CASE REPORT

Iatrogenic Cushing's syndrome and osteoporosis due to an interaction between fluticasone and ritonavir

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SUMMARY

The advent of highly active antiretroviral therapy for HIV infection dramatically changed the landscape of the disease. Ritonavir, a protease inhibitor (PI) frequently used in low doses to 'boost' the concentrations of other PIs, inhibits the cytochrome P450 3A4 isoenzyme, a common metabolic pathway to multiple drugs, so the potential for drug interactions is not negligible. A 39-year-old man with HIV-1 infection, treated with a ritonavir-boosted PI, was started on fluticasone/salmeterol inhaler and intranasal fluticasone, in 2009, in the setting of asthma and allergic rhinitis. In 2013, he presented with 1-year evolution of symptoms suggesting Cushing's syndrome, and was experiencing recurrent falls. A spine CT showed a vertical L3 fracture and thoracolumbar erosions; a bone density scan revealed severe osteoporosis. Hormonal assays were compatible with hypothalamic–pituitary–adrenal axis suppression, and iatrogenic Cushing's syndrome due to ritonavir–fluticasone interaction was considered. Fluticasone was suspended and oral corticosteroid replacement initiated, with a favourable outcome.

BACKGROUND

The introduction of highly active antiretroviral therapy (HAART) represented a paradigm shift in the natural history of HIV infection, by improving life expectancy in these patients. To a certain degree, our focus has shifted from the infection itself and associated opportunistic diseases, to managing increasing age-related comorbidities, which raises the need for polypharmacy. Although current regimens have evolved towards greater simplicity and tolerability, the potential for drug interactions is not negligible, nor are the side effects of antiretroviral therapy.

International treatment guidelines recommend several first-line combinations, including regimens containing ritonavir-boosted protease inhibitors (PI/r), particularly advantageous for their high genetic barrier to resistance.¹ Ritonavir (RTV) in small doses (≤ 200 mg/day) acts as a booster, inhibiting the hepatic cytochrome P450 3A4 isoenzyme (CYP3A4), and, thus, increasing the area under the curve (AUC) of the second PI. This is a valuable drug–drug interaction that reduces pill burden and increases dosing intervals, thereby facilitating adherence to antiretroviral therapy, and preventing resistance and treatment failures.² The CYP3A4 is a common metabolic pathway to multiple drugs and, therefore, one needs to consider the potential for significant harmful side effects and interactions involving ritonavir (even in low-doses) and

substrates of this isoenzyme. Some interactions are well recognised by clinicians, such as those with amiodarone and simvastatin, where plasma exposure increases. A less-recognised interaction, however, can occur between ritonavir and inhaled corticosteroids, namely fluticasone, which is widely used in the treatment of asthma, allergic rhinitis and chronic obstructive pulmonary disease. Under normal circumstances, low plasma concentrations of fluticasone propionate are achieved after inhaled dosing, due to extensive first pass metabolism and high systemic clearance mediated by CYP3A4. When there is concomitant CYP3A4 inhibitor use, this can result in hypercortisolism/Cushing's syndrome, hypertension, osteoporosis and decreased CD4 cell count.³ HIV-associated lipodystrophy syndrome as a consequence of antiretroviral therapy can make clinical suspicion of Cushing's syndrome more challenging, as they both have many overlapping characteristics (eg, central obesity, weight gain and a dorsocervical fat pad).⁴ The pathophysiology of HIV-associated lipodystrophy syndrome is complex and thought to be multifactorial. The main risk factor, however, is exposure to thymidine analogue nucleoside reverse transcriptase inhibitors (NRTI), such as stavudine and zidovudine, which are no longer considered first-line drugs; evidence is less robust for the association with PI.

CASE PRESENTATION

A 39-year-old man diagnosed with HIV-1 infection in 2004 was initiated on an HAART regimen containing zidovudine 300 mg+lamivudine 150 mg two times a day+atazanavir 300 mg+RTV 100 mg once daily shortly after diagnosis. His nadir CD4T lymphocyte count was 202 cells/mm³ (12%), viral load was $>500\,000$ copies/mL and, by the ninth month of therapy, viraemia became undetectable and progressive immunological improvement was observed. In May 2008, his NRTI backbone was simplified to tenofovir 300 mg+ emtricitabine 200 mg once daily and, on account of jaundice, atazanavir was switched to ritonavir-boosted darunavir (DRV 800 mg+RTV 100 mg once daily). His known medical history was also remarkable for chronic hepatitis C, former intravenous drug use (assumed as the probable route of transmission of both infections) and active smoking.

In June 2009, due to symptoms indicative of asthma and allergic rhinitis, the patient was assessed by pneumology team and prescribed an inhaled combination of salmeterol 50 µg+fluticasone propionate 250 µg two times a day, as well as intranasal fluticasone furoate 110 µg once daily. At

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this time, his CD4 cell count was 869 cells/mm³ (26%) and viral load was undetectable.

In June 2013, he presented for a routine appointment in the immunodeficiency clinic, reporting a 1-year history of muscle weakness leading to recurrent falls and lower back pain, as well as progressive abdominal distension, ankle oedema, easy bruising, decreased libido and a general sense of fatigue and depression. On physical examination, centripetal obesity was apparent with a 'full moon' facies, discrete dorsocervical ('buffalo hump') and supraclavicular fossae fat pads, abdominal distension with purpuric striae, muscular atrophy and proximal muscle weakness, distal lower limb oedema, skin fragility, decreased pilosity, onychomycosis and systodiastolic hypertension—clinical features suggesting hypercortisolism (figure 1). Serum cortisol, 24 h urinary free cortisol and serum adrenocorticotrophic hormone (ACTH) measurements were, however, very low, compatible with blockage of the hypothalamus–pituitary–adrenal axis (table 1). To further investigate the back pain, CT and MRI of the thoracolumbar spine were performed, showing sclerosis and erosions across the 12th thoracic to 5th lumbar (T12–L5) vertebrae segment and a vertical fracture on L3 (figure 2). A bone density scan revealed significant deviation from the estimated bone mineral density (BMD) for age/sex with a Z-score of −3.8 (T-score of −4.1). In terms of his immunological status, although maintaining undetectable HIV viral load, a gradual decrease in CD4 cell count was also evident in the previous few years (figure 3). On reviewing his medication and excluding any oral or intravenous corticosteroid administration, a hypothesis of iatrogenic Cushing's syndrome secondary to enhanced systemic exposure of inhaled and intranasal fluticasone due to interaction with ritonavir was considered. Hence, fluticasone

Table 1 Hormone assays at presentation—compatible with suppression of the hypothalamic–pituitary–adrenal axis—and 7 months after intervention

	Presentation	7 Months later	Normal range
Serum cortisol (μg/dL)	1.0	12.7	6.7–22.6
24 h urinary cortisol (μg/24 h)	6.3	18.2	10–176
Serum ACTH (pg/mL)	<5	41.6	7–46
1,25 dihydroxyvitamin D (pg/mL)	26	–	20.2–46.2
PTH (pg/mL)	44.1	–	12–88

ACTH, adrenocorticotrophic hormone; PTH, parathyroid hormone.

was switched to beclomethasone 250 μg twice daily and low-dose systemic corticosteroid (prednisolone 5 mg once daily) was started to prevent adrenal insufficiency.

OUTCOME AND FOLLOW-UP

After a slow weaning period of 7 months, the prednisolone was eventually suspended with dramatic clinical improvement, namely, an increase in muscle strength, reduction of abdominal perimeter, and disappearance of the 'full moon' facies and fat pads, among other features (figure 4). Normalisation of hormonal assays and increase in CD4 cell count were also noted (table 1, and figures 3 and 5). The patient started treatment for osteoporosis with alendronate 70 mg and cholecalciferol 2800 UI. Additionally, the case was discussed with neurosurgery and interventional neuroradiology team, who, considering a

Figure 1 Cushingoid features on presentation.

Figure 2 MRI of the thoracolumbar spine showing L3 vertical fracture and erosion features across the T12-L5 segment.

non-recent and stable fracture, found no indication for vertebroplasty, suggesting lumbostatis. Furthermore, while a decision to maintain the PI was made, tenofovir was suspended and substituted to abacavir because of its potential contribution to reduced BMD. A 1-year follow-up bone density scan showed dramatic improvement with a Z-score of -0.5 , hence within normal range.

DISCUSSION

This case illustrates the potential for a clinically significant interaction between inhaled fluticasone propionate and ritonavir, even within daily recommended doses. Cushing's syndrome has also been reported with other routes of steroids (eg, injectable

Figure 3 CD4 cell count evolution. Note the decrease in CD4 cell count even before the clinical picture of Cushing's syndrome was apparent and the marked improvement after therapeutic intervention (symbolised here by the green arrow).

triamcinolone).⁵ The same rationale can be applied for other CYP3A4 inhibitors such as cobicistat (used to boost elvitegravir in the fixed-dose combination Stribild),⁶ imidazoles,⁷ macrolides and calcium-channel blockers, among others.

In 2013, Saberi *et al*⁸ reviewed published case reports regarding this drug-drug interaction. They found 45 cases of inhaled corticosteroids (of which 91% were fluticasone and 9% budesonide), 2 intranasal (fluticasone) and 4 where a combination of inhaled and intranasal corticosteroids was used. Ritonavir was part of the antiretroviral regimen in 94% of the cases, with a mean dose of 224 mg/day (100–1200 mg/day). The mean daily dose of inhaled fluticasone was 841 µg (200–2000 µg) and of intranasal fluticasone, 400 µg (200–800 µg); therefore, in the majority of cases, inhaled doses were within the recommended daily dose range. Symptoms reported varied, although the most frequent were typically associated with Cushing's syndrome, and the most common clinical management consisted of discontinuation of the inhaled/intranasal corticosteroid. In this series, the typical onset of Cushing's syndrome was <6 months after drug co-prescription. Although it may be difficult to ascertain the onset in our patient, it appears likely that symptoms developed approximately 3 years later, despite, to the best of our knowledge, both dose and adherence to inhaled/intranasal steroids being unchanged from initial prescription. This, we feel, rendered the diagnosis more challenging.

Furthermore, Foisy *et al*⁹ reviewed the literature on the pharmacokinetics of inhaled and intranasal corticosteroids. Although most drugs are substrates of hepatic CYP3A4 and have the potential to interact with ritonavir, fluticasone propionate is nearly exclusively metabolised by this pathway, whereas beclomethasone, for instance, is predominantly metabolised by esterase enzymes, thus presenting itself as an interesting alternative. In addition, fluticasone has increased affinity to the glucocorticoid receptor as well as greater lipophilicity, which results in a higher volume of distribution, increased tissue accumulation and longer elimination half-life. Hence, of the available inhaled corticosteroids, fluticasone exhibits the greatest suppressive effect on the hypothalamic–pituitary–adrenal axis.

Therapeutic strategies can include: switching the PI to another antiretroviral agent that does not inhibit the CYP3A4 isoenzyme, such as non-NRTI (NNRTI) or integrase strand transfer inhibitors (INSTI; eg, raltegravir or dolutegravir), if drug resistance and treatment history allows it; tapering and eventually discontinuing the inhaled/intranasal corticosteroid; or suspending the inhaled/intranasal corticosteroid and initiating a slow taper of oral corticosteroid to correct the adrenal suppression until recovery of pituitary–adrenal axis.¹⁰ This is of particular importance, as these patients may not be able to mount a stress response to acute illness or injury. To manage respiratory symptoms, clinicians may choose another corticosteroid with less potential for drug interaction, such as beclomethasone, as mentioned, or an alternative drug class, such as a leukotriene receptor antagonist or an anticholinergic agent. It is important to highlight, however, that the combination of salmeterol and RTV is not recommended due to risk of QT interval prolongation.

Although our patient's CD4 cell count decreased significantly and then rebounded once fluticasone was discontinued, his HIV viral load remained undetectable. This has been reported elsewhere^{3 11 12} and, though the exact mechanism is not well-understood, the prolonged hyperglucocorticoid state is believed to activate T-lymphocyte apoptosis.

In this setting, osteoporosis, a particular expressive feature in our patient, deserves a further look. Although hypercortisolism

Figure 4 Clinical improvement
7 months after fluticasone suspension.

undeniably played a major contribution in this patient, in the HIV-infected population, this condition can be multifactorial,

Figure 5 Serum adrenocorticotrophic hormone (ACTH) evolution. As the graphic shows, ACTH suppression was only overcome after 4 months of therapy.

and growing evidence links long-term use of tenofovir disoproxil fumarate (TDF) and PI/r to a greater decrease in BMD compared with other NRTI and INSTI. Accordingly, international guidelines recommend avoidance of TDF in these cases and using alternatives such as abacavir as elected here.¹³

As mentioned, in this population, HIV-associated lipodystrophy should be considered in the differential diagnosis. Nevertheless, clinical features such as the 'full moon' facies versus the typical facial lipoatrophy, as well as laboratory evidence of low ACTH, can help exclude it.

Given the widespread use of inhaled and intranasal corticosteroids, some sold over-the-counter, it is essential to obtain a thorough medication history in patients exhibiting early signs or symptoms of hypercortisolism/Cushing's syndrome, and to consider the potential interaction between ritonavir and fluticasone. Also of note is the fact that some patients overuse inhalers, although, as shown here, even within daily recommended doses the interaction can be clinically evident. Hopefully, this can contribute to raise awareness and prevent the co-prescription of these drugs or at least allow for an earlier diagnosis, so that we do not overlook the important pillar of medical ethics, *primum non nocere*.

Learning points

- ▶ Ritonavir acts as a 'booster' by inhibiting the cytochrome P450 3A4 isoenzyme (CYP3A4), a common metabolic pathway to multiple drugs; thus, clinicians need to be aware of potential drug–drug interactions, including with agents not traditionally regarded as having significant serum levels, such as inhaled corticosteroids.
- ▶ Particularly, the interaction with fluticasone, due to its pharmacokinetics properties, can result in iatrogenic Cushing's syndrome and decreased CD4 cell count.
- ▶ In the HIV-infected population, lipodystrophy as a consequence of antiretroviral therapy can make clinical suspicion of Cushing's syndrome more challenging.
- ▶ Management may involve switching ritonavir-boosted protease inhibitors to non-nucleoside reverse transcriptase inhibitors or integrase strand transfer inhibitors; tapering and eventually discontinuing the inhaled/intranasal corticosteroid; or suspending it and initiating a slow taper of oral corticosteroid to avoid adrenal insufficiency.
- ▶ It is essential to obtain a thorough medication history, irrespective of administration route, in patients exhibiting signs or symptoms of Cushing's syndrome under CYP3A4 inhibitors.

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