MEDICINAL MISHAP

Iatrogenic Cushing's syndrome with inhaled fluticasone

Thomas Ledger
Registrar, Royal North Shore Hospital, Sydney

Winnie Tong
Immunologist, St Vincent's Hospital, Sydney

Janet Rimmer
Respiratory physician and allergist, St Vincent's Hospital, Sydney

Keywords
Cushing's syndrome, fluticasone furoate

Aust Prescr 2019;42:139–40
https://doi.org/10.18773/austprescr.2019.040

Case 1

A 52-year-old female with HIV and allergic bronchopulmonary aspergillosis had been taking co-formulated elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, itraconazole and inhaled fluticasone furoate/vilanterol for many months. When she developed a respiratory tract infection she was prescribed amoxicillin/clavulanic acid and subsequently erythromycin.

The patient was referred with facial swelling and she was noted to have developed moon facies and vocal hoarseness. On examination there was proximal myopathy, skin thinning with bruising, a small buffalo hump, and a blood pressure of 200/90 mmHg. Investigations revealed a low morning cortisol of 37 nmol/L (reference range (RR) 150–520 nmol/L).

Case 2

A 65-year-old male with a history of smoking-related chronic obstructive pulmonary disease was treated with inhaled fluticasone furoate/vilanterol. He also had HIV and was commenced on elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide which was well tolerated when he was followed up after one month.

Five months later, the patient reported fatigue, mood changes, facial puffiness, development of a buffalo hump, and weight gain. Proximal myopathy was noted on examination. There was a low serum cortisol of 14 nmol/L (RR 100–400 nmol/L).

Comment

These two cases illustrate the potential for iatrogenic Cushing's syndrome to result from drug interactions with inhaled corticosteroids. During 1971–2017, 24 cases were reported to the Therapeutic Goods Administration relating to fluticasone and nine relating to budesonide.[1] Most of these cases involved co-administration with itraconazole and ritonavir.[2,3]

Most of the dose of an inhaled corticosteroid remains in the oropharynx, but a proportion is swallowed and a smaller proportion remains bioactive after extensive first-pass metabolism by the liver. Both fluticasone and other corticosteroids require metabolism by the cytochrome P450 (CYP) 3A4 enzyme for inactivation and elimination.[2] The potency of inhaled corticosteroids also differs. These cases involved fluticasone furoate, a formulation approximately five times more potent than fluticasone propionate.

Potent inhibitors of CYP3A4 include itraconazole and the antiretroviral 'boosters' such as ritonavir and cobicistat, along with many other drugs such as erythromycin.[4] Itraconazole inhibits the fungal cytochrome system, with a collateral impact on human cytochromes including CYP3A4. HIV 'boosters' increase the bioavailability of other anti-HIV drugs, but also affect fluticasone and other drugs metabolised by CYP3A4.

Appropriate management of iatrogenic Cushing's syndrome includes glucocorticoid replacement for adrenal suppression and screening for, and prevention and management of, common comorbidities associated with glucocorticosteroid excess (such as dyslipidaemia, osteoporosis, diabetes and hypertension). Optimally the risk of this adverse effect could be reduced by either lowering the dose or frequency of the inhaled corticosteroid, selecting a less potent corticosteroid, or selecting alternatives for the azole antifungal or the 'booster' HIV drugs that do not inhibit CYP3A4.

To minimise systemic absorption, patients should be educated when using inhaled corticosteroids to rinse with water, gargle and spit out after use. The potential interaction of inhaled fluticasone and CYP3A4 inhibitors has been known for some time. These two recent cases are a timely reminder for clinicians to pay attention to inhaled corticosteroids, especially fluticasone, when taking a medication history and when prescribing potent cytochrome inhibitors such as the azole antifungals and particular antiretrovirals.

Conclusion

- Inhaled corticosteroids are metabolised by CYP3A4.
- Inhaled corticosteroids can cause Cushing's syndrome when co-administered with CYP3A4 inhibitors.
- Significant inhibitors of CYP3A4 include itraconazole, the HIV 'boosters' ritonavir and cobicistat, and erythromycin.
- Strategies to minimise these interactions include patient education, careful selection and dosing of the inhaled corticosteroid, and choice of antifungal drugs, as well as selecting non-interacting antiviral drugs.

Conflict of interest: none declared

REFERENCES

1. Therapeutic Goods Administration. Database of Adverse Event Notifications (DAEN) [Internet]. Canberra: Australian Government Department of Health; 2019. www.tga.gov.au/database-adverse-event-notifications-daen [cited 2019 Jul 1]
2. Bolland MJ, Bagg W, Thomas MG, Lucas JA, Ticehurst R, Black PN. Cushing's syndrome due to interaction between inhaled corticosteroids and itraconazole. Ann Pharmacother 2004;38:46-9. https://doi.org/10.1345/aph.1D222
3. Foisy MM, Yakiwchuk EM, Chiu I, Singh AE. Adrenal suppression and Cushing's syndrome secondary to an interaction between ritonavir and fluticasone: a review of the literature. HIV Med 2008;9:389-96. https://doi.org/10.1111/j.1468-1293.2008.00579.x
4. Day RO, Snowden L, McLachlan AJ. Life-threatening drug interactions: what the physician needs to know. Intern Med J 2017;47:501-12. https://doi.org/10.1111/imj.13404