Iatrogenic Cushing’s Syndrome Induced by Posaconazole

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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, and some azole treatments are causes of iatrogenic Cushing’s syndrome. We present a patient with common-variable immunodeficiency who received 7 years of itraconazole therapy for bronchial colonization with *Aspergillus* in combination with inhaled fluticasone without any Cushingoid 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 a 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 metabolized mainly 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, 4, 5). Posaconazole is an orally active broad-spectrum antifungal triazole that inhibits cytochrome P450-dependent CYP3A4 and therefore decreases synthetic glucocorticoid hepatic metabolism (6). We report a case of a patient who presented with Cushing’s syndrome following a treatment switch to posaconazole after 7 years of itraconazole therapy without any Cushingoid symptoms.

A 51-year-old woman with common-variable immunodeficiency associated with autoimmunity, bronchiectasis, asthma diagnosed in 1996, and a lymphoid follicular hyperplasia diagnosed in 2010 was treated by montelukast sodium (10 mg once daily), tiamcinolone acetonide (55 μg once daily), a long-acting β2-adrenergic agonist associated with inhaled glucocorticoid (salmeterol and fluticasone), risedronate (35 mg weekly), levothyroxine (75 μg daily), desloratadine (5 mg daily), sertraline (25 mg daily), and intravenous immunoglobulins (IVIG). Since 2000, she was on triamcinolone acetonide (55 mg daily), risedronate (35 mg weekly), levothyroxine (75 μg daily), desloratadine (5 mg daily), sertraline (25 mg daily), and inhaled steroids supplementation was introduced by hydrocortisone (40 mg per day), and inhaled steroids were stopped.

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 corticosteroid insufficiency resulting from adrenocorticotropic 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 showed any side effects during the first year of treatment. After 12 months of posaconazole treatment, she progressively presented at first skin fragility and then a venous stasis dermatitis with weight gain (6 kg) and a moon face. Her blood pressure was 130/80 mm Hg with no postural drop, and she had a fasting blood glucose level of 5.1 mmol/liter.

Initial investigations detected a low serum cortisol level (35.6 ng/ml) at 8 a.m. (normal range, >210 ng/ml). A standard short Synachten test was abnormal, with a baseline serum cortisol concentration of 46 nmol/liter (normal, 170 to 740 nmol/liter), rising only to 206.9 nmol/liter (normal, >600 nmol/liter) at 60 min, leading to the diagnosis of corticotroph insufficiency.

There was no evidence of impaired glucose tolerance. Search for antiadrenal autoantibodies was negative, with limits of interpretation in this patient in IVIG substitution, and pituitary MRI was normal. An adrenocorticotropin (ACTH; at 8 a.m.) concentration of <10 pg/ml reflects the corticotrop insufficiency. Other hormonal investigations of the hypothalamic-pituitary axis were normal (at 8 a.m.): prolactin = 11.1 μg/liter (normal, 3 to 29 μg/liter), T4 = 4.7 pmol/liter (normal, 11 to 39 pmol/liter), IGF1 = 91.9 μg/ml (normal, = 70 to 300 μg/ml). Corticosteroids supplementation was introduced by hydrocortisone (40 mg per day), and inhaled steroids were stopped.

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presented any Cushingoid symptoms. A review of the literature performed in 2008 revealed that budesonide, beclometasone, flunisolide, and triamcinolone induce less-iatrogenic Cushing’s syndrome than fluticasone (10). A literature search did not reveal any case report of Cushing’s syndrome resulting from interactions between nonfluticasone 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’s 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 ofitraconazole (200 mg 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 coprescription 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 the 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 potentials between each azole.

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