Secondary adrenal suppression and Cushing’s syndrome caused by ritonavir-boosted effects of inhaled fluticasone, injected triamcinolone and topical clobetasol: A case series

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Background

- Most glucocorticoids are hepatically metabolised but there is very limited information on the extent to which this occurs and which CYP enzymes are responsible for this.
- Fluticasone is known to be metabolised by CYP 3A4, and drug-drug interactions (DDI) between ritonavir and inhaled or nasal formulations are well described, leading to accumulation of glucocorticoid and increasing the risk of iatrogenic Cushing’s syndrome and suppression of the Hypothalamic-Pituitary-Adrenal axis (HPA-A).
- There are 7 cases in the literature describing the potential interaction of triamcinolone showing similar outcomes, including avascular necrosis of femoral heads of femur in 2 cases.
- We describe a series of patients on ritonavir-based ART who developed evidence of adrenal suppression.

Methods

- Case series based on 11 patients presenting to the HIV clinic who are known or subsequently discovered to have received a variety of glucocorticoids whilst taking ritonavir-based ART leading to adverse drug-drug interactions (DDI)
- 4 patients presented with symptoms of adrenal suppression after exposure to inhaled (n=4) and/or nasal (n=2) fluticasone whilst on ritonavir-based ART
- One patient (ID 7) presented with impaired mobility due to back pain and proximal muscle weakness, which on imaging showed osteoporotic vertebral crush fractures in thoracic and lumbar spine (fig 1) secondary to inhaled fluticasone use with LPV/r. He presented with cushingoid appearance with central obesity and truncal striae, and developed CMV viraemia, transaminitis, and influenza A1H1N1 during inpatient admission.

Fluticasone inhaled/nasal (1)

- 4 patients presented with symptoms of adrenal suppression after exposure to inhaled fluticasone (n=4) and/or nasal fluticasone whilst on ritonavir-based ART

Triamcinolone injection

- 6 patients on PI/r-based HAART presented after receiving triamcinolone injections.
- 4/6 presented with signs of Cushing’s syndrome and adrenal suppression.
- 2/6 were identified very early after injection, before symptoms of glucocorticoid excess had developed. In one case (patient 6) ATIV was switched to latalgravir within 3 weeks of injection to expedite clearance of triamcinolone. Patient 3 required PI-based HAART due to resistance.
- Triamcinolone injection was prescribed via the pain team, neurology, rheumatology and orthopaedic specialties, typically from the hospital.

Clobetasol cream

- One black-African female presented with Cushing’s syndrome after months of exposure to topical clobetasol, used for skin whitening. It is unclear to what extent the cream is absorbed but her PI-based regimen may have contributed to adrenal suppression.

Practice Points

- General:
  - Interactions between glucocorticoids and ritonavir are common and can lead to significant morbidity
  - Due to CYP inhibition by ritonavir, there is likely to be an increase in systemic exposure from most glucocorticoids irrespective of route of administration, with the possible exception of beclometasone
  - A tapering steroid dose may be required after exposure to short term oral glucocorticoid due to the increased exposure related to DDI with ritonavir
  - HIV diagnoses and potential for interaction should be stated on all referral letters, especially when referring patients for X-ray guided glucocorticoid injections.

Inhaled steroids and ritonavir:

- Fluticasone inhaled and nasal sprays should be avoided wherever possible.
- Beclometasone is the preferred inhaled steroid due to lack of observed interactions.
- When beclometasone is ineffective then inhaled budesonide may be an alternative but used at the lowest dose with titration, counselling, and monitoring of cortisol.
- Steroid sparing therapies should be considered.

Injectable steroids:

- Triamcinolone should be avoided for patients prescribed ritonavir, and potentially other CYP 3A4 inhibitors such as the HCV NS53 protease inhibitors.
- Methylprednisolone may be a suitable alternative, although there is limited data on DDI and safety.

- A morning cortisol should be performed 2 weeks after any glucocorticoid injection with referral to endocrinology if measured cortisol is low.

ART modifications:

- If a glucocorticoid is indicated with high risk of DDI then switching to a PI/r sparing regimen should be considered for the duration of glucocorticoid exposure.
- If a PI/r sparing regimens are not possible due to significant HIV resistance, a discussion should be had over choice and dose of glucocorticoid, plus planned follow up between the HIV team and referring clinician.

Conclusions

- As we increasingly involve primary care and other specialties in our patient’s care we will need to be vigilant for the potential of these interactions, and provide colleagues and patient alike with information resources for drug interactions.
- When patients on ritonavir-based HAART require glucocorticoids which interact, a multi-disciplinary approach is necessary to avoid increased morbidity.

References

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- Sultana I, et al. CROI 2014; Seattle, Session 110, poster O102
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