Iatrogenic Cushing Syndrome from Interaction Between Ritonavir and Oral Budesonide During Direct Acting Antiviral Hepatitis C Therapy

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Direct acting antiviral (DAA) regimens containing ritonavir have been developed to treat hepatitis C, with fewer side effects than that by interferon-based regimens. However prescribers must be aware of drug–drug interactions. There are multiple reports of iatrogenic Cushing syndrome (CS) caused by ritonavir, when used to treat human immunodeficiency virus, increasing the bioavailability of exogenous steroids by inhibiting cytochrome p450 enzymes in the liver and gut wall and thus reducing steroid metabolism. We herein report a novel scenario of CS due to interaction between ritonavir for hepatitis C treatment and oral budesonide for autoimmune hepatitis. (J CLIN EXP HEPATOL 2016;6:246–249)

INTRODUCTION

Iatrogenic Cushing syndrome (CS) denotes symptoms caused by supraphysiological exogenous steroids, as opposed to excessive endogenous cortisol.¹ It is the most common cause of CS and is easy to diagnose with a clear history of high dose oral or intravenous steroids. However, there are scenarios, in which the diagnosis is more difficult: factitious CS, where steroid ingestion is concealed; CS due to topical formulations; or CS due to drug–drug interactions leading to increased bioavailability of low dose steroids. The latter phenomenon has been described with the co-prescription of ritonavir and inhaled steroids in HIV infected patients. We report a novel scenario of iatrogenic CS due to ritonavir and oral budesonide for the concomitant treatment of hepatitis C and autoimmune hepatitis respectively.

CASE REPORT

A 41-year-old Caucasian male musician presented with 6 weeks of increasing fatigue, swelling in the legs and face, peripheral limb weakness causing difficulty ambulating, night sweats, 7 kg of weight loss and poor healing of wounds on his limbs sustained by recent falls. He had a

history of autoimmune hepatitis treated for 3 years with oral budesonide 9 mg daily. This diagnosis had been not histologically confirmed as the patient had refused biopsy, but made on the basis of elevated serum immunoglobulin G levels, anti-nuclear antibody titers and anti-smooth muscle antibody titers. He also had hepatitis C genotype 1a due to previous intravenous drug use; with Child–Pugh A cirrhosis diagnosed on the basis of an elevated liver stiffness of 15.0 kPa measured on transient elastography testing. Three days prior to presentation he had finished a 3-month course of direct acting antiviral (DAA) treatment with ombitasvir 12.5 mg daily, paritaprevir 75 mg daily, dasabuvir 250 mg daily, ritonavir 50 mg daily and ribavirin 1000 mg daily obtained via a pharmaceutical compassionate access program. He had achieved an undetectable viral load and a significant improvement in liver function tests after the first month of treatment. At that point budesonide had been reduced to 6 mg daily as it was felt that autoimmune hepatitis was not the primary cause of his liver function test derangements, given the response to DAA treatment. He had not taken any other illicit or prescribed drugs and reported compliance to all therapy.

On examination, he had a height of 1.75 m and weight of 86 kg. He was hypertensive with a blood pressure of 150/90 mmHg and had an anxious, irritable affect with pressure of speech, pressure of thought and disinhibited behavior. He had central obesity (Figure 1), peripheral muscle wasting and bruising with poor healing wounds on his legs (Figure 2), as well as a dorsocervical fat pad (Figure 3) and rounded facies. He displayed bilateral proximal myopathy as evidenced by weak arm abduction and hip flexion, and was unable to stand from a sitting position with his arms crossed. There were no abdominal striae or visual field disturbances. Bedside finger-prick blood glucose testing was unremarkable with a level of 5.2 mmol/L. Nonetheless, CS was clinically suspected.

Keywords: Cushing syndrome, hepatitis C, drug interactions, ritonavir, budesonide

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Abbreviations: ACTH: adrenocorticotrophic hormone; ALP: alkaline phosphatase; ALT: alanine aminotransferase; CS: Cushing syndrome; DAA: direct acting antiviral; HIV: human immunodeficiency virus; HMG CoA: 3-hydroxy-3-methylglutaryl-coenzyme A; SVR: sustained virological response

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Figure 1 Central obesity.

Figure 3 Dorsocervical fat pad.

Figure 2 Muscle wasting and bruising on legs.

Laboratory tests revealed suppressed morning serum cortisol levels of 190 nmol/L (normal 200–550 nmol/L) and ACTH levels of 9.0 pmol/L (normal = 10–60 pmol/L), consistent with excessive exogenous steroid administration. 24-h urinary cortisol levels were at the lower range of normal 44 mmol/L (normal 27–486 mmol/L), ruling out endogenous CS. He was mildly hypokalaemic with potassium of 3.1 mmol/L (normal 3.5–5 mmol/L). Liver function tests were stable compared to a month prior with bilirubin 11 μ mol/L (normal <22 μ mol/L), ALP 79 IU/L (normal 30–110 IU/L), GGT 190 IU/L (normal 10–71 IU/L), ALT 117 IU/L (normal 5–40 IU/L), and albumin 31 g/L (normal 34–47 g/L). Other tests including full blood examination, creatinine, creatine kinase, serum cryoglobulins, serum electrophoresis, lactate dehydrogenase, erythrocyte sedimentation rate, anti-nuclear antibodies, immunoglobulin levels, thyroid function tests, and HIV serology were normal. An ultrasound of the abdomen revealed no significant abnormalities—notably, there was no sign of portal hypertension which could have led to portosystemic shunting of budesonide.

It was initially unclear to the gastroenterology team why the patient would have CS despite a reduction in budesonide dosage 2 months prior. However with endocrinologist consultation, a diagnosis of exogenous CS due to a drug-drug interaction between ritonavir and budesonide was made. With the ritonavir having been ceased, his peripheral

weakness and ambulation improved over a 5-day inpatient stay. Budesonide was continued at 6 mg daily. He was subsequently transferred to a rehabilitation center, where he regained strength over a further 7 days and was discharged. On review 2 months after discharge, he no longer displayed any physical or psychiatric signs of CS. Though he refused to repeat 24-h urinary cortisol testing, serum morning cortisol levels returned to normal limits (265 nmol/L), as did ACTH levels (28 pmol/L).

DISCUSSION

Inhaled budesonide causing iatrogenic CS in combination with ritonavir has been reported in 7 patients,²⁻⁷ predominantly in patients with HIV and asthma. However to our knowledge, this is only the second case in the literature where oral budesonide has been implicated—Frankel et al. previously reported a HIV-positive patient on ritonavir 100 mg daily who developed CS 3 weeks after commencing budesonide 9 mg daily for lymphocytic colitis, whose CS symptoms resolved 15 days after budesonide cessation.⁸ This is the also first such case in a patient being treated with ritonavir for hepatitis C, as well as the first in a patient being treated with budesonide for autoimmune hepatitis. The natural history of iatrogenic CS is reported to be reassuringly brief after cessation of either ritonavir or steroids, with normalization of laboratory tests often within 2 months^{4,5} and resolution of symptoms within 4 months.^{3,5}

Oral budesonide undergoes extensive first pass metabolism in the gut wall and liver, thus having little systemic bioavailability.⁹ As such, this patient had no symptoms of CS for many years. However ritonavir is a potent inhibitor of hepatic cytochrome p450 enzymes, in particular those of the subfamily CYP3A (CYP3A4, CYP3A5 and CYP3A7) which usually catalyze phase 1 metabolism of budesonide as well as other substrates including carbamazepine, rifabutin, ciclosporin, tacrolimus and HMG Co-A reductase inhibitors.¹⁰ Therefore co-prescription of ritonavir increased systemic bioavailability of budesonide in this patient with resultant development of iatrogenic CS; as evidenced by morphological changes, proximal myopathy, hypertension, hypokalaemia, irritability, thought disorder and suppressed serum cortisol and ACTH levels.

The DAA combination of ritonavir with ombitasvir, paritaprevir, dasabuvir and ribavirin for 3 months has been demonstrated in multicenter randomized controlled trials to achieve high rates of SVR in patients with genotype 1 hepatitis C, even in compensated cirrhotics and in those with prior treatment. Zeuzem et al. reported a 96.2% SVR rate in 297 treatment-experienced (interferon and ribavirin) non-cirrhotic patients.¹¹ Poordad et al. reported a 92% SVR rate in 208 Child-Pugh A cirrhotic patients.¹² Ritonavir has no direct antiviral mechanism in this combination, but instead serves to boost systemic bioavailability of

paritaprevir (another substrate of CYP3A enzymes) by the mechanisms described above.

The low burden of side effects from DAA's, compared to previous interferon-based regimens, are a great boon for hepatitis C patients and relieves stress for prescribing hepatologists. However this case illustrates the need to maintain vigilance against drug-drug interactions in the DAA era. In Australia, the federal government's decision in December 2015 to subsidize alternative DAA medications (sofosbuvir with ledipasvir or daclatasvir)¹³ rather than regimens including ritonavir may ensure that this case remains a rarity. Sofosbuvir is neither metabolized by, nor an inducer or inhibitor of, cytochrome p450 enzymes. Ledipasvir and daclatasvir are only very weak inducers of CYP3A4 in vitro, having no demonstrated effect on the circulating concentration of co-administered substrates in vivo.¹⁴ However the Australian situation does not yet apply globally and ritonavir prescription may continue elsewhere by hepatologists who, unlike HIV physicians, do not enjoy the benefit of decades of experience in its use. Furthermore, in patients with severe renal insufficiency, sofosbuvir (which is renally eliminated) has not been studied and safety data has not been established.¹⁴ In contrast, ritonavir, ombitasvir, dasabuvir and paritaprevir are all hepatically eliminated. In the RUBY-1 study, these drugs were shown to be safe in 20 patients with an estimated glomerular filtration rate below 30 mL/min and may thus be preferentially prescribed in those with severe renal insufficiency instead of sofosbuvir containing regimens.¹⁵ Drug-drug interactions and iatrogenic complications must be considered in the diagnosis of unusual presentations when ritonavir is involved.

CONFLICTS OF INTEREST

The author has none to declare.

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