

56. Drug Interaction between Inhaled Corticosteroids and Enzymatic Inhibitors

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Background: oral corticosteroids can induce adrenal insufficiency and paradoxical Cushing's syndrome. A few cases have been published with inhaled corticosteroids, mostly when administered at high dose or concomitantly with an enzymatic inhibitor.

Aim: to identify cases of adrenal insufficiency and Cushing's syndrome possibly due to a drug interaction between inhaled corticosteroids and enzymatic inhibitor.

Methods: a recent retrospective study, conducted between January 2000 and September 2005, in order to estimate the incidence of adrenal insufficiency / Cushing's syndrome in inhaled corticosteroids users, identified 32 biologically confirmed cases of adrenal insufficiency / Cushing's syndrome. From this study, we analysed 14 cases which could be due to a drug interaction.

Results: among those 14 cases, 11 patients were treated with fluticasone and 3 with budesonide, concomitantly with an enzymatic inhibitor: itraconazole in 6 cases, ritonavir in 5 cases (combined with lopinavir in 4 cases or with fosamprenavir in 1 case), verapamil in 2 cases and diltiazem in 1 case.

Discussion: inhibition of the isoenzyme 3A4 of cytochrome P450 (CYP3A4) by enzymatic inhibitors decreases the clearance of drugs usually metabolised by this enzyme, their effects being thereby increased. Fluticasone and budesonide are mainly metabolised by CYP3A4 to inactive metabolites and CYP3A4 inhibitors may affect their metabolisms. In the literature, cases are mainly reported with itraconazole, ritonavir and clarythromycin, but neither with diltiazem nor verapamil.

Conclusion: when the association of an inhaled corticosteroids with a CYP3A4 inhibitor is needed, patients should be strictly monitored for any sign of adrenal insufficiency / Cushing's syndrome, in the same way than for oral corticosteroids and dosage of corticosteroids must be reduced to avoid corticosteroid toxicity. Furthermore, beclometasone seems to be safer as its metabolism does not pass through the CYP3A4.