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1 **Iatrogenic Cushing's syndrome induced by posaconazole**

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34 **Abstract**

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

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

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66 **Case report**

67 A 51-year-old woman with common variable immunodeficiency associated with
68 autoimmunity, bronchiectasis, asthma diagnosed in 1996 and a lymphoid follicular
69 hyperplasia diagnosed in 2010 was treated by montelukast sodium (10 mg once daily),
70 triamcinolone acetonide (55 µg once daily), a long-acting β₂-adrenergic agonist associated
71 with inhaled glucocorticoid (salmeterol and fluticasone respectively), risedronate (35 mg
72 weekly), levothyroxine (75µg daily), desloratadine (5mg daily), sertraline (25mg daily) and
73 intravenous immunoglobulins (IVIG). Since 2000, she was treated with itraconazole as
74 prophylaxis for bronchial colonization with *Aspergillus fumigatus* without any radiologic
75 signs of invasive aspergillosis or elevated fungal biomarkers (galactomannan or beta-D-
76 glucan). In 2007, following the persistent bronchial colonization with *Aspergillus fumigatus*
77 and the concomitant isolation of *Aspergillus nidulans* a switch for posaconazole as
78 prophylaxis (200mg three times daily) was done.

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

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

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

91 prolactin = 11.1 µg/l (N = 3 – 29 µg/l), T4 = 4.7 pmol/L (N = 11-39 pmol/l), IGF 1 = 91.9
92 µg/ml (N= 70-300 µg/ml). Corticosteroids supplementation was introduced by hydrocortisone
93 (40mg per day) and inhaled steroids were stopped.

94 **Discussion**

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

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

115 Here, we report the first case of iatrogenic Cushing syndrome in the context of long-term
116 administration of inhaled steroids (fluticasone) and posaconazole therapy. This event may
117 have been promoted by the preceding use of itraconazole (200mg per day from 2000 to 2007).

118 Posaconazole is a wide-spectrum antifungal drug active against common and emerging
119 pathogenic fungi and molds such as *Mucorales*. Posaconazole is effective in chronic invasive
120 aspergillosis (11). Because mold infections are often complications of chronic obstructive
121 pulmonary diseases (12), long-term co-prescription of inhaled steroids and posaconazole with
122 subsequent occurrence of Cushing's syndrome is expected to occur. Posaconazole does not
123 inhibit CYP1A2, 2C8/9, 2D6 or 2E1 but inhibits CYP3A4 (6). All azole antifungals interfere
124 with cytochrome P450 enzyme system and they can cause serious side effects when given
125 with other drugs that are metabolized by P450 enzymes. It is interesting to note that
126 interaction with azoles may not be a class effect and that there could be differences in
127 interaction potential between each azole.

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