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Adrenal Suppression and Cushing's Syndrome Secondary to Ritonavir and Inhaled Budesonide

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Abstract

A 65 year old male with HIV and COPD developed Cushing's syndrome and adrenal suppression after receiving low-dose inhaled budesonide and ritonavir. Discontinuation of ritonavir led to improvement in Cushingoid complications, however evidence of adrenal suppression still persisted 6 months later. Low-dose budesonide is often viewed as a safer alternative to fluticasone when inhaled corticosteroid therapy is required in a patients on ritonavir. Our case illustrates that patients receiving low-dose budesonide and ritonavir should also be considered at high risk of Cushingoid complications.

Key words: Ritonavir; Budesonide; Cushing's syndrome; Adrenal suppression.

INTRODUCTION

Ritonavir-based inhibition of the hepatic cytochrome P450 CYP3A4 isoenzyme can be used to pharmacologically boost the levels of other protease inhibitors in antiviral regimens for human immunodeficiency virus (HIV) and more recently, Hepatitis C. However, a consequence of CYP3A4 inhibition is the accumulation of other substrates that are metabolized by the CYP3A4 system, including many of the inhaled corticosteroids (ICS) used in the treatment of asthma and chronic obstructive pulmonary disease (COPD) [1,2]. This can lead to iatrogenic Cushing's syndrome and has been frequently reported in patients with combined use of inhaled/intranasal fluticasone and ritonavir [3]. As a result, budesonide is a preferred ICS in patient's taking ritonavir because of its reported shorter half-life, lower lipophilicity and reduced systemic absorption [4].

Although iatrogenic Cushing's syndrome with the use of ritonavir and budesonide has been documented, these patients typically received doses of inhaled budesonide as high as 1600 micrograms or 800 micrograms twice a day [5,6]. We describe a case that illustrates the risk of iatrogenic Cushing's syndrome even when budesonide is administered at low doses (160 micrograms twice a day), highlighting the need for careful monitoring of these patients.

Case Report

A 65 year-old African American male with HIV, GOLD Stage IV chronic obstructive pulmonary disease (COPD), chronic Hepatitis B and hypertension, presented with a six-month history of fatigue, weakness and mild persistent leukocytosis. The patient's anti-retroviral regimen consisted of emtricitabine 200 mg, tenofovir 300 mg, darunavir 800 mg and ritonavir 100 mg once daily. In addition, the patient was taking inhaled albuterol as required and daily inhaled tiotropium bromide for control of his COPD. Budesonide-formoterol (80/4.5 micrograms) two puffs, twice a day was added one year prior to his presentation to improve control of COPD related symptoms. Physical examination was notable for uncontrolled hypertension (155/94 mmHg), and new-onset proximal myopathy of the upper and lower extremities with power grading of 4 out of 5. No hepatosplenomegaly or systemic lymphadenopathy was present.

Laboratory tests revealed a white blood count of 15,000 cells/ml (71% neutrophils), hemoglobin of 14.6 g/dL, platelets of 263/µL, creatinine of 1.2 mg/dL. His hemoglobin A1C was found to be 8.2%, increased from 6.5% five months prior. His CD4 count was 942 cells/µL with an HIV viral load of < 20 copies/mL.

The patient underwent evaluation for steroid accumulation and secondary adrenal suppression. A morning cortisol level was < 0.2 µg/dL (reference range 7-28 µg/dL). Subsequent ACTH (cosyntropin) stimulation testing (250 µg intravenously) revealed a baseline ACTH of 7.7 pg/ml (reference range 7-60 pg/ml) and cortisol levels of < 0.2 µg/dL (baseline), 1.2 µg/dL (30 minutes post ACTH) and 1.3 µg/

dL (60 minutes post-ACTH) with normal reference range of > 18-20 µg/dL 1 hour post ACTH stimulation. The patient was diagnosed with Cushing's syndrome and secondary adrenal suppression due to budesonide and ritonavir. Due to the severity of his COPD, inhaled budesonide was continued at the same dose but the patient's anti-retroviral regimen was adjusted to emtricitabine 200mg, tenofovir 300mg and dolutegravir 50mg daily with discontinuation of darunavir/ritonavir. Replacement hydrocortisone (total daily dose of 20 mg administered orally) was started to prevent adrenal crisis with a goal to eventually taper. Insulin therapy, along with nutrition and an exercise program was instituted to improve control of his diabetes mellitus. Six months later, the patient's hypertension was under control, his hemoglobin A1C had reduced to 6.3% and his white blood cell count had normalized. In addition, he reported improvement in his strength. His HIV remained well controlled with viral load < 20 copies/ml. Despite recovery of his morning cortisol level to 8µg/dL he failed his repeat cosyntropin stimulation test, and therefore continued on hydrocortisone supplementation for the prevention of Adrenal insufficiency.

Discussion

COPD is an important comorbidity in patients with HIV and many patients require maintenance therapy with ICS [7]. Those who receive both ICS and ritonavir [usually as part of a boosted protease inhibitor (PI)-based regimen], are at risk of iatrogenic Cushing's syndrome due to steroid accumulation from CYP3A4 inhibition by ritonavir. However, this risk differs among ICS types and is thought to be lower with beclomethasone and budesonide compared to fluticasone because of preferential pharmacokinetic properties [8]. To our knowledge, only two other reports in adult patients have documented the development of iatrogenic Cushing's syndrome and adrenal suppression with the use of low dose budesonide (160 micrograms once or twice a day). In both cases, Cushingoid symptoms and recovery of adrenal axis rapidly resolved following cessation of budesonide [9, 10]. In our patient, where we felt that continuation of budesonide was necessary for control of pulmonary disease, removal of ritonavir led to resolution of Cushingoid complications but adrenal suppression still persisted at six months.

Based on these cases, careful monitoring for the development of iatrogenic Cushing's syndrome is warranted in patients receiving ritonavir and ICS, even if low-dose budesonide is used. Along with management of the medical complications of steroid excess, substitution of ICS and/or ritonavir should be considered with alternative agents that have less or no interaction via the CYP3A4 system. Furthermore, if patients are at risk of adrenal insufficiency following medication changes, endocrine consultation should be sought regarding the administration of replacement hydrocortisone to prevent adrenal crisis [11].

Conclusion

Although inhaled budesonide is seen as a preferred ICS in patients on ritonavir, the risk of iatrogenic Cushing's syndrome still exists with this combination and patients should be monitored carefully for this complication.

Conflicts of Interests: The authors declare that there is no conflict of interest.

Patient Consent: Written informed consent was obtained from the patient prior to publication of this manuscript.

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