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LETTER TO THE EDITORS

Drug interactions between inhaled corticosteroids and enzymatic inhibitors

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Drug-drug interactions may explain an important part of the systemic adverse effects of inhaled corticosteroids. A recent retrospective study aimed at estimating the incidence of adrenal insufficiency in users of inhaled corticosteroids reported 46 cases (involving fluticasone, budesonide, or beclomethasone) [1]. Subsequently, all of these cases were systematically analyzed in order to highlight cases resulting from an interaction. Of these, 15 were possibly due to an interaction and are detailed in Table 1. Eleven patients treated with fluticasone and four with budesonide were concomitantly treated with an enzymatic inhibitor: itraconazole (six cases), ritonavir (five cases), verapamil (two cases), and diltiazem (two cases). In adults, mean daily dose was lower in cases where a drug interaction was suspected [2,277 μg beclomethasone equivalent (BE) vs. 2,883 μg BE in cases where no drug interaction was suspected; data not shown]. The delay for diagnosis ranged from less than 1 month to 16 months after initiation of the enzymatic inhibitor treatment.

It is recognized that high doses of corticosteroids may induce Cushing's syndrome, and secondary adrenal insufficiency may result from negative feedback effects of glucocorticosteroids on the hypothalamic-pituitary-adrenal axis. Systemic adverse effects of inhaled corticosteroids are rare, although cases of Cushing's syndrome or adrenal insufficiency have previously been reported [1]. The lower doses administered in the cases where a drug interaction was suspected, in comparison with doses administered when no interaction was suspected, are evidence in favour of a mechanism of drug interaction. Indeed, the metabolism via CYP3A4 of corticosteroids, taken by oral or parenteral route, including dexamethasone, methylprednisolone or prednisolone, can be decreased by enzymatic inhibitors such as itraconazole [2, 3], clarithromycin [4], grapefruit juice [5], and calcium-channel blockers [6]. Among inhaled corticosteroids, fluticasone and budesonide are mainly metabolized by CYP3A4 [7, 8]. Thus an enzymatic inhibitor may increase the bioavailability of the inhaled dose fraction, leading to systemic complications as has been substantiated by the literature.

Six cases of Cushing's syndrome or adrenal insufficiency resulting from an interaction between fluticasone and itraconazole [9–11] and 14 cases resulting from an interaction between budesonide and itraconazole [12–14] have been described. The latter interaction has been

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Table 1 Cases of adrenal insufficiency and Cushing's syndrome in patients treated concomitantly with inhaled corticosteroids and an enzymatic inhibitor

	Gender	Age (years)	Type of effect	Inhaled corticosteroid	Dose µg/day (BE µg/day)	Associated enzymatic inhibitor	Other drugs
1	F	9	CS	Fluticasone	250 (500)	Ritonavir, lopinavir	Abacavir, didanosine
2	F	10	CS	Fluticasone	1,000 (2,000)	Ritonavir, lopinavir	Abacavir, topical beclomethasone
3	F	13	CS	Fluticasone	1,000 (2,000)	Itraconazole	Mycophenolate, tacrolimus, cotrimoxazole
4	M	14	AI	Budesonide	1,000 (1,250)	Itraconazole	–
5	M	16	CS	Fluticasone	500 (1,000)	Ritonavir, fosamprenavir	Zidovudine, tenofovir
6	F	26	AI	Budesonide	1,600 (2,000)	Itraconazole	–
7	F	27	AI	Fluticasone	1,000 (2,000)	Itraconazole	Dornase alpha
8	F	30	CS	Fluticasone	500 (1,000)	Itraconazole	Salmeterol, formoterol
9	F	31	CS	Fluticasone	1,000 (2,000)	Ritonavir, lopinavir	Lamivudine, tenofovir
10	F	36	CS	Fluticasone	1,500 (3,000)	Verapamil	Sertraline, omeprazole, zolpidem
11	M	42	CS	Fluticasone	2,000 (4,000)	Ritonavir, lopinavir	Lamivudine, stavudine
12	F	69	AI	Budesonide	1,600 (2,000)	Diltiazem	Theophylline, terbutaline, insulin, metoprolol, molsidomine, ranitidine, enalapril, atorvastatin, diclofenac, clomipramine, flecainide
13	F	58	AI	Fluticasone	1,000 (2,000)	Itraconazole	–
14	M	72	AI	Budesonide	2,000 (2,500)	Diltiazem	Atorvastatin, molsidomine, aspirin
15	F	75	AI	Fluticasone	NA	Verapamil	Salmeterol, molsidomine, aspirin

AI Adrenal insufficiency, *CS* Cushing's syndrome, *BE* beclomethasone equivalent, *M* male, *F* female, *NA* not available

confirmed by a pharmacokinetic study [15]. A case of Cushing's syndrome attributed to an interaction between budesonide and clarithromycin has also been reported [13]. In a recent review, 25 cases of adrenal suppression or Cushing's syndrome due to an interaction between ritonavir and inhaled or intranasal fluticasone were described [16]. In 2004, a Canadian press release was issued on the risk of adrenal insufficiency or Cushing's syndrome when ritonavir and fluticasone were administered together. A case of Cushing's syndrome has also been published with oral budesonide co-prescribed with amiodarone, also an enzymatic inhibitor [17].

This report of an important series of cases involving either fluticasone or budesonide adds to the body of evidence for such interactions. An interaction is also suspected in children [13, 14, 16]. However, in our series, too few children were included to be conclusive; doses were very variable and sometimes very important. Moreover, in one case, topical beclomethasone was associated.

Among CYP3A4 inhibitors, some are well-known (imidazole antifungals, ritonavir), but others are less notorious (calcium-channel blockers, amiodarone). When the administration of an inhaled corticosteroid with a CYP3A4 inhibitor is needed, patients should be strictly monitored for any sign of adrenal insufficiency or Cushing's syndrome. According to consensus guidelines, inhaled corticosteroids should be given at the lowest effective dose to reduce the risk of adrenal insufficiency in such patients.

To conclude, when choosing a glucocorticoid, the fact that beclomethasone is hydrolyzed and not metabolized via cytochrome P450 [18] should be taken into account in patients receiving potent CYP3A4 inhibitors.

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