

Acute rhabdomyolysis following a single dose of methylprednisolone in an HIV-positive subject receiving ritonavir-boosted antiretroviral therapy

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ABSTRACT:

— In this paper, we present a case of a 57-year old HBV-HIV positive male receiving ritonavir-boosted antiretroviral therapy that started glucocorticosteroids following a diagnosis of immunoglobulin A nephropathy. After receiving a single pulse of 1 g of methylprednisolone, the patient developed an impaired motor function of the lower limbs. Rhabdomyolysis was diagnosed also based on a remarkable increase in serum creatine phosphokinase (CPK) and myoglobin. Steroid therapy was discontinued and hydration with intravenous fluids was started, resulting in a progressive decrease of CPK and complete clinical recovery within a few days. Antiretroviral therapy was continued. Several possible causes of rhabdomyolysis, including trauma, physical exercise, immobilization, and consumption of illicit substances were ruled out. Blood tests also excluded electrolyte disorders and ongoing infections or inflammatory myopathies. Our hypothesis was “steroid-induced muscular toxicity” caused by a high concentration of methylprednisolone due to metabolic pathway inhibition by ritonavir.

— **Keywords:** Rhabdomyolysis, Methylprednisolone, Ritonavir, Drug interactions, HIV.

INTRODUCTION

HIV infected patients' survival is improving, thanks to the effectiveness of antiretroviral therapy (ART). The prolonged life expectancy increases the burden of co-morbidities and the need for medication. HIV-positive patients often need to take other drugs with the unavoidable risk of drug-to-drug interactions (DDI). Antiretroviral drug interactions are common, difficult to approach and hard to predict, and may involve multiple enzymatic pathways¹. We report an unusual case of rhabdomyolysis caused by a DDI between ritonavir and methylprednisolone.

CASE PRESENTATION

We present a case of a 57-year old Caucasian male infected with HIV and HBV acquired by intravenous drug use. His HIV infection was controlled with darunavir/ritonavir (600/100 mg twice daily) plus abacavir 600 mg/lamivudine 300 mg once daily. His most recent plasma tests showed HIV-RNA to be undetectable. His CD4+ T lymphocyte count was 513 cells/mm³ and CD4+/CD8+ ratio 1.7. HBV-DNA was not detectable in his last test. In addition to his anti-HIV medications, the patient was only assuming ramipril 10 mg qd. The patient underwent a

renal biopsy because of the progressive increase in proteinuria (2.5 g/day) and in serum creatinine (1.4 mg/dl) with an estimated creatinine clearance calculated by the CKD-EPI equation of 55 ml/min/1.73 m². An immunoglobulin A Nephropathy (IgAN) was diagnosed, with a MEST score M1-S1-T1. A glucocorticosteroids therapeutic regimen was prescribed, consisting of three methylprednisolone pulses given every two months and oral steroids for six months². Physical examination and other routine laboratory tests were unremarkable. The patient received the first gram of intravenous methylprednisolone without any immediate complications. One day later the patient was admitted to the Emergency Department complaining of lower limb muscle weakness with functional impairment and moderate pain. Blood tests revealed a remarkable increase in serum creatine phosphokinase (CPK) (55.000 UI/l, reference range <190 UI/l) and serum myoglobin (5.933 ng/ml, reference range <72 ng/ml). Serum creatinine (1.5 mg/dl) and potassium (4.3 mEq/l) were stable. Other tests were unremarkable, including C reactive protein. A diagnosis of acute rhabdomyolysis was made. Methylprednisolone was discontinued, and the patient was admitted to the Nephrology Unit. Intravenous fluids were started (300 ml per hour, 0.9% saline solution plus 10 ml per hour of a solution of 8% NaHCO₃ and 10 ml/h of mannitol 18%). ART was continued. The patient rapidly recovered with a progressive decrease of CPK and complete resolution of the symptoms. He was discharged after four days. No similar episodes were reported at follow up visits.

DISCUSSION

IgAN is the most frequent form of idiopathic glomerulonephritis, and it has often been reported in HIV patients, especially among Caucasians³. Glucocorticosteroid therapy is recommended in case of proteinuria above 1 g/day despite a 3-6-month course of therapy with renin-angiotensin system blockers⁴. Our patient developed acute rhabdomyolysis after the first intravenous administration of methylprednisolone. He reported no trauma, physical exercise, forced immobilization or consumption of illicit substances, alcohol or medication, except for his usual therapy. Physical examination was normal apart from the complaint of muscle weakness and pain. Blood tests excluded electrolyte disorders and ongoing infections or inflammatory myopathies. Symptom onset occurred a few hours after methylprednisolone administration, while other causes of acute rhabdomyolysis were ruled out. It may be hypothesized that the episode was related to hyperacute steroid muscular toxicity. Glucocorticoid-induced myopathy is a well-known event and frequently occurs in the chronic form related to long-term steroid therapy and fluorinated preparations⁵, or in an acute form often in the Intensive Care Unit setting⁶. Nevertheless, in the literature there are no reported cases of rhabdomyolysis after a single administration of methylprednisolone;

even with very high doses that are used in acute spinal cord injuries, steroid-induced myopathy takes several days to develop⁷. Thus, we believe that this unusual side effect could be the result of toxic steroid concentration, due to a possible DDI. The patient was taking a double dose of ritonavir, a strong inhibitor of the CYP3A4 enzyme¹ that directly metabolizes several drugs, including methylprednisolone. This inhibition results in an increased drug concentration that may lead to enhanced toxicity, as often described for statins⁸, antiarrhythmics such as amiodarone or quinidine, and other drugs such as midazolam, quetiapine and cisapride. In fact, co-administration of ritonavir with these drugs is contraindicated. Likewise, interactions between ritonavir and steroids are described mainly with inhaled fluticasone and budesonide, and may result in adrenal suppression and secondary Cushing's syndrome⁹. A muscle biopsy or electromyography, to identify the type of muscular damage, was not performed given the rapid and complete recovery. However, clinical timing of presentation and pathophysiological plausibility support a cause-effect relationship.

CONCLUSIONS

DDIs are a clinically relevant problem in HIV-positive ageing patients. Our case is the first to highlight that steroid induced muscular toxicity could be related to toxic concentrations of methylprednisolone due to metabolic interference by CYP3A4 inhibitors (e.g. ritonavir and cobicistat).

CONFLICT OF INTEREST:

The authors declare that they have no conflict of interests.

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