



Inhaled Corticosteroids: Watch for Drug Interactions

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Corticosteroids have traditionally been considered to have relatively few clinically important drug–drug interactions. While it has been known for many years that systemic corticosteroids do not work very well in patients taking enzyme inducers such as barbiturates or rifampin, only occasional cases of corticosteroid toxicity have been reported with concurrent use of enzyme inhibitors (usually CYP3A4 inhibitors). Now cases are starting to appear describing drug interactions with inhaled corticosteroids, however, and it seems likely that they are real.

What Do the Case Reports Show?

The typical case is an individual on full doses of an inhaled corticosteroid who is then started on a potent inhibitor of CYP3A4 (Table) such as itraconazole or ritonavir. For example, a 20-year-old woman with cystic fibrosis on inhaled budesonide 1600 µg daily developed Cushing’s syndrome after long-term treatment with itraconazole 800 mg daily.¹ A similar reaction was seen in a 4-year-old boy with cystic fibrosis on combined therapy with inhaled budesonide and itraconazole.² Another patient on inhaled budesonide 1200 µg daily developed Cushing’s syndrome after starting itraconazole 400 mg daily.³ Several case reports of Cushing’s syndrome have also been reported in patients on inhaled fluticasone who were then given the potent CYP3A4 inhibitor, ritonavir.^{4–6}

What Are the Usual Symptoms of the Interaction?

The symptoms result from corticosteroid toxicity, also known as Cushing’s syndrome. Findings in Cushing’s syndrome include moon-face, buffalo hump, bruising, weakness, menstrual irregularities, mood swings, acne, and hirsutism. Other findings in patients with excessive corticosteroid concentrations can include hypertension, edema, hyperglycemia, osteoporosis, poor wound healing, ocular cataracts, and glaucoma.

Are There Any Supporting Data?

Yes, in a double-blind crossover study in healthy subjects, itraconazole (200 mg daily for 5 days) produced a more than 4-fold increase in plasma concentrations of budesonide given by inhalation.⁷ The increased plasma budesonide was accompanied by substantial suppression of endogenous cortisol production. These results support the findings in the case reports, and suggest that the interaction is predictable rather than idiosyncratic.

Is the Duration of CYP3A4 Inhibitor Treatment Important?

Yes. While increased budesonide concentrations may be seen after only a few days of use of a CYP3A4 inhibitor, it usually takes at least a week—sometimes much longer—for serious corticosteroid toxicity to become manifest. In 1 case cited above, Cushing’s syndrome occurred after 2 weeks of combined therapy with budesonide and itraconazole, and this was considered “rapid.”² Thus, therapy with a CYP3A4 inhibitor for less than a week seems unlikely to result in significant adverse outcomes. Of course, patients with disorders such as diabetes or hypertension may be very sensitive to the adverse effects of

Table

Examples of CYP3A4 Inhibitors
Antibiotics Clarithromycin (Biaxin)* Erythromycin* Quinupristin (Synercid)
Antidepressants Fluvoxamine (Luvox) Nefazodone (Serzone)
Antifungal Fluconazole (Diflucan) Itraconazole (Sporanox) Ketoconazole (Nizoral) Voriconazole (Vfend)
Calcium-Channel Blockers Diltiazem (Cardizem)* Verapamil (Calan)*
HIV Drugs Amprenavir (Agenerase) Atazanavir (Reyataz) Delavirdine (Rescriptor) Indinavir (Crixivan) Nelfinavir (Viracept) Ritonavir (Norvir) Saquinavir (Invirase)
Miscellaneous Cyclosporine (Neoral) * moderate CYP3A4 Inhibitors

corticosteroids, and may have a rapid deterioration of their disease.

What About Nasal Corticosteroids?

Case reports have been published in which patients developed Cushing’s syndrome with concurrent use of nasal fluticasone and ritonavir.^{8,9} In 1 case, there was a positive dechallenge and rechallenge, a finding which supports the existence of an interaction between nasal fluticasone and ritonavir. Thus, at least with fluticasone, one should be alert for possible corticosteroid toxicity if potent CYP3A4 inhibitors are used concurrently. Theoretically, nasal budesonide would have a similar effect, but little is known about other nasal corticosteroids. ¶