Exogenous Cushing Syndrome: simultaneous use of Advair® and boosted protease inhibitors

Abstract
We report 3 patients with HIV infection who developed exogenous Cushing Syndrome following the concomitant use of Advair Diskus (fluticasone and salmeterol) with ritonavir boosted protease inhibitors (PI). Currently, ritonavir is used almost exclusively in smaller doses to increase (boost) other PI levels given its potent inhibitory properties of the cytochrome P450. Fluticasone propionate, a potent synthetic corticosteroid used by inhalation for the treatment of asthma, is a substrate of cytochrome P450. This report intent to demonstrate the potential severity of this interaction and increase awareness about the risks of the concomitant use of these two medications.

Key words: Cushing syndrome, HIV, drug interactions, antiviral agents.

Introduction
With the advent of potent antiretroviral therapy, HIV has become a chronic, more manageable infection rather than a progressively fatal condition. Antiretroviral therapy has also evolved, with more tolerable and potent regimens; however the complexity of HIV therapy and potential for drug interactions has also greatly increased with 25 individual medications from 5 different classes. Drug interactions in HIV-infected patients can be complex and sometimes counterintuitive, and practitioners should regularly consult the drug interaction sections of prescribing information for antiretroviral drugs and rely on a concerted approach to gathering information on drug interactions that goes beyond studies sho-
wing exposure changes for co-administered drugs. Currently almost all protease inhibitors used in the treatment of HIV are used with a low dose (booster) of ritonavir (protease inhibitor that is also a potent inhibitor of the cytochrome P450 CYP 3A) to increase their levels. As a result there is greater probability of pharmacologic interactions with concomitant therapy used for morbidity unrelated to HIV. Inhaled fluticasone, a corticosteroid and substrate of hepatic CYP3A4, is known to interact with ritonavir, resulting in steroid accumulation, adrenal suppression and even florid Cushing’s syndrome. As intranasal and inhaled corticosteroids (ICSs) are widely prescribed for conditions such as allergic rhinitis, asthma, and chronic obstructive lung disease, there is increasing potential for both pediatric and adult HIV-positive patients to be exposed to ICSs while on ritonavir-based antiretroviral therapy.

We report a series of 3 cases of a human immunodeficiency virus type 1 infected individuals receiving combination antiretroviral therapy, which included ritonavir, who developed iatrogenic Cushing syndrome with profound complications after inhalational fluticasone for asthma and chronic obstructive pulmonary disease.

Cases
Case one
A 52 year old Hispanic man with HIV infection was on treatment with atazanavir 300 mg, ritonavir 100 mg and tenofovir/emtricitabine 300/200 mg all once a day, for several years. His HIV infection was well controlled with an undetectable viral load and stable CD4 count. About six months prior to admission to the hospital, he was prescribed fluticasone and salmeterol (Advair® 250/50) for treatment of his chronic obstructive pulmonary disease (COPD). Approximately 4 months after the concomitant use of fluticasone and salmeterol and his HIV medications, he complained of edema, weight gain and moon face. On examination he was found to have abdominal striae, truncal obesity and lipoatrophy of the lower limbs. His serum cortisol was <1 micrograms/dL, ACTH < 5 picograms/dL and 24 h urinary cortisol was <1 microgram/dL. MRI of the brain and adrenals were normal. A diagnosis of exogenous Cushing Syndrome was made and Advair® was discontinued and she was started on QVAR® (beclomethasone 80 mcg/spray, 2 sprays twice daily and Serevent 50 mcg inhalation every 12 hours). He received a short course of tapering steroids due to concern of adrenal insufficiency. He made an uneventful recovery and six months later he has not had any exacerbation of COPD and his weight gain has stopped. His serum cortisol level has returned to normal levels.

Case two
A 43 year-old Hispanic man with HIV infection and COPD was on treatment with darunavir 600 mg twice a day, ritonavir 100 mg twice a day and tenofovir/emtricitabine 300/200 mg once a day. He has been in the same antiretroviral regimen for over one year with undetectable viral load and stable CD4 count. For several years he was on treatment with darunavir 600 mg twice a day, ritonavir 100 mg twice a day and tenofovir/emtricitabine 300/200 mg once a day, for severe asthma (montelukast and albuterol). After her last admission to the hospital for asthma exacerbation, her medications were changed. She was started on Advair 250/50® and tiotropium bromide inhaler once a day and continued on albuterol inhaler as needed. Four months after the concomitant use of Advair® and ritonavir, she developed a clinically evident cushingoid syndrome with moonface and truncal striae and her diabetes became more difficult to manage requiring increasing doses of insulin. A diagnosis of exogenous Cushing syndrome was made. Advair® was discontinued and she was started on beclomethasone dipropionate HFA 80 mcg/spray, 3 puffs twice a day, and dexametasone tapering. Six months later her cushingoid symptoms have resolved and her diabetes mellitus has become under control with oral hypoglycemic agents.

Discussion
Exogenous Cushing’s syndrome usually presents with the same signs and symptoms as the endogenous or spontaneous Cushing’s syndrome. However, there are subtle but well recognized differences between them: characteristically, the exogenous form presents with: more striking manifestations, relatively lower rate of hypertension and hypokalemia, less hirsutism and other virilizing features, increased incidence of glaucoma and other ocular diseases such as posterior subcapsular cataracts; and increased incidence of avascular necrosis. Additionally, patients receiving supraphysiologic doses of steroids are at risk of adrenal insufficiency that is a potentially life-threatening condition. All forms of steroids with glucocorticoid activity are capable of producing Cushing’s syndrome even lower-potency agents with short half lives can cause the syndrome if given in adequate amounts with frequent delivery. The use of topical, intra-articular, or aerosol therapy has the advantage of a more targeted therapy with less systemic exposure; however it is clear now that inhaled corticoste-
roids have the potential to cause Cushing’s syndrome, alone or as result of interaction with other medications, such as ritonavir and itraconazole. Ritonavir is an HIV protease inhibitor that was originally licensed in the United States in 1996. Shortly after its approval it became apparent that the full dose needed for its antiviral effect was poorly tolerated. The lower doses (usually 100 mg to 200 mgs a day) needed to “boost” other protease inhibitors are better tolerated than the “antiretroviral” doses (600mg twice a day). The mechanism of action of this PI-boosting effect is related to the potent inhibition of the P450 CYP3A4 isoenzyme. This inhibition leads to sustained higher levels of most PI’s since that system is the primary pathway involved in the metabolism of most PIs. These higher, sustained levels of PI’s will usually prevent or overcome viral resistance and allow less frequent dosing, potentially improving adherence.

However, the activity of ritonavir over the cytochrome P450 metabolic pathway systems is not restricted to PI’s, and is the basis of an extensive list of known and potential drug interactions. This concern is highlighted by the widespread use of ritonavir since almost all PI’s currently used in the treatment of HIV infection are “boosted” with low dose of ritonavir. Fluticasone propionate is a synthetic corticosteroid with potent anti-inflammatory activity. It has a human glucocorticoid receptor agonist affinity 18 times greater than dexamethasone, almost twice that of fluticasone and is a substrate of cytochrome P450 3A4. A drug interaction study has shown that ritonavir (100 mg twice daily) can significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced (86%) serum cortisol concentrations. Salmeterol/fluticasone propionate (Seretide, Advair, Viani) administered using a multidose dry powder inhaler (Diskus®, Accuhaler®) is approved for the treatment of COPD and asthma in numerous countries. This combination is administered twice daily and has been found effective and generally well tolerated. These two components appear to have additive, or even synergistic, effects. ADVAIR DISKUS® (100/50, 250/50, and 500/50) are specially designed plastic devices containing a powder formulation of 100, 250, or 500 mcg of fluticasone and 50 mcg of salmeterol base in a double-foil blister strip, after a blister containing the medication is opened by activating the device, the medication is dispersed into the airstream created by the patient inhaling through the mouthpiece.

During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal suppression. This is in contrast with the scarcity of reports of significant interaction between ritonavir and other inhaled corticosteroids (budesonide, beclomethasone and ciclesonide) and intranasal corticosteroids (budesonide, beclomethasone, mometasone, triamcinolone and flunisolide) despite their widespread use.

The likelihood of managing patients with both, HIV infection and COPD or asthma is increasing given the growing prevalence of HIV infection on one hand, and the increased incidence of COPD in HIV infected individuals (increasing age of HIV-positive individuals on treatment and the high incidence of smoking in HIV infected individuals). It also has been suggested that HIV infection accelerates the course of COPD.

This report intent to demonstrate the potential severity of the interaction between these two drugs and increase awareness among practitioners about the risks of the concomitant use of ritonavir and fluticasone and the development of Cushing’s syndrome. Lack of awareness may lead to the wrong diagnosis of this condition as lipodystrophy with serious consequences.

References
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