Iatrogenic Cushing's Syndrome Induced by Posaconazole

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Iatrogenic Cushing's syndrome induced by posaconazole

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Abstract

Iatrogenic Cushing's syndrome is an undesirable outcome of glucocorticoids treatment. It can be increased by pharmacologic interactions. Glucocorticoid therapy, given in association with ritonavir or some azole treatments are providers of iatrogenic Cushing's syndrome. We present a patient with common variable immunodeficiency who received seven years of itraconazole therapy for bronchial colonization with *Aspergillus* in combination with inhaled fluticasone without any Cushing symptoms. After a switch to posaconazole, the patient developed Cushingoid symptoms.

Iatrogenic Cushing's syndrome is caused by exposure to glucocorticoids and may be promoted by interaction with additional drugs that result in hypothalamic-pituitary-adrenal axis suppression. It is well documented in asthmatic human immunodeficiency virus (HIV)-infected patients receiving inhaled steroids in combination with ritonavir-containing antiretroviral regimen (1, 2). Steroids, whether inhaled, or injected by intranasal or epidural routes, have usually minimal systemic effects at recommended dosages. They are mainly metabolized by CYP3A4. The combination of long-term inhaled steroids with azole derivatives such as itraconazole, fluconazole or voriconazole has been reported to exacerbate hypothalamic-pituitary adrenal axis suppression (3–5). Posaconazole is an orally active broad-spectrum antifungal triazole that inhibits cytochrome P450-dependent CYP3A4 and therefore decreases synthetic glucocorticoids hepatic metabolism (6). We report a case of a patient who presented with Cushing's syndrome as following a treatment switch to posaconazole after seven years of itraconazole therapy without any Cushing symptoms.

Case report

A 51-year-old woman with common variable immunodeficiency associated with autoimmunity, bronchiectasis, asthma diagnosed in 1996 and a lymphoïd follicular hyperplasia diagnosed in 2010 was treated by montelukast sodium (10 mg once daily), triamcinolone acétonide (55 µg once daily), a long-acting ß2-adrenergic agonist associated with inhaled glucocorticoid (salmeterol and fluticasone respectively), risedronate (35 mg weekly), levothyroxine (75µg daily), desloratadine (5mg daily), sertraline (25mg daily) and intravenous immunoglobulins (IVIG). Since 2000, she was treated with itraconazole as prophylaxis for bronchial colonization with *Aspergillus fumigatus* without any radiologic signs of invasive aspergillosis or elevated fungal biomarkers (galactomannan or beta-D-glucan). In 2007, following the persistent bronchial colonization with *Aspergillus fumigatus* and the concomitant isolation of *Aspergillus nidulans* a switch for posaconazole as prophylaxis (200mg three times daily) was done.

She doesn't present any side effects during the first year of treatment. After 12 months of posaconazole treatment, she progressively presented at first a skin fragility and then a venous stasis dermatitis with weight gain (6 kgs) and a moon face. Blood pressure was 130/80 mmHg with no postural drop and fasting blood glucose level of 5.1 mmol/L.

Initial investigations detected low serum cortisol level (35.6 ng/mL) at 8.00 AM (normal range > 210 ng/mL). A standard short Synacthen test was abnormal with a baseline serum cortisol concentration at 46 nmol/L (normal: 170-740 nmol/L) rising only to 206.9 nmol/L (normal > 600 nmol/L) at 60 minutes, leading to the diagnosis of corticotroph insufficiency.

There was no evidence of impaired glucose tolerance. Search for anti-adrenal autoantibodies was negative, with limits of interpretation in this patient in IVIG substitution, and pituitary MRI was normal. ACTH (at 8:00 AM) < 10 pg/ml reflect the corticotrop insufficiency. Other hormonal investigations of the hypothalamic-pitituary axis were normal (at 8.00 AM),

prolactin = 11.1 µg/l (N = 3 – 29 µg/l), T4 = 4.7 pmol/L (N = 11-39 pmol/l), IGF 1 = 91.9 µg/ml (N= 70-300 µg/ml). Corticosteroids supplementation was introduced by hydrocortisone (40mg per day) and inhaled steroids were stopped.

Discussion

Oral glucocorticoid therapy is a common cause of iatrogenic Cushing's syndrome. Other routes of steroid administration such as inhalation, topical, ocular, nasal drops or epidural injections may also result in hypercorticism (7). This can be promoted by interaction between glucocorticoids and other drugs interfering with glucocorticoid metabolism such as ritonavir, itraconazole or fluconazole (8). We hypothesize that our patient probably developed clinical Cushing's syndrome as a result of elevated systemic concentrations of inhaled steroids, which led to corticotroph insufficiency resulting from adrenocorticotrophic hormone suppression. Inhibition of the cytochrome P450 CYP3A4 type-enzyme system by posaconazole leads to a reduction in fluticasone hepatic metabolism. With prolonged use, inhaled steroids have previously been associated with adrenal suppression. The combination of itraconazole, fluconazole or voriconazole with inhaled steroids has occasionally been reported to cause Cushing's syndrome after a few months of combination therapy, often reversible after treatment interruption (9). Our patient was on 7 years of itraconazole therapy in combination with fluticasone and never presented any Cushingoid symptoms. A review of the literature performed in 2008 pointed that budesonide, beclometasone, flunisolide and triamcinolone induce less iatrogenic Cushing's syndrom than fluticasone (10). A literature search did not reveal any case report of Cushing's syndrome resulting from interactions between non-fluticasone inhaled corticosteroids and ritonavir or triazoles. Unexpectedly, in three case

reports, inhaled beclometasone or budesonide was substituted by fluticasone with resolution of Cushingoid symptoms (10) .

Here, we report the first case of iatrogenic Cushing syndrome in the context of long-term administration of inhaled steroids (fluticasone) and posaconazole therapy. This event may have been promoted by the preceding use of itraconazole (200mg per day from 2000 to 2007). Posaconazole is a wide-spectrum antifungal drug active against common and emerging pathogenic fungi and molds such as *Mucorales*. Posaconazole is effective in chronic invasive aspergillosis (11). Because mold infections are often complications of chronic obstructive pulmonary diseases (12), long-term co-prescription of inhaled steroids and posaconazole with subsequent occurrence of Cushing's syndrome is expected to occur. Posaconazole does not inhibit CYP1A2, 2C8/9, 2D6 or 2E1 but inhibits CYP3A4 (6). All azole antifungals interfere with cytochrome P450 enzyme system and they can cause serious side effects when given with other drugs that are metabolized by P450 enzymes. It is interesting to note that interaction with azoles may not be a class effect and that there could be differences in interaction potential between each azole.

References

1. **Lipworth BJ**. 1996. Airway and systemic effects of inhaled corticosteroids in asthma: dose response relationship. Pulm Pharmacol **9**:19–27.
2. **Arrington-Sanders R, Hutton N, Siberry GK**. 2006. Ritonavir-fluticasone interaction causing Cushing syndrome in HIV-infected children and adolescents. Pediatr. Infect. Dis. J. **25**:1044–1048.
3. **Woods DR, Arun CS, Corris PA, Perros P**. 2006. Cushing's syndrome without excess cortisol. BMJ **332**:469–470.
4. **Wong J, Black P**. 1992. Acute adrenal insufficiency associated with high dose inhaled steroids. BMJ **304**:1415.
5. **Monoz-Cortes A, Montesdeoca A, Boada-Fernades del Campo C, Garcia-Sanchez-Colomer M, Fernandez-Quintana E, Garcia-Saiz M**. 2011. Interaction between voriconazole and budesonide with clinical relevance (Cushing's syndrom). Poster Abstracts. Basic & Clinical Pharmacology & Toxicology **109**:41–71.
6. **Wexler D, Courtney R, Richards W, Banfield C, Lim J, Laughlin M**. 2004. Effect of posaconazole on cytochrome P450 enzymes: a randomized, open-label, two-way crossover study. Eur J Pharm Sci **21**:645–653.
7. **Baş VN, Cetinkaya S, Aycan Z**. 2012. Iatrogenic Cushing syndrome due to nasal steroid drops. Eur. J. Pediatr. **171**:735–736.

8. **Hoover WC, Britton LJ, Gardner J, Jackson T, Gutierrez H**. 2011. Rapid onset of iatrogenic adrenal insufficiency in a patient with cystic fibrosis-related liver disease treated with inhaled corticosteroids and a moderate CYP3A4 inhibitor. Ann Pharmacother **45**:e38.

9. **Daveluy A, Raignoux C, Miremont-Salamé G, Girodet P-O, Moore N, Haramburu F, Molimard M**. 2009. Drug interactions between inhaled corticosteroids and enzymatic inhibitors. Eur. J. Clin. Pharmacol. **65**:743–745.

10. **Foisy MM, Yakiwchuk EMK, Chiu I, Singh AE**. 2008. Adrenal suppression and Cushing's syndrome secondary to an interaction between ritonavir and fluticasone: a review of the literature. HIV Med. **9**:389–396.

11. **Felton TW, Baxter C, Moore CB, Roberts SA, Hope WW, Denning DW**. 2010. Efficacy and safety of posaconazole for chronic pulmonary aspergillosis. Clinical infectious diseases **51**:1383–1391.

12. **Cornillet A, Camus C, Nimubona S, Gandemer V, Tattevin P, Belleguic C, Chevrier S, Meunier C, Lebert C, Aupée M, Caulet-Maugendre S, Faucheux M, Lelong B, Leray E, Guiguen C, Gangneux J-P**. 2006. Comparison of epidemiological, clinical, and biological features of invasive aspergillosis in neutropenic and nonneutropenic patients: a 6-year survey. Clin. Infect. Dis. **43**:577–584.