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

NJ Marshall[1], K Gurazada[2], P Bouloux[2], B Khoo[2], and MA Johnson[1]
1. Ian Charleson Centre for HIV medicine, Royal Free London NHS Foundation Trust
2. Department of Endocrinology, Royal Free London NHS Foundation Trust

Royal Free London NHS
NHS Foundation Trust

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

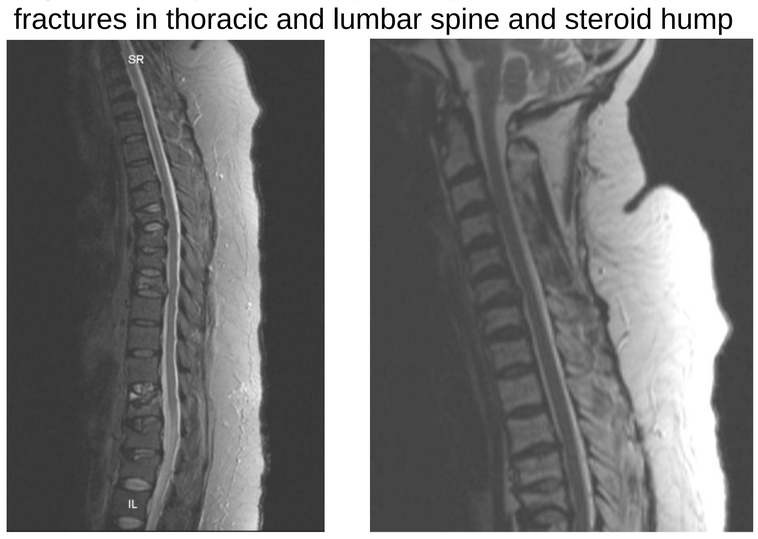
- Case series based on 11 patients presenting to the HIV clinic who are known or subsequently discovered to have received a variety of glucocorticoids whilst taking ritonavir-based ART leading to adverse drug-drug interactions (DDI)

Fluticasone inhaled/nasal (1)

- 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 AH1N1 during inpatient admission

Fluticasone inhaled/nasal (2)

Fig 1: MRI Spine showing osteoporotic vertebral crush fractures in thoracic and lumbar spine and steroid hump



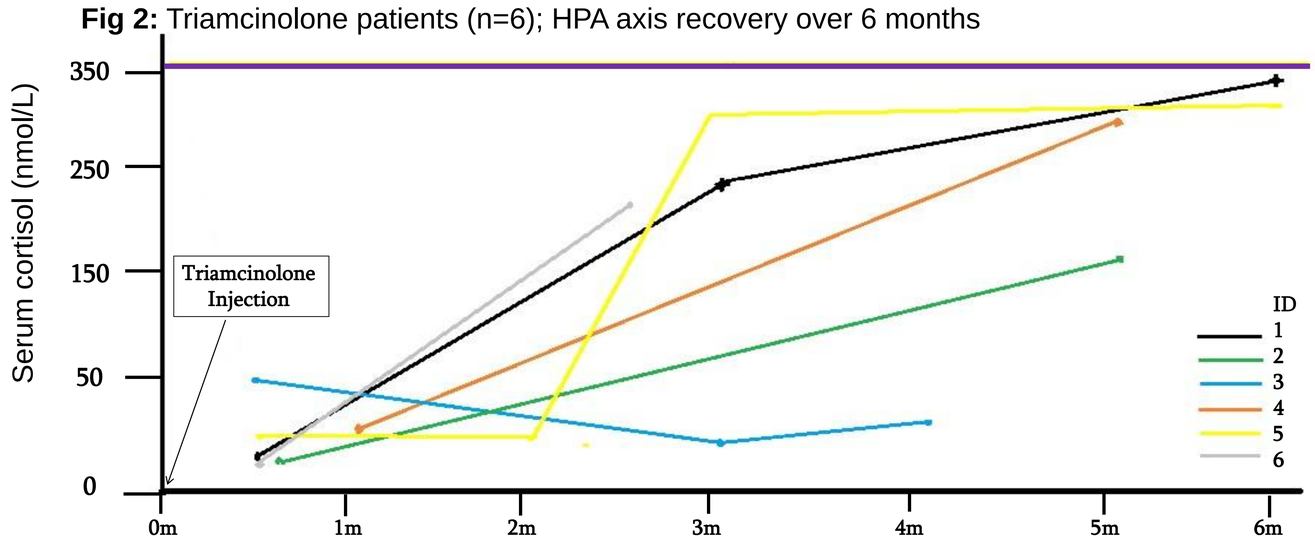
Triamcinolone injection

- Six 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) ATV/r was switch to raltegravir 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 specialities, typically from with 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

Fig 2: Triamcinolone patients (n=6); HPA axis recovery over 6 months



Cortisol of <80nmol/L: adrenal suppression requiring replacement. Cortisol 80-450nmol/L: possible adrenal suppression, investigate with SST. Cortisol >450nmol/L: adequate response, no further investigation

Fig 3: Patient exposed to triamcinolone, fluticasone or clobetsol

ID	Age/Sex	Glucocorticoid	Route of exposure / Dose	Duration of exposure	ART regimen	Presented with	Effect of interaction	Hydrocortisone replacement therapy given	Change in ART
1	47 M	Triamcinolone	IA 40mg	2 doses	ATV/r/ TDF/TFC	Fatigue, dizziness on standing, chest infection	Adrenal suppression	No	No
2	47 M	Triamcinolone	IA 80mg	stat	LPV/r	Nausea, vomiting, diarrhea, urine infection, worsened type 2 diabetes	Adrenal suppression	No	No
3	65 M	Triamcinolone	IA 40mg	2 doses	ATV/r/ MVC/RAL	No symptoms as early recognition	Adrenal suppression	Yes	No
4	39 F	Triamcinolone	IA 40mg	2 doses	DRV/r/ TDF/FTC OD	Weight gain, moon face, acne, oral candiasis, worsening depression	Cushing's syndrome with adrenal suppression	Yes	DRV/r → RAL at month 4
5	42 M	Triamcinolone	IA 80mg	Stat	ATV/r/ NVP/TDF	Severe proximal myopathy	Adrenal Suppression	No	No
6	42 M	Triamcinolone	IA 40mg	2 doses	ATV/r/ TDF/FTC	No symptoms as early recognition	Adrenal Suppression	Yes	ATV/r → RAL at wk3
7	55 M	Fluticasone	INH 1000mcg/day	2 yrs	LPV/r/ TDF/FTC	Back pain (Osteoporotic crush fracture, see image 1) with overt Cushing's syndrome, Aspergilloma	Cushing's syndrome with adrenal suppression	Yes	No
8	45 M	Fluticasone	INH 1000mcg/day	2 yrs	ATV/r/ TDF/TFC	Weight gain, plethoric puffy face, centripetal obesity, striae, proximal weakness	Cushing's syndrome with adrenal suppression	Yes, short term	No
8	45 M	Fluticasone	INH 1000mcg/day	7 days	ATV/r/ TDF/TFC	Tiredness, plethoric facies after ritonavir re-commenced	Adrenal Suppression	Yes, short term	No
9	71 M	Fluticasone	INH 400mcg/day + nasal spray	Months + weeks	ATV/r/ TDF/FTC	Overt Cushing's syndrome	Cushing's syndrome with adrenal suppression	No	No
10	42 F	Fluticasone / betamethasone	Nasal spray / 0.1% cream	4 weeks	LPV/r/ SAQ/NVP	No symptoms as early recognition	Adrenal suppression	No	No
11	72 F	Clobetsasol	Skin whitening cream	Several months	ATV/r/ ABC/3TC	Overt Cushing's syndrome	Cushing's syndrome with adrenal suppression	Yes	No

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

Fig 4: Potential interactions of ritonavir with available corticosteroid preparations (author's opinion)

Drug	Injection	PO	Inhaled	Nasal	Top
Fluticasone	●	na	●	●	■
Budesonide	na	■	■ / ●	■	na
Triamcinolone	●	na	na	●	■
Mometasone	■	na	■	■	■
Methylpred	■	■	na	na	na
Prednisolone	■	■	na	na	■
Hydrocortisone	■	■	na	na	♦
Dexamethasone	■	■	na	na	■
Beclometasone	♦	♦	♦	♦	♦

Key: ● Contraindicated/risk of severe AE, ■ Caution, ♦ minor risk, na not applicable

Inhaled steroids and ritonavir:

- Fluticasone inhaler 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 NS3 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 modification:

- 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

- Foisy MM et al. HIV medicine 2008;9:389-396
- Mollman et al. Eur J clin pharmacol 1998;53:459-467;
- Ramanathan R et al. CID 2008;475
- Sarita B et al. CROI 2012, Seattle, Session 109, poster 611
- Sarita B et al. CROI 2012, Seattle, Session 109, poster 610
- www.hivclinic.ca accessed 10/4/2012