

CASE REPORT

Inhaled Fluticasone Causes Iatrogenic Cushing's Syndrome in Patients Treated with Ritonavir

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Introduction: Ritonavir, a protease inhibitor (PI), is commonly used in the treatment of HIV-1 infection. It is a potent inhibitor of the hepatic cytochrome P450 superfamily. Therefore, its usage with other PI medications leads to significant increases in the levels of the latter PI, which allows a reduction in pill burden. Intranasal and inhaled corticosteroids are widely used for the treatment of allergic rhinitis and asthma. Inhaled steroids do not usually lead to systemic adverse events, since their plasma concentrations are quite low due to extensive first-pass metabolism and clearance by CYP3A4. However, the coadministration of Ritonavir with inhaled (or intranasal) corticosteroids may result in an increase in the plasma corticosteroid levels due to the potent CYP3A4 inhibition by Ritonavir. This may cause Cushing's syndrome (laboratory and clinical) with adrenal suppression. **Methods:** Plasma cortisol and urinary-free cortisol levels were determined using immunoassays. In the Synacthen test, plasma cortisol levels were measured at time 0 as well as at times 60, 120, and 150 minutes following an intramuscular injection of 0.25 mg Synacthen. **Results:** We present here three HIV-1 female patients aged 12, 55 and 65 years who developed iatrogenic Cushing's syndrome with adrenal suppression following the coadministration of Ritonavir and inhaled Fluticasone, both at the standard recommended doses. **Conclusions:** The coadministration of Ritonavir and Fluticasone at the recommended doses caused, in our three patients, iatrogenic Cushing's syndrome with adrenal suppression. We suggest that this adverse event is underdiagnosed and high clinical suspicion is needed for early diagnosis and prevention of Addisonian crises. Thus, Fluticasone treatment should be avoided in patients who are treated with Ritonavir. Alternative therapeutic options for asthma control such as oral Montelukast or bronchodilators alone should be considered.

Keywords CYP3A4, HIV infection, iatrogenic Cushing's syndrome, inhaled steroids, Ritonavir

INTRODUCTION

Ritonavir, a protease inhibitor (PI), is commonly used in the treatment of HIV infection. Ritonavir is a potent inhibitor of the hepatic cytochrome P450 superfamily; therefore, the usage of Ritonavir with other PI medications leads to significant increases in the circulating levels of the latter PI. This enables a reduction in pill burden and an increase of dosing intervals, facilitating both patient adherence and the success of highly active anti-retroviral treatment (HAART) (1, 2). Intranasal and inhaled corticosteroids are widely used for the treatment of allergic rhinitis and asthma (3). Inhaled steroids, even when used for extended periods of time, do not usually lead to systemic adverse events since their plasma concentrations remain low due to extensive first-pass metabolism and clearance by CYP3A4 (4). However, the coadministration of Ritonavir and inhaled (or intranasal) corticosteroids may result in an increase of plasma corticosteroid levels due to the potent CYP3A4 inhibition by Ritonavir. This may then cause Cushing's syndrome (laboratory and clinical) with adrenal suppression (5–18). We present here three HIV-1 patients who developed

iatrogenic Cushing's syndrome with adrenal suppression following the coadministration of Ritonavir and inhaled Fluticasone, both at the standard recommended doses.

METHODS

The diagnosis of HIV-1 was made by a positive ELISA test (Abbott, Wiesbaden, Germany) and confirmed by Western blot analysis (Innogenetics N.V., Gent, Belgium). The viral load (VL) was determined using a nucleic acid amplification test (Roche Diagnostics, Mannheim, Germany). Values of more than 40 copies/mL were considered as virological failure. Plasma cortisol and urinary-free cortisol levels were determined using immunoassays (Beckman Coulter, Brea, CA, USA). In the Synacthen test, plasma cortisol levels were measured at time 0 as well as at times 60, 120, and 150 minutes following an intramuscular injection of 0.25 mg Synacthen (19).

PATIENT AND RESULTS

Case 1

A 12-year-old female weighing 37 kg was diagnosed with HIV-1. She was successfully treated (VL <40 copies/mL) for 10 years with Zidovudine 300 mg/Lamivudine 150 mg

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FIGURE 1.—Cushingoid features of patient 1, 24 weeks following treatment with inhaled Fluticasone (100 μ g $\times$ 2/day) and Ritonavir (100 mg $\times$ 2/day) containing HAART.

1 $\times$ 2/day and Ritonavir 50 mg/Lopinavir 200 mg 2 $\times$ 2/day. Due to recurrent asthma exacerbations, she was also treated for a period of 24 weeks with inhaled corticosteroids (Fluticasone 100 mcg $\times$ 2/day). Thereafter, she was admitted with fatigue, weight gain (5.8 kg), malar telengectasis, and a rounded face with prominent cheeks (more commonly described as “moon facies”) (Figure 1). The initial diagnosis was HIV-related lipodystrophy. However, iatrogenic Cushing’s syndrome with severe adrenal suppression was diagnosed by low levels of morning cortisol (20 nmol/L; N 200–600 nmol/L), low free urinary cortisol (13 nmol/L; N 42–254 nmol/L), low levels of adrenocorticotropic hormone (ACTH) (4.7 pmol/L; N 2.2–11 pmol/L), and severe adrenal suppression. Following the injection of 0.25 mg Synacthen (cortisol levels were 70, 94, 99, and 88 nmol/L at 60, 90, 120, and 150 minutes, respectively, N > 500 nmol/L) (Table 1). Although she was normoglycemic (93 mg/dL), her insulin levels were elevated at 152.9 mU/L (N 2–23 mU/L) demonstrating severe insulin resistance. The inhaled Fluticasone was gradually tapered and discontinued and replaced by oral Montelukast (without any change of her HAART regimen). This resulted in good control of her asthma and gradual improvement of her Cushingoid features (Figure 2). Concomitantly, normalization of her cortisol, ACTH, and insulin levels were observed (Table 1).



FIGURE 2.—Patient 1, 3 months after the discontinuation of Fluticasone inhalation.

Case 2

A 55-year-old woman (weighing 61 kg) with HIV-1 infection was successfully (VL < 40 copies/mL) treated for 10 years with Zidovudine 300 mg/Lamivudine 150 mg 1 $\times$ 2/day and Ritonavir 50 mg/Lopinavir 200 mg 2 $\times$ 2/day. Following her diagnosis of asthma, she used inhaled Budesonide 200 mcg $\times$ 2/day for 6 months. Thereafter, her pulmonologist switched her Budesonide to inhaled Salmeterol 50 mcg/Fluticasone propionate 500 mcg 1 $\times$ 2/day. Three weeks later, she was admitted with fatigue, weight gain (5 kg), and “moon facies.” Laboratory evaluation revealed a low basal cortisol level (11 nmol/L; N 200–600 nmol/L) and an abnormal (flat) Synacthen test. Her serum cortisol level 60 minutes following a Synacthen injection was 89 nmol/L (N > 500 nmol/L) (Table 1). Her Fluticasone dosage was then gradually reduced and eventually replaced by inhaled Budesonide 200 mcg $\times$ 2/day. Three months after the switch was made (from Fluticasone to Budesonide), all her symptoms disappeared concomitantly with the normalization of her basal cortisol levels and Synacthen test (Table 1). There was no change in her HAART combination.

Case 3

A 65-year-old woman with HIV-1 (weighing 57 kg) was treated successfully (VL < 40 copies/mL) for 12

TABLE 1.—Basal and ACTH-stimulated (Synacthen test) cortisol levels during the coadministration of Ritonavir and inhaled Fluticasone, and after Fluticasone discontinuation.

Patient	Ritonavir + Fluticasone therapy		Ritonavir only (2–3 months after Fluticasone discontinuation)	
	Blood cortisol (nmol/L; N 200–600)	60 minutes after 0.25 mg Synacthen (nmol/L; N > 500)	Blood cortisol (nmol/L; N 200–600)	60 minutes after 0.25 mg Synacthen (nmol/L; N > 500)
1	20	70	307	ND
2	11	89	247	700
3	15	72	320	ND

Note: ND, not done.

years with Zidovudine 300 mg/Lamivudine 150 mg $\times$ 2/day and Ritonavir 50 mg/Lopinavir 200 mg 2 $\times$ 2/day. Due to asthma, she was also treated for 6 months with inhaled Salmeterol 50 mcg/Fluticasone propionate 250 mcg $\times$ 2/day. One month prior to her admission, she complained of a 4 kg weight gain, fatigue, and facial swelling. The diagnosis of Cushing's syndrome with adrenal suppression was confirmed based on low cortisol levels (15 nmol/L; N 200–600 nmol/L) and an abnormal (flat) Synacthen test (cortisol level of 72 nmol/L 60 minutes following a Synacthen injection; N > 500) (Table 1). All clinical and laboratory disturbances were resolved following the gradual discontinuation of her inhaled Fluticasone (Table 1).

DISCUSSION

The three patients presented in this article were diagnosed with iatrogenic Cushing's syndrome, as a result of the interactions between Ritonavir and inhaled Fluticasone. Both drugs were used at the regular recommended doses (Ritonavir 200 mg/day; mean dose of Fluticasone 566 ± 216 ; range 200–1000 μ g/day).

The early clinical and laboratory diagnosis of iatrogenic Cushing's syndrome with adrenal suppression is crucial in order to prevent both adverse events associated with excess levels of corticosteroids and Addisonian crises. The latter may occur following a rapid and uncontrolled discontinuation of Fluticasone.

Ritonavir, mainly as a PI boosting agent (200 mg/day), is commonly used in the treatment (HAART) of HIV patients. Since inhaled or intranasal corticosteroids are widely used in patients with allergic rhinitis, asthma, and chronic obstructive lung disease, it is likely for HIV-1 patients with these comorbidities to be exposed to inhaled corticosteroid treatment concurrently with Ritonavir-based HAART. Ritonavir is a well-known potent inhibitor of cytochrome P450 3A4 activity. Therefore, it may significantly increase the plasma concentrations of inhaled corticosteroids which are metabolized by the same hepatic cytochrome via first-pass metabolism (4).

Fluticasone has a higher affinity for the glucocorticoid receptor, a longer binding time, and is more lipophilic (20) when compared with other inhaled corticosteroids (e.g., Beclomethasone and Budesonide). Thus, it is more likely for Fluticasone, when compared to other inhaled corticosteroids, to interact with cytochrome

P450 3A4 inhibitors such as Ritonavir. As mentioned earlier, this leads to the accumulation of corticosteroids thereby causing iatrogenic Cushing's syndrome with adrenal suppression. Indeed, clinically significant drug interactions with Ritonavir have been previously reported with inhaled Fluticasone and there is only one report of such interaction with Budesonide (17, 21, 22). However, it is important to note that cases of iatrogenic Cushing's syndrome with adrenal suppression following the interaction of Budesonide with other cytochrome P450 3A4 inhibitors have been reported, two cases with Itraconazole (21) and two cases with diltiazem (23). It is vital, therefore, that the administration of Ritonavir with Budesonide be done with great caution using the lowest effective dose of Budesonide. This is further supported by the product label of Budesonide which has a warning regarding possible interactions with cytochrome P450 3A4 inhibitors.

Most previous cases of interactions between Fluticasone and Ritonavir were observed following Fluticasone inhalation (7, 9, 11, 12, 15, 16). There are also a few reports of iatrogenic Cushing's syndrome resulting from the use of intranasal Fluticasone. The actual incidence of iatrogenic Cushing's syndrome with adrenal suppression that is induced by Fluticasone–Ritonavir interactions is not known. Nevertheless, we believe that iatrogenic Cushing's syndrome due to the coadministration of Ritonavir and Fluticasone is underdiagnosed and mismanaged in this population due to a lack of clinical awareness. Thus, higher clinical suspicions will lead to the diagnosis of more cases of this adverse effect.

As was shown in our patients (Table 2), Cushing's syndrome with adrenal suppression can develop following the coadministration of Ritonavir and Fluticasone at the standard recommended dosages (24). The recovery of adrenal function in such patients may take up to 1 year. Therefore, a careful follow-up of the hypothalamic–pituitary–adrenal axis is essential during this period (25). It should be noted that other cytochrome P450 3A4 inhibitors such as Macrolides, Itraconazole, and Diltiazem (which were not used by our patients) may further contribute to the accumulation of inhaled corticosteroids (particularly Fluticasone). Thus, the coadministration of these agents with Fluticasone should be avoided or undertaken with a great caution.

The clinical signs and symptoms of Cushing's syndrome include increased appetite with weight gain, "moon facies," buffalo (cervical) hump, central adiposity,

TABLE 2.—Clinical characteristics, duration, and daily dosage of inhaled Fluticasone therapy prior to the development of iatrogenic Cushing's syndrome.

Patient	Gender	Age (years)	Weight (kg)	Ritonavir containing HAART duration (years)	Fluticasone therapy	
					Daily dose (μ g)	Duration (weeks)
1	Female	12	37	10	200	24
2	Female	55	61	10	1000	3
3	Female	65	57	12	500	24

facial plethora, easy bruising, abdominal stria, proximal muscle weakness, hirsutism, thin delicate skin, hypertension, glucose intolerance, osteopenia, emotional lability, and insomnia (19). It is important, although challenging, to distinguish between Cushing's syndrome and HIV-1-related lipodystrophy syndromes. Notably, the presence of abdominal stria and facial plethora favor the diagnosis of Cushing's syndrome over lipodystrophy syndromes (8). In any case of clinical suspicion, the diagnosis of iatrogenic Cushing's syndrome should be established by low morning plasma cortisol level and a blunted (flat) Synacthen test (<500 mmol/L) (26). The low basal ACTH levels point toward the diagnosis of secondary or iatrogenic adrenal insufficiency rather than a primary adrenal disorder (26).

CONCLUSIONS

In order to prevent the development of Cushing's syndrome with adrenal suppression in patients who are treated with Ritonavir and require intranasal or inhaled corticosteroids, Fluticasone treatment should be avoided. Other corticosteroids such as Beclomethasone, Budesonide, or Triamcinolone should be prescribed with great caution at the lowest effective dose, if indicated. Alternative therapeutic options such as oral Montelukast or bronchodilators alone should also be considered. Upon the diagnosis of iatrogenic Cushing's syndrome in patients treated concurrently with Ritonavir and Fluticasone, the latter should be gradually discontinued to avoid an Addisonian crisis.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

REFERENCES

- Flexner C. Dual protease inhibitor therapy in HIV-infected patients: Pharmacologic rationale and clinical benefits. *Annu Rev Pharmacol Toxicol* 2000; 40:649–674.
- Motwani B, Khayr W. Pharmacoenhancement of protease inhibitors. *Am J Ther* 2006; 13(1):57–63.
- Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001; 108(Suppl. 5): 147–334.
- Barnes PJ. Inhaled glucocorticoids for asthma. *N Engl J Med* 1995; 332:868–875.
- Hillebrand-Haverkort ME, Prummel MF, ten Veen JH. Ritonavir-induced Cushing's syndrome in a patient treated with nasal fluticasone. *AIDS* 1999; 13(13):1803.
- Chen F, Kearney T, Robinson S, Daley-Yates PT, Waldron S, Churchill DR. Cushing's syndrome and severe adrenal suppression in patients treated with Ritonavir and inhaled nasal Fluticasone. *Sex Transm Infect* 1999; 75(4):274.
- Clevenbergh P, Corcostegui M, Gérard D, Hieronimus S, Mondain V, Chichmanian RM, Sadoul JL, Dellamonica P. Iatrogenic Cushing's syndrome in an HIV-infected patient treated with inhaled corticosteroids (Fluticasone propionate) and low dose Ritonavir enhanced PI containing regimen. *J Infect* 2002; 44(3):194–195.
- Gupta SK, Dubé MP. Exogenous Cushing syndrome mimicking human immunodeficiency virus lipodystrophy. *Clin Infect Dis* 2002; 35(6):E69–E71.
- Rouanet I, Peyrière H, Mauboussin JM, Vincent D. Cushing's syndrome in a patient treated by ritonavir/lopinavir and inhaled fluticasone. *HIV Med* 2003; 4(2):149–150.
- Soldatos G, Sztal-Mazer S, Woolley I, Stockigt J. Exogenous glucocorticoid excess as a result of ritonavir–fluticasone interaction. *Intern Med J* 2005; 35(1):67–68.
- Samaras K, Pett S, Gowers A, McMurchie M, Cooper DA. Iatrogenic Cushing's syndrome with osteoporosis and secondary adrenal failure in human immunodeficiency virus-infected patients receiving inhaled corticosteroids and ritonavir-boosted protease inhibitors: Six cases. *J Clin Endocrinol Metab* 2005; 90(7):4394–4398.
- Gillett MJ, Cameron PU, Nguyen HV, Hurley DM, Mallal SA. Iatrogenic Cushing's syndrome in an HIV-infected patient treated with ritonavir and inhaled fluticasone. *AIDS* 2005; 19(7):740–741.
- Johnson SR, Marion AA, Vrhoticky T, Emmanuel PJ, Lujan-Zilbermann J. Cushing syndrome with secondary adrenal insufficiency from concomitant therapy with ritonavir and fluticasone. *J Pediatr* 2006; 148(3):386–388.
- Arrington-Sanders R, Hutton N, Siberry GK. Ritonavir-fluticasone interaction causing Cushing syndrome in HIV-infected children and adolescents. *Pediatr Infect Dis J* 2006; 25(11):1044–1048.
- Pessanha TM, Campos JM, Barros AC, Pone MV, Garrido JR, Pone SM. Iatrogenic Cushing's syndrome in a adolescent with AIDS on ritonavir and inhaled fluticasone. Case report and literature review. *AIDS* 2007; 21(4):529–532.
- Bhumra NA, Sahloff EG, Oehrtman SJ, Horner JM. Exogenous Cushing syndrome with inhaled fluticasone in a child receiving lopinavir/ritonavir. *Ann Pharmacother* 2007; 41(7):1306–1309.
- Foisy MM, Yakiwchuk EM, Chiu I, Singh AE. Adrenal suppression and Cushing's syndrome secondary to an interaction between ritonavir and fluticasone: A review of the literature. *HIV Med* 2008; 9(6): 389–396.
- Valin N, De Castro N, Garrait V, Bergeron A, Bouche C, Molina JM. Iatrogenic Cushing's syndrome in HIV-infected patients receiving ritonavir and inhaled fluticasone: Description of 4 new cases and review of the literature. *J Int Assoc Physicians AIDS Care (Chic)* 2009; 8(2):113–121.
- Williams GH, Dluhy RG. Disorders of the Adrenal Cortex. *Harrison's Principles of Internal Medicine* 17e. New York: McGraw-Hill, 2008.
- Johnson M. Development of fluticasone propionate and comparison with other inhaled corticosteroids. *J Allergy Clin Immunol* 1998; 101(4):434–439.
- Molimard M, Girodet PO, Pollet C, Fourrier-Reglat A, Daveluy A, Haramburu F, Fayon M, Tabarin A. Inhaled corticosteroids and adrenal insufficiency, prevalence and clinical presentation. *Drug Saf* 2008; 31(9):769–774.
- Kedem E, Shachar E, Hassoun G, Pollack S. Iatrogenic Cushing's Syndrome due to Coadministration of Ritonavir and Inhaled Budesonide in an Asthmatic Human Immunodeficiently Virus Infected Patient. *J Asthma* 2010; 47(7):830–831.
- Daveluy A, Raignoux C, Miremont-salame G, Girodet PO, Moore N, Haramburu F, Molimard M. Drug interaction between inhaled corticosteroids and enzymatic inhibitors. *Eur J Clin Pharmacol* 2009; 65:743–745.
- Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy. *Arch Intern Med* 1999; 159:941–955.
- Hopkins RL, Leinung MC. Exogenous Cushing's syndrome and glucocorticoid withdrawal. *Endocrinol Metab Clin North Am* 2005; 34(2):371–384.
- Bornstein SR. Predisposing factors for adrenal insufficiency. *N Engl J Med* 2009; 360:2328.

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