Secondary Adrenal Insufficiency Due to the Co-Administration of Ritonavir and Inhaled Fluticasone Propionate

Case report

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Abstract: Ritonavir is a powerful inhibitor of the cytochrome P450 3A4 (CYP3A4) isoenzyme. It is used as a pharmaceutical enhancer in the management of HIV-positive patients. However, when co-administered with other drugs that are metabolised via the CYP3A4 pathway, ritonavir can potentially cause serious drug-drug interactions. Inhaled fluticasone propionate, which is used to treat asthma and chronic obstructive airway disease, is particularly prone to such interactions due to its physiological attributes. We report a HIV-positive 48-year-old male patient who presented to Al Nahdha Hospital, Muscat, Oman, in 2012 with weight loss, generalised weakness and fatigue and diagnosed with secondary adrenal insufficiency as a result of concomitant ritonavir and inhaled fluticasone.

Keywords: Human Immunodeficiency Virus; Ritonavir; Fluticasone; Drug Interactions; Adrenal Insufficiency; Case Report; Oman.
Case Report

A 48-year-old man presented to the HIV clinic of Al Nahda Hospital, Muscat, Oman, in 2012 for a routine check-up. He had initially been diagnosed with an asymptomatic HIV infection in 1999 with a baseline cluster of differentiation (CD)4 count of >200 cells/mL³. At the time of diagnosis, his only comorbidity was bronchial asthma. Subsequently, the patient had developed an atypical mycobacterial infection in 2008 after which HAART was initiated in the form of 150 mg of lamivudine and 300 mg of zidovudine twice a day and 600 mg of efavirenz once a day. Six months later, due to virological failure, his medication regimen was changed to 400 mg of oral didanosine once a day and 40 mg of oral stavudine and 800/100 mg of oral ritonavir-boosted indinavir/ritonavir twice a day. This resulted in a satisfactory immunological response and complete viral load suppression. However, due to intolerance, these antiretroviral (ARV) drugs were again changed in 2010 to 150 mg of oral lamivudine, 300 mg of oral abacavir and 400/100 mg of oral lopinavir/ritonavir twice a day. From 1999 until 2007, the patient also took 200 μg of inhaled salbutamol as required and 100 μg of inhaled beclomethasone twice a day for his asthma. In 2008, the beclomethasone was substituted for 250 μg of inhaled fluticasone propionate twice a day. 

At presentation, the patient reported a two-month history of weight loss, generalised weakness and fatigue. His vital signs were normal apart from low blood pressure (90/60 mmHg). His examination results were unremarkable, with no signs of Cushing’s syndrome or lipodystrophy. Routine investigations, including a complete blood count and urea, electrolyte, liver function, thyroid function and lipid profile tests, were all within normal limits. His CD4 count was 425 cells/mL³ and the HIV viral load was <20 copies/mL.

Table 1: Serial basal and stimulated cortisol and adrenocorticotropic hormone levels of a HIV-positive 48-year-old male patient with secondary adrenal insufficiency

<table>
<thead>
<tr>
<th>Time</th>
<th>Basal cortisol level in nmol/L</th>
<th>Stimulated* cortisol level in nmol/L</th>
<th>Serum ACTH in pg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>At presentation</td>
<td>7</td>
<td>71</td>
<td>5.4</td>
</tr>
<tr>
<td>1 month later</td>
<td>11</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8 months later</td>
<td>136</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11 months later</td>
<td>317</td>
<td>-</td>
<td>43.1</td>
</tr>
<tr>
<td>16 months later</td>
<td>390</td>
<td>880</td>
<td>-</td>
</tr>
</tbody>
</table>

*One hour after the administration of 250 μg of synthetic ACTH.

At baseline, his morning serum cortisol levels were 7 nmol/L (normal range: 200–550 nmol/L) on two occasions and his plasma adrenocorticotropic hormone (ACTH) level was 5.4 pg/mL (normal range: 7–50 pg/mL). One hour after administering 250 μg of synthetic ACTH, his cortisol level increased to 71 nmol/L. Levels of other pituitary hormones, plasma sodium and potassium were within normal limits.

A diagnosis of secondary adrenal insufficiency was made. The administration of inhaled fluticasone propionate was immediately halted and the patient was instead prescribed 20 mg of oral hydrocortisone in two divided doses per day. Within four weeks, symptoms of weakness and fatigue had dramatically improved; moreover, the asthma symptoms did not worsen and the patient continued using 200 μg of inhaled salbutamol as required. Following the fluticasone withdrawal, basal cortisol levels were 136 nmol/L and 317 nmol/L at 8 and 11 months, respectively. His ACTH level was 43.1 pg/mL at 11 months. After a period of one year, the hydrocortisone dose was tapered successfully over a three month period. Finally, one month after the hydrocortisone was discontinued, the patient’s response to synthetic ACTH was normal. Table 1 shows the patient’s serial basal and stimulated cortisol levels and plasma ACTH levels over time.

Discussion

Previous research has indicated that the concomitant use of inhaled fluticasone propionate and ritonavir leads to the systemic accumulation of fluticasone, consequently causing iatrogenic Cushing’s syndrome and secondary adrenal insufficiency.⁷⁻¹⁴ In a recent literature review, Epperla et al. reported a total of 37 cases of iatrogenic Cushing’s syndrome and adrenal suppression as a result of concomitant use of fluticasone and ritonavir in which the time between co-administration and the development of symptoms ranged from two weeks to two years.⁷ Another review showed that it took between two weeks and 12 months for patients to experience a complete resolution of symptoms after either drug was discontinued.⁸ In the current case, the patient had low ACTH and morning cortisol levels and a subnormal response to synthetic ACTH. This confirmed the diagnosis of secondary adrenal insufficiency. Moreover, the recovery of the hypothalamic-pituitary-adrenal axis after the withdrawal of fluticasone propionate established the cause of the adrenal insufficiency to be a drug-drug interaction.

In the present case, the patient initially reported symptoms of adrenal suppression four years after the concurrent use of fluticasone propionate and ritonavir.
was initiated; however, it is difficult to ascertain when the symptoms first appeared. In addition, although the resolution of the symptoms of adrenal insufficiency occurred within four weeks of discontinuing fluticasone propionate and initiating hydrocortisone treatment, it took 11 months for the full recovery of function of the pituitary and adrenal glands. The replacement of lopinavir/ritonavir with another ARV drug which does not inhibit the CYP 3A4 pathway, such as raltegravir, would have been an alternative management strategy.

However, in view of the patient’s history of virological failure with non-nucleoside reverse transcriptase inhibitor-based HAART, ritonavir-boosted protease inhibitors were continued to ensure control of the HIV infection. Fortunately, the patient’s asthma symptoms did not deteriorate after the withdrawal of fluticasone propionate and he did not require an inhaled steroid. Notably, no phenotypic changes indicative of Cushing’s syndrome were observed at the time of the initial diagnosis of adrenal insufficiency. The treating physician might have mistaken such features, namely central obesity and the presence of a dorsocervical fat pad, to be those of ARV-induced lipodystrophy.

To the best of the authors’ knowledge, this is the first case of secondary adrenal insufficiency as a result of concomitant ritonavir and inhaled fluticasone propionate reported from the Middle East and North African region. The Joint United Nations Programme on HIV/AIDS has advocated for a treatment target of 90% of all HIV-infected people to receive antiretroviral therapy (ART) by 2020; it is therefore likely that the use of ART in this region will increase as the deadline for this target approaches. This expansion of ART provision will require support and vigilance from both pharmacists and HIV physicians in order to avoid serious drug-drug interactions between ART—especially ritonavir—and the medications used to manage other comorbidities. Enhanced communication between HIV clinics and primary healthcare workers is highly recommended to help minimise the frequency of these events. Furthermore, where resources allow, the allocation of an HIV-specialist pharmacist to HIV clinics would ensure that all drug prescriptions are monitored prior to being filled. If this is unfeasible, a more pragmatic approach would be to provide prescribers with a list of common drug-drug interactions and/or access to computerised software to enable drug-drug interaction screening.

Conclusion

This case highlights the potential for serious drug-drug interactions when prescribing a potent CYP3A4 inhibitor (i.e. ritonavir) with other commonly-used medications that are substrates of the CYP3A4 isoenzyme. It is important that both HIV care providers and primary care physicians are aware of this risk to minimise the occurrence of such events.

References


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