Administering steroids with HIV treatment-boosting agents

GURMIT KAUR JAGJIT SINGH, RACHAEL JONES AND KEVIN SHOTLIFF

Co-administration of a steroid with an HIV treatment-boosting agent such as ritonavir or cobicistat increases the risk of iatrogenic Cushing syndrome and subsequent secondary adrenal suppression. This article discusses the strategies to help prevent this and describes how to identify and manage such interactions.

Steroids are used for a variety of indications in the HIV-infected population, for example in managing chronic respiratory disease, chronic back pain or immune reconstitution inflammatory conditions of the skin and eyes. A recent service evaluation of three major London HIV tertiary centres found that steroids were primarily being used in asthma/COPD and musculoskeletal conditions.1

Pharmacokinetic boosters are agents that work by inhibiting the metabolism of other drugs, thereby increasing the levels and prolonging the action of these drugs. Ritonavir and its structural analogue cobicistat are HIV treatment-boosting agents that potently inhibit the cytochrome P450 3A (CYP3A) enzyme group in the liver2-4 in order to prolong the action of some antiretroviral medications.5 A disadvantage of this pharmacological enhancement is the significant potential for interaction with CYP3A substrates, leading to side-effects.

A majority of prescribed and endogenous steroids are metabolised by the CYP3A subfamily, particularly by CYP3A4.4,6 Therefore, corticosteroid metabolism is decreased with the CYP3A inhibitors ritonavir and cobicistat.7 Subsequent increases in plasma concentrations of the prescribed steroid can induce iatrogenic Cushing syndrome (ICS) and through the hypothalamic-pituitary adrenal (HPA) axis feedback mechanism, ICS leads to secondary adrenal suppression and low endogenous cortisol levels.3-4,8

There is potential for this interaction to occur even with non-orally administered steroid formulations, including intranasal, inhaled, intra-articular, topical and intra-ocular routes.4,6,9-23 The importance of these reactions is being increasingly recognised4,10,14 but cases remain under-reported as non-oral steroid use is rarely disclosed by patients and poorly documented in medical records. Intra-articular steroid injections in particular are often administered by healthcare professionals who may not be aware of the individual’s HIV status, exposure to antiretroviral therapy (ART) or the potential for this interaction, the effects of which may manifest as early as...
four weeks after the injection is administered. In December 2016, the Medicines and Healthcare products Regulatory Agency (MHRA) released a drug safety update, advising on the choice of beclometasone with HIV treatment-boosting agents, particularly if long-term steroid co-administration is deemed necessary, as beclometasone is less dependent on CYP3A metabolism. This article outlines recommendations on the co-administration of a steroid with an HIV treatment-boosting agent as a guide to empower GPs to identify, prevent and manage this interaction as there are currently no established standardised guidelines.

Strategies to prevent ICS and secondary adrenal suppression

The current evidence on the effects of co-administration of HIV treatment-boosting agents and individual steroids by route is reviewed below.

Inhaled or intranasal steroids

No significant interactions have been reported between beclometasone and ritonavir-boosted ART. Beclometasone has low lipophilicity, a short elimination half-life and uses alternative pathways, making it the preferred option. Steroids to avoid are fluticasone and budesonide.

Oral

One case of ICS has been reported with oral budesonide and ritonavir. Short-term courses of oral steroids should be used at reduced doses, although evidence for this is lacking. If longer-term steroids are required, referral to the HIV specialist is recommended so that a switch can be made to non-ritonavir/cobicistat ART.

Injectable (intramuscular, epidural or intra-articular)

There are at least 30 published cases of ICS/secondary adrenal suppression in HIV-infected patients taking antiretrovirals following co-administration with an injectable steroid, all of whom were treated with triamcinolone, except for one patient who was injected with methylprednisolone. Intra-articular triamcinolone must be avoided in view of the strong evidence of ICS/secondary adrenal suppression when used with CYP3A inhibitors. Use of methylprednisolone, a CYP3A4-metabolised steroid, may theoretically result in ICS/secondary adrenal suppression but may be a preferred alternative at a lower dose in patients on ritonavir or cobicistat.

Topical and intra-ocular

The use of topical corticosteroids (for one month or more involving ≥4.5% of total body surface area) in combination with ritonavir has been shown to cause ICS. The development of ICS with subsequent secondary adrenal suppression was reported in a patient treated with ritonavir and corticosteroid eye drops. There is a lack of data on the risk of developing ICS/secondary adrenal suppression with varying strengths of topical preparations when used in conjunction with HIV treatment-boosting agents.

General advice

Co-administration of multiroute CYP3A-metabolised corticosteroids with an HIV treatment-boosting agent is not recommended unless the potential benefit to the patient outweighs the risk. Routine use of specific potent steroids including fluticasone, budesonide and triamcinolone in patients treated with CYP3A4 inhibitors is not recommended via any route. Steroid-sparing alternatives should always be considered. If these are not available, referral to the HIV specialist is advised so that switching to a non-ritonavir/cobicistat antiretroviral combination may be considered. In all cases, patients who have been prescribed steroids in primary care should be provided with written information on steroid sickness rules and advised to attend accident and emergency if they become unwell. The University of Liverpool’s free online resource on HIV drug interactions should be consulted to ensure safe and appropriate steroid prescribing.

Diagnosing ICS and secondary adrenal suppression

Physical features

The manifestations of ICS with subsequent secondary adrenal suppression with varying strengths of topical preparations when used in conjunction with HIV treatment-boosting agents.

Medication history

It is imperative to record a thorough medication history in patients with signs and symptoms of ICS, including date and method of administration of the steroids.

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**Table 1. Clinical features of iatrogenic Cushing syndrome, secondary adrenal suppression and adrenal crises**

<table>
<thead>
<tr>
<th>Iatrogenic Cushing syndrome</th>
<th>Secondary adrenal suppression</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Decreased libido</td>
<td>• Weakness/fatigue</td>
</tr>
<tr>
<td>• Obesity/weight gain</td>
<td>• Myalgia</td>
</tr>
<tr>
<td>• Plethora</td>
<td>• Arthralgia</td>
</tr>
<tr>
<td>• Round face</td>
<td>• Depression</td>
</tr>
<tr>
<td>• Menstrual changes</td>
<td>• Psychosis</td>
</tr>
<tr>
<td>• Hirsutism</td>
<td>• Malaise</td>
</tr>
<tr>
<td>• Hypertension</td>
<td>• Nausea*</td>
</tr>
<tr>
<td>• Ecchymoses</td>
<td>• Vomiting*</td>
</tr>
<tr>
<td>• Lethargy, depression</td>
<td>• Abdominal pain*</td>
</tr>
<tr>
<td>• Dorsal fat pad</td>
<td>• Anorexia/weight loss*</td>
</tr>
<tr>
<td>• Abnormal glucose tolerance</td>
<td>• Hypotension*</td>
</tr>
<tr>
<td>• Recurrent infections</td>
<td>• Decreased consciousness*</td>
</tr>
<tr>
<td>• Striae</td>
<td>• Unexplained fever*</td>
</tr>
<tr>
<td>• Oedema</td>
<td>• Unexplained hypoglycaemia*</td>
</tr>
<tr>
<td>• Proximal muscle weakness</td>
<td>• Hyponatremia/hypercalcaemia*</td>
</tr>
</tbody>
</table>

*Features suggestive of an adrenal crisis*
(intranasal, inhaled, injected, intraocular and topical).

**Diagnostic tests**

A 9am cortisol test is useful to screen for consequent secondary adrenal suppression because ICS is a clinical diagnosis. The most important biochemical finding in ICS/secondary adrenal suppression is a suppressed cortisol level.

A cortisol level of >450nmol/L generally indicates an intact HPA axis and if sampled between 8 and 9am, a cortisol level measuring <100nmol/L indicates deficient basal cortisol secretion. Of note, a peak level of >550nmol/L may be reported with older assays that are still used in many laboratories. Individuals with cortisol levels of <450nmol/L should be investigated further to distinguish those with an intact HPA axis from those with secondary adrenal suppression. A standard short synacthen test (SST) is recommended (cortisol levels are measured at 0, 30, 60 minutes after an intramuscular injection of 250µg tetracosactide is administered). Cortisol assays and reference ranges may vary, therefore it is important to check with the local laboratory.

**Figure 1.** Recommendations for investigating and managing suspected secondary adrenal suppression caused by the interaction between ritonavir/cobicistat and co-prescribed steroids

ICS = iatrogenic Cushing syndrome; SST = short synacthen test
When possible, screening for secondary adrenal suppression should occur at least one week after the dose has been tapered to a once-daily physiological dose (preferably with hydrocortisone, which has a shorter half-life). If a patient is on either prednisolone or hydrocortisone cover, ensure that neither of these is taken the night prior to, or on the morning of the test (9am cortisol or SST) as there is a potential for cross-reactivity in the assay, producing falsely elevated results. The final dose of steroids should be midday on the day prior to the test. On the day of testing, steroids should be withheld until the last blood sample is taken. A 9am cortisol may be performed within three days of stopping an inhaled steroid and monitored every two to four weeks until cortisol levels normalise.

**Monitoring HPA axis recovery**

The duration of impact of ritonavir/cobicistat-boosted ART on the HPA axis, recognising that it can take a year or longer for return to normal function, mandates a slow taper of replacement corticosteroid therapy and monitoring of symptoms. The recovery rate from adrenal suppression secondary to inhaled fluticasone has not been established.

Repeated 9am cortisol (every six to eight weeks until levels normalise) can be used to identify patients in whom the HPA axis has recovered. Steroid replacement can be stopped once 9am cortisol levels ≥450nmol/L.

In an individual who has received an injectable steroid, a referral should be made to the patient’s HIV team to switch ART to a non-ritonavir/cobicistat combination, if the patient is likely to continue to require the injectable steroid and there are no alternative disease-modifying agents. In asymptomatic patients, we advise a six-weekly cortisol level, the first measured at least four to six weeks post-steroid injection for 6–12 weeks to identify if the HPA axis has recovered.

**Management: steroid replacement and switching antiretrovirals**

Physiological glucocorticoid levels are equivalent to prednisolone 5.0–7.5mg daily, or hydrocortisone 20mg daily (in two to three doses). Symptomatic patients with secondary adrenal suppression should be treated with daily replacement steroid doses plus ‘stress doses’ during physiological stress (illness, injury or surgery). Giving stress doses of steroids involves doubling the oral steroid dose, or using parenteral steroids in patients unable to receive oral steroids.

As hydrocortisone has a short half-life, it is a preferred choice for steroid cover in some centres as there may be more opportunity for the HPA axis to recover compared with longer acting steroids. An asymptomatic individual with biochemical evidence of secondary adrenal suppression is also at risk of adrenal crisis during physiological stress and should receive stress doses, with or without daily physiological steroids. However, treating asymptomatic patients with secondary adrenal suppression may not necessarily delay HPA axis recovery.

An algorithm for the investigation and management of suspected secondary adrenal suppression is summarised in Figure 1. We recommend symptomatic patients taking ritonavir/cobicistat-boosted ART with suspected secondary adrenal suppression to start steroid cover with oral hydrocortisone 10mg daily in three divided doses (5mg/2.5mg/2.5mg in the morning, midday and late afternoon respectively) while planning investigations.

Corticosteroids and ritonavir/cobicistat should not be switched at the same time without steroid replacement cover or evidence of an intact HPA axis, as there is a significant risk of adrenal suppression. If patients have been switched off ritonavir/cobicistat-boosted ART and steroids simultaneously in error, we advise a hydrocortisone replacement regimen of 20mg/10mg/10mg daily in the morning, midday and late afternoon respectively.

**Role of the GP**

As front-line clinicians, GPs are usually the first to spot the systemic cortico-steroid side-effects in their patients, ie hypertension, weight gain or raised glucose levels. GPs who prescribe and administer steroids to patients with HIV should have a high index of suspicion for drug interactions between steroids and HIV treatment-boosting agents. They should be aware of safe steroid prescribing in the community and how to monitor for systemic corticosteroid-related side-effects in asymptomatic patients. Suggested reasons for referral and referral pathways into secondary care for patients identified with this drug interaction are listed in Table 2.

**Conclusion**

It is important that primary care physicians are aware of this rare but important drug interaction that can occur in patients taking HIV-treatment boosting agents and corticosteroids, so that they understand the harm it can cause and proactively monitor those at risk of related side-effects. Providing patients

<table>
<thead>
<tr>
<th>Reasons for referral</th>
<th>Relevant departments and/or immediate action</th>
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<tbody>
<tr>
<td>If patient has recently received a CYP3A4-metabolised injectable, inhaled, intranasal or a topical steroid and will continue to need it long-term with no suitable alternative</td>
<td>HIV multidisciplinary meeting</td>
</tr>
<tr>
<td>When a short synacthen test is required to distinguish an intact HPA from secondary adrenal suppression</td>
<td>Endocrinology team</td>
</tr>
<tr>
<td>If patient is unwell (hyponatraemic or hypotensive)</td>
<td>Measure serum cortisol, start hydrocortisone replacement and discuss with endocrinology</td>
</tr>
</tbody>
</table>

Table 2. Reasons for referral of patients on ritonavir/cobicistat and co-prescribed steroids to secondary care and recommended referral pathways
with written information on the type of steroid they are on and its indication, as well as what action to take when feeling unwell, is also extremely important.

References
15. Maviki M, et al. Injecting epidural and intra-articular triamcinolone in HIV-positive...

Declaration of interests
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