

High risk of unrecognised adrenal suppression and symptoms of steroid excess in HIV+ clinic patients exposed to Ritonavir and topical fluticasone: Results of a case-control study

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ABSTRACT

Background: Case reports of exogenous steroid excess and adrenal insufficiency in patients on inhaled or nasal fluticasone propionate (FP) and ritonavir (RTV) –containing, Protease Inhibitor (PI) regimens have underscored the potential for this interaction. **Methods:** To determine whether unsuspected adrenal suppression occurs in HIV+ patients using RTV-FP in a clinic setting, fasting morning cortisol screening was done on sequential unselected patients undergoing routine HIV followup at St Paul's Hospital Immunodeficiency Clinic, Vancouver British Columbia between July and October 2005. Cases, defined as those with a cortisol value <100 nmol/L were assessed for symptoms of either adrenal suppression or exogenous steroid excess. Controls were those with a normal fasting serum cortisol (175-685 nmol/L). All patients who underwent cortisol screening had their medication records abstracted from both the provincial anti-retroviral (ARV) and prescription drug databases (Pharmanet). P values were calculated for the comparison between cases and the unmatched control group for the RTV-FP pharmacologic interaction as a cause of a suppressed fasting cortisol. **Results:** 50 patients were screened. The average age was 49yrs and 88% were male. 92% of the patients were on ARVs, and 93% of the ARV regimens contained RTV-boosted PIs. 7 patients were identified with suppressed fasting cortisols (<28nmol/L in 7/7) (cases), and 43 patients (controls) were un-suppressed. All 7 were on RTV-containing PI regimens and FP (inhaled=6, nasal =1) versus only 1 control (p.value <0.0001, Fishers exact test). 6/7 cases were virologically suppressed, with a median CD4 of 340/mm³ (240-430). For cases the median time on ARV regimens was 8 months (range 2-15months) and 6/7 had been on FP for >10months. Of the 7 adrenally suppressed patients, 3 were asymptomatic and 4 were symptomatic: 2 had Cushingoid features, 1 had easy bruising and 1 experienced loss of diabetic control. **Conclusions:** A high proportion of RTV-FP-exposed patients were identified with suppressed fasting cortisols (7/8-88%), including 57% with associated but unrecognized symptoms, highlighting the need for increased clinical vigilance. RTV-FP combinations should be avoided where alternatives exist, and routine fasting cortisol screening applied in patients on this combination

Background

- Inhaled corticosteroids serve as the mainstay in the management of chronic mild to moderate asthma and are prescription drugs in Canada.
- Normally there is limited systemic absorption of these agents from lung or GI tract, with clearance via the small intestine or liver via the CYP3A4 isoform.
- Fluticasone (FP) is available as both an inhaled and nasal preparation and differs pharmacokinetically in that it is highly lipophilic, has a large volume of distribution and therefore prolonged half-life (14hrs vs. 2-6 hrs for other agents in this class), but initial studies of FP use in asthma patients did not reveal significant adrenal suppression.
- A multiple-dose crossover study previously conducted in 18 healthy volunteers with FP aqueous nasal spray 200µg daily co-administered for 7d with RTV 100mg BID showed an increase in FP Cmax and AUC of 25 and 350-fold respectively, along with a concomitant 86% decrease in plasma cortisol AUC.
- The putative mechanism of this interaction is RTV mediated CYP3A4 inhibition of FP metabolism at the intestinal and/or hepatic level.
- Since 1999 numerous case reports have documented iatrogenic Cushing's syndrome due to this interaction and product monographs were altered in 2004 to caution against concomitant use of FP and RTV.
- The study objective was to determine the frequency of adrenal suppression in HIV+ patients using inhaled FP and Ritonavir in a clinic setting.

Methods

- Patients seen through the tertiary care HIV clinic at St Paul's hospital, Vancouver, British Columbia from July 1, 2005 to October 15, 2005 were included.
- Routine fasting cortisol values were collected on sequential patients.
- Cases** were defined as those patients with cortisol values <100nmol/L while **Controls** were those with normal values (175-685nmol/L)
- Cases were assessed clinically by an Endocrinologist for signs and symptoms of adrenal dysfunction – either of adrenal suppression or exogenous steroid excess.
- Database records were then abstracted for current active prescriptions using the Provincial prescription drug database- Pharmanet – to capture outpatient exposure and dose of FP containing products.
- Information on type and dose of antiretroviral treatment was obtained through chart review and the BC Centre for Excellence in HIV/AIDS Drug Treatment Program.
- The cases and unmatched control groups were compared, and p values were calculated for the RTV-FP interaction as the cause for a suppressed fasting cortisol.

Table 1: Baseline Characteristics of Study Population

Median Age	49yrs (range 38-63yrs)
# Male Patients (%)	44 (88%)
# Current Antiretroviral Use (%)	46 (92%)
# PI-based ARVs	43 (93%)
PI Therapy in Use	19 Lopinavir-ritonavir (LPV-RTV) (44%) 16 Atazanavir (37%) 4 combination PIs (9%) 4 Other PI's (9%)

Table 2: Cases and Controls based on suppressed fasting cortisol vs. Exposure to Ritonavir and fluticasone therapy.

		FASTING CORTISOL <100nmol/L	
		+	-
RTV-FP Use	+	7	1
RTV- FP Use	-	0	42



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Results

- 7/50 patients screened were identified with fasting cortisol <100nmol/L and hence were defined as "cases".
- All 7 had cortisol values <28nmol/L (normal 175-685nmol/L).
- 7/7 were on RTV-FP combinations vs. only one patient in the un-suppressed group (p value <0.001, Fisher's exact test) See Tables 2, 3.
- 3/7 (42%) cases were on LPV-RTV and 5/7 (71%) cases were on a dose of RTV > 100mg/d.
- For cases the median time on the current ARV regimen was 8 months (2-15 months) and the median time on FP was 12months (2-15months)
 - 6/7 were virologically suppressed, with a median CD4 count of 340/mm³.
- 4/7 cases had symptoms of steroid excess which had been clinically unrecognized, including Cushingoid features, excess bruising, osteoporosis and loss of diabetic control.

Table 3: Characteristics of patient's with documented adrenal suppression

Patient	Age	Gender	Ritonavir dose/d (mg)	FP daily dose (µg), preparation	Symptoms Present	Abnormal ACTH Stimulation Test
1	44	M	200	500 inhaled	Asymptomatic	Not tested
2	59	F	100	500 inhaled	Cushingoid	Yes
3	42	M	200	1200 Inhaled/nasal	Cushingoid, osteoporosis	Yes
4	49	M	200	500 inhaled	Easy bruising	Yes
5	48	M	200	400 inhaled	Loss of diabetic control	Not tested
6	50	F	266	500 inhaled	Asymptomatic	Yes
7	51	M	100	500 inhaled	Asymptomatic	Not Tested

Conclusions

- A high proportion of RTV-FP exposed patients were identified with suppressed fasting cortisol values (7/8 – 88%) with 57% experiencing associated, but unrecognized symptoms.
- Heightened clinical vigilance for RTV-FP interactions is needed, particularly since patients may not report FP use and non-prescription preparations are available in some countries.
- Further studies are needed regarding the effect of RTV dose and other nasal/inhaled steroids on adrenal suppression.
- RTV-FP combinations should be avoided where alternatives exist, and routine fasting cortisol serves as a useful screening test in patients on this combination.