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Clinicians who may prescribe or administer steroids to patients with HIV should be aware that concomitant use of a corticosteroid metabolised by cytochrome P450 3A (CYP3A) and a HIV-treatment-boosting agent (ritonavir, cobicistat) may increase the risk of systemic corticosteroid adverse effects.

Coadministration of these medicines is not recommended unless the potential benefit to the patient outweighs the risk, in which case patients should be monitored for systemic corticosteroid-related adverse reactions (eg, Cushing’s syndrome, adrenal insufficiency). Further information is on page 2.

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Cobicistat, ritonavir and coadministration with a steroid: risk of systemic corticosteroid adverse effects

Coadministration of a corticosteroid with an HIV-treatment-boosting agent may increase the risk of adrenal suppression due to a pharmacokinetic interaction.

Advice for healthcare professionals:

- all clinicians who may prescribe or administer steroids to patients with HIV should be aware that concomitant use of a corticosteroid metabolised by cytochrome P450 3A (CYP3A) and a HIV-treatment-boosting agent may increase the risk of systemic corticosteroid-related adverse effects
- although these reactions are rarely reported, there is potential for this interaction to occur even with non-systemically administered steroid formulations, including intranasal, inhaled, and intra-articular routes
- coadministration of a HIV-treatment-boosting agent with a CYP3A-metabolised corticosteroid is not recommended unless the potential benefit to the patient outweighs the risk, in which case patients should be monitored for systemic corticosteroid-related reactions
- if coadministration is necessary, use of beclomethasone should be considered where possible—particularly for long-term use. Beclomethasone is less dependent on CYP3A metabolism and, although the risk of an interaction leading to adverse corticosteroid effects may not be completely removed, it may be lower

Background

Pharmacokinetic boosters are agents that are used to inhibit the metabolism of other substances, thereby increasing or prolonging the action of these substances. Ritonavir and its structural analogue cobicistat, being inhibitors of the CYP3A subfamily, are boosting agents that prolong the action of some antiretroviral medicines.¹

Corticosteroids are mainly metabolised by the CYP3A enzyme group, particularly CYP3A4.²³ Therefore, use of a CYP3A inhibitor with a corticosteroid is anticipated to increase systemic steroid levels.

Cobicistat

An EU-wide review has identified 8 cases worldwide (including 1 published report⁴) of adrenal suppression during treatment with a cobicistat-containing regimen (Stribild) and subsequent prescription of an inhaled, intranasal, or intra-articular corticosteroid.

Reported reactions were adrenal insufficiency, adrenal suppression, and Cushing’s syndrome. The corticosteroids involved were intranasal and inhaled fluticasone, oral budesonide, and intra-articular triamcinolone. From clinical trials, a further report of adrenal insufficiency was identified where epidural

methylprednisolone had been used together with intranasal fluticasone.

Most reports involved long-term use of corticosteroids, ranging from 9 months to over 1 year—also a known risk factor for development of adrenal suppression.

Product information for cobicistat-containing products is being strengthened to: warn of the potential for systemic corticosteroid-related reactions occurring with concomitant use; highlight the need for monitoring of patients for these events during treatment; and to advise consideration of lower-risk alternatives where possible (particularly, inhaled or intranasal beclomethasone).

Beclomethasone is less dependent on CYP3A metabolism than some other corticosteroids, and in general interactions are unlikely. However, the possibility of systemic effects with concomitant use of cobicistat cannot be excluded, and therefore caution and appropriate monitoring is still advised with the use of beclomethasone.

Product information for corticosteroids is also being updated to warn of the potential for the interaction, resulting in systemic corticosteroid-related effects. This update excludes, however, formulations intended for cutaneous use only because of limited evidence of an interaction with cobicistat.

Ritonavir

Reports of corticosteroid related effects have been received concerning patients taking HIV-protease inhibitors boosted with ritonavir who were also given epidural, intra-articular, or intramuscular injections of triamcinolone. Up to 21 November 2016, 26 UK Yellow Card reports of an interaction with triamcinolone and ritonavir have been reported: 18 reactions of Cushing’s syndrome or cushingoid features, and 17 of adrenal suppression. Product information for injectable formulations that contain triamcinolone is being updated to warn about the interaction with ritonavir.

A separate EU review identified 2 reports of Cushing’s syndrome from interactions between ocular dexamethasone and ritonavir. The review also noted an increased risk of systemic adrenal effects occurring with both ocular and cutaneous use after intensive or long-term therapy, and also considered these factors to be a risk for interactions with ritonavir. Product information for dexamethasone ocular and cutaneous formulations is being updated with warnings about a potential interaction with CYP3A4 inhibitors, including ritonavir; warnings are already present in product information for dexamethasone administered via oral or parenteral routes.

Interactions are also expected to occur with other corticosteroids that are metabolised by CYP3A. Suspected adverse drug reactions, including interactions, should be reported to us on a Yellow Card.

Spironolactone and renin-angiotensin system drugs in heart failure: risk of potentially fatal hyperkalaemia—clarification

In light of feedback, we have clarified our article on concomitant use of these medicines in heart failure.

In February 2016, we published an article about the use of spironolactone and renin-angiotensin system drugs in patients with heart failure.

Following publication, we received feedback from a small number of readers and a professional organisation that the article was inconsistent with clinical guidelines.

We sought advice from the Commission on Human Medicine’s Pharmacovigilance Expert Advisory Group, who considered that the advice outlined in the article was consistent with the spironolactone Summary of Product Characteristics, and was proportionate to the risk associated with concomitant use. Moreover, they advised that the article was consistent with clinical guidelines (for both chronic and acute heart failure).

However, the Group acknowledged that a number of readers had interpreted the recommendation in the article to mean that spironolactone should not be used with an angiotensin converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB), and that the message could be clarified to avoid any confusion.

We now clarify that concomitant use of spironolactone with ACEi or ARB increases the risk of severe hyperkalaemia, particularly in patients with marked renal impairment, and should be used with caution.

The article now also clarifies that the same advice applies for concomitant use of the aldosterone antagonist eplerenone with ACEi or ARB in heart failure. The full article can be accessed here.


Letters sent to healthcare professionals in November 2016

In November 2016, the following letters were sent to relevant healthcare professionals:

- apremilast (Otezla®): risk of suicidal ideation and behaviour
- lenalidomide (Revlimid®): new advice about viral reactivation

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