg qd and ritonavir with established CS [12]. In contrast to the last two cases, our patient developed CS while on a lower dose of budesonide. All of these patients were successfully managed with reduction of inhaled budesonide dose and/or to replacing ritonavir regimen.

Fig. 1. (A and B) Hypercortisolism features in a 43-year-old woman with a budesonide induced Cushing’s syndrome.
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