Case Report

INHALED CORTICOSTEROIDS IN PERSONS WITH HIV INFECTION: NOT THAT HARMLESS.

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ABSTRACT

There is a growing group of HIV-seropositive patients at risk for chronic lung disease due to their life style and age. The interaction between certain antiretroviral drugs and corticosteroid inhalation therapy is potentially dangerous but often unrecognised.

We present three cases from our HIV-clinic of whom two developed full blown Cushing's syndrome over a short period of time and one presented with asymptomatic hypocortisolaemia due to serious drug interactions between HIV-drugs and inhaled corticosteroids.

General practitioners, HIV and chest physicians should all be aware of this potentially life-threatening interaction and the combination of those products should be avoided where possible.

Key words: Cushing, fluticasone, budesonide, HIV, ritonavir

INTRODUCTION

The prevalence of human immunodeficiency virus (HIV) infection worldwide is still rising. With adequate control of the virus and HIV-related illness through antiretroviral therapy (ART), this patient group is also growing older and is prone to other chronic illnesses, such as chronic obstructive pulmonary disease (COPD) or asthma which might require specific treatment. We report three cases from our HIV-clinic: two developed full blown Cushing's syndrome over a short period of time; another presented with asymptomatic hypocortisolaemia due to serious drug interactions between HIV drugs and inhaled corticosteroids (ICS).

CASES

Case 1

A 60-year-old man with a history of HIV-infection and COPD (GOLD II, moderate disease) had been on ART for the last five years. From January 2004 until August 2005 his therapy consisted of saquinavir, lamivudine, nelfinavir and zidovudine. In addition, he received chronic inhalation therapy (salmeterol 50 µg and fluticasone 500 µg one inhalation twice daily). In June 2005 his body weight was 70 kg, the $CD4^+$ lymphocyte count 560/µl (25%) and the HIV-viral load < 50 copies/ml. Since a few months he had been complaining of gynaecomastia, facial oedema, relapsing anal herpes simplex infections and diarrhoea. The morning serum cortisol level was unexpectedly low: 19 nmol/l (normal range 166-787 nmol/l). A work-up to detect the cause of this low cortisol level was not done at that time. Initially, some of these complaints were considered secondary to the ART. In August 2005, his therapy was switched to atazanavir, ritonavir, lamivudine and tenofovir Eight weeks later he developed an extensive cellulitis of the back of his right hand which was treated with intravenous flucloxacillin. Another 2 weeks later, in October 2005, he was admitted because of general weakness (especially in the legs), sudden weight gain (+4 kg) and bilateral pitting oedema of the legs. He then presented with a Cushingoid face, bilateral parotid swelling and a thin 'corticoid-impregnated' skin. The morning serum cortisol level was 4 nmol/l, the 24-hour free cortisoluria 14 µg/24 h (normal range 20-90 µg/24 h) and the adrenocorticotropic hormone (ACTH) was 5 pg/ml (normal range 9-52 pg/ml). The $CD4^+$ lymphocyte -count was 354/µl (20%) and the viral load was still undetectable. Other investigations (echocardiography, abdominal and cerebral CT scan, ECG, EMG) did not reveal abnormalities. Another week later, he developed a staphylococcal cellulitis at his right elbow, which was drained and also treated with flucloxacillin. His ART was temporarily interrupted on October 28, 2005 but the inhaled corticosteroids

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for his COPD were continued. Gradually, the malleolar oedema, the weakness, the parotid swelling and the weight gain subsided. Three months later, he was feeling well, with a body weight of 69 kg, a morning cortisol of 177 nmol/l and an ACTH of 12 pg/ml. On August 11, 2006 he was restarted on an ART regimen without ritonavir (emtricitabine, tenofovir and nelfinavir). Nevertheless, one month later he again had a very low morning serum cortisol (9 nmol/L) and a suppressed ACTH (<2 pg/ml). The inhaled corticosteroids were then switched to formoterol 4.5 µg/budesonide 160 µg. Two months later, he was doing well with almost normalised hormonal values (cortisol 124 nmol/l) and an undetectable viral load. About two years later the patient was still doing fine and on the same ART, with a normal serum cortisol of 306 nmol/l.

Case 2

A 48-year-old HIV seropositive man was admitted on September 11, 2005 with a diagnosis of Pneumocystis jirovecipneumonia and oropharyngeal candidiasis. He was treated with high-dose cotrimoxazole for 3 weeks and fluconazole. On October 1st 2005 he was started on zidovudine, lamivudine, lopinavir, ritonavir plus fluconazole, omeprazole and maintenance cotrimoxazole. The $CD4^+$ lymphocyte count was 30/µl (1.8%) and the viral load: 46.500 copies/ml. His body weight was 65 kg.

After two weeks, he complained of persisting dry cough without dyspnoea or fever. In view of the normal chest X-ray and blood gas analysis, a tentative diagnosis of post-infectious bronchial hyperreactivity was made and he was started on salmeterol 50 µg/fluticasone 500 µg one inhalation twice daily. Four weeks later he complained of sudden hoarseness, a swollen, puffy face and a sudden weight gain (+7 kg), despite little food intake. There was a marked bilateral parotid swelling. The $CD4^+$ lymphocyte count was 21 (3.2%) and the viral load <500 copies/ml. The morning cortisol was 25 nmol/L and the ACTH 5 pg/ml.

Inhaled corticosteroids were discontinued, and gradually the facial swelling and hoarseness subsided. After 4 weeks, the morning cortisol was 425 nmol/l and the ACTH 20 pg/ml. His body weight was 68.2 kg, the $CD4^+$ lymphocyte count 76/µl (3,6%) and the viral load remained undetectable.

Case 3

A 45-year-old Thai man with an HIV/hepatitis B virus coinfection since 2000 was started on ART (atazanavir, ritonavir, abacavir, lamivudine, tenofovir) since November 2005. He very rarely used inhaled fluticasone for his allergic asthma. In May 2006 he was admitted with a serious asthma attack requiring a short course of systemic methylprednisolone. He was then started on daily inhalation therapy (formoterol 4,5 µg/budesonide 160 µg, one inhalation once daily). Two months later he was doing well but the morning cortisol was low (27 nmol/l) with a low-normal ACTH of 16 pg/ml. In view of his asthma's seasonality, budesonide inhalations were discontinued and replaced by montelukast 10 mg once daily. Another two months later he was doing well with a normalised cortisol (532 nmol/L) and ACTH (64 pg/ml).

DISCUSSION

The potential interaction between ritonavir and inhaled fluticasone has been described earlier (1), but is being reported more frequently in recent years (2-6). In contrast, very few reports have been published concerning the interaction between non-fluticasone inhaled corticosteroids and ritonavir. Only very recently some similar cases of adrenal suppression have been described with budesonide (7, 8).

Cushingoid symptoms in combination with low serum cortisol and low serum ACTH can appear during exogenous corticosteroid use and are referred to as Cushing's syndrome. Distinction should be made with Cushing's disease, which is characterised by elevated serum cortisol and urinary free cortisol, together with lack of normal suppression by dexamethasone, due to endogenous production of excessive corticosteroids by the adrenal cortex (due to ACTH hypersecretion by the pituitary gland, due to ectopic ACTH production or adrenal tumours).

Ritonavir, and to a lesser extent other protease inhibitors inhibit the cytochrome P 450 fraction 3A4 (CYP 3A4) hence slowing down the metabolisation of any corticoid and increasing its systemic concentration (9-14). After inhalation of a corticosteroid, twenty percent is deposited in the lungs, with the more lipophilic molecules (e.g. fluticasone and beclomethasone) being retained most. The remaining eighty percent of the product is swallowed, enters the circulation through gastrointestinal absorption and undergoes a first pass metabolism in the liver. This results in a bioavailability of the oral fraction of these inhaled corticosteroids which is respectively less than 20%, 11% and 1% for beclomethasone, budesonide and fluticasone. In contrast, the entire pulmonary fraction enters the systemic circulation through the pulmonary vascular system so that the total bioavailability of the drug equals 20-40% of the original dose (15).

Fluticasone, with its highly lipophilic character, appears to be a very effective inhaled corticosteroid. Moreover, it is at least as effective as other inhaled corticosteroids at a much lower dose (16, 17). But it has also shown to exhibit greater dose-related systemic bioactivity compared to other ICS, particularly at doses above 0.8 mg/dl (18).

These two elements could have contributed to the more frequent reports on adverse events with ritonavir + fluticasone compared to ritonavir + budesonide or ritonavir + beclomethasone. Additionally, in patients with HIV infection, other frequently prescribed drugs (itraconazole, doxycyclin, isoniazide and macrolides) could lead to a similar interaction with (inhaled) corticosteroids (19). Since protease inhibitors (PI) other than ritonavir also have a certain cytochrome P450 inhibiting activity, this probably explains why our first case developed adrenal suppression in the absence of ritonavir but presence of one, and at a certain moment two PI's (nelfinavir-saquinavir). In addition the strength of the interaction has a high interindividual variability, probably due to genetic differences in the cytochrome system and protein binding.

The reason for the recent increase in published reports on this 'iatrogenic Cushing's syndrome' caused by the interaction ritonavir/inhaled corticosteroids is not clear. Increased awareness of the phenomenon or increased use of inhaled corticosteroids (and more specifically fluticasone) in this chronically ill population may play a role. With HIV-infection becoming a chronic illness in a progressively ageing and often smoking population, the prevalence of concomitant use of antiviral products and inhaled corticosteroids is on the rise, as well as the risk for potential interactions. Awareness of this risk by

the HIV physician, pulmonologist and general practitioner is of importance, as well as the selection of a safe combination of drugs where inhaled corticosteroids and antiviral therapy are needed. This could imply either an ART without protease inhibitors or at least without ritonavir when inhaled corticosteroids cannot be avoided. Likewise, prescribing inhaled corticosteroids in patients taking ART requires a very strict indication. If unavoidable, screening for adrenal suppression by measuring the serum cortisol and ACTH should be performed in those patients, especially when presenting with Cushingoid symptoms. Equally important is the choice of inhalation molecules with the least systemic effect and emphasising the rinsing of the mouth after use of an ICS. Ciclosonide, a new generation inhaled corticosteroid could possibly be of interest in these situations but this remains to be proven (20, 21).

CONCLUSION

We described three cases of interaction between inhaled corticosteroids and protease inhibitors with serious hormonal and/or clinical consequences. One case relates to a combination of ritonavir and budesonide, an ICS that only recently has been put forward to cause a similar adrenal suppression as seen with fluticasone. General practitioners, HIV and chest physicians should all be aware of this potentially life-threatening interaction and the combination of those drugs should be avoided where possible.

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