Case Report

First Reported Case of Rhabdomyolysis Associated with Concomitant Use of Cyclosporin, Diltiazem, and Simvastatin

Abstract

Rhabdomyolysis is a syndrome with a wide range of symptoms ranging from asymptomatic raised serum creatinine kinase to life-threatening metabolic disturbances and acute kidney injury. A careful history taking and high clinical suspicion on drug-drug interaction are crucial to identify the etiology of rhabdomyolysis. Here, we present a case of rhabdomyolysis due to a rare drug-to-drug interaction of simvastatin, diltiazem, and cyclosporin in a patient with IgA nephropathy. Early renal replacement therapy was initiated, and the insulting agents were withheld. Despite the metabolic disturbances were corrected, the patient succumbed to possible venous thromboembolism event during the prolonged hospital stay. Therefore, heightened awareness is required in dealing with patients with glomerulonephritis who are frequently prescribed on polypharmacy, in order to reduce unwarranted adverse events.

Keywords: *Cyclosporin, diltiazem, drug-drug interaction, rhabdomyolysis, simvastatin*

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Introduction

Rhabdomyolysis is a syndrome characterized by muscle necrosis with the release of intracellular muscle constituents into the circulation.[1] Serum creatinine kinase (sCK) is usually elevated with a variable degree. Myalgia and myoglobinuria may be present in some cases. The severity of illness may range from asymptomatic to life-threatening extreme enzyme elevations, electrolytes imbalances, and acute kidney injury.[2] The etiologies of rhabdomyolysis are categorized into infective, traumatic, electrolytes imbalance related, inflammatory disease, and drug/toxin induced. The specific cause of rhabdomyolysis is usually evident from the history or the immediate circumstances preceding the disorder. However, in a minority of the cases, the precipitating cause is not clearly evidenced. Here, we describe a young patient with IgA nephropathy who has presented with rhabdomyolysis due to drug interaction between cyclosporin, diltiazem, and simvastatin.

Case History

A 30-year-old obese man who has metabolic syndrome, obstructive sleep apnea, and IgA nephropathy for the past 3 years experienced multiple relapses of nephrotic syndrome, and multiple courses of induction with steroid was started. His usual medication consisted of simvastatin, prednisolone, and telmisartan. Three weeks ago, he was started on oral cyclosporin A as a strategy to lower the dose of prednisolone. Diltiazem was subsequently added as an attempt to increase the oral cyclosporin level as his cyclosporin level was subtherapeutic. On this occasion, he presented to the emergency department with tremors and diarrhea. When he was examined in the emergency department, he was conscious but appeared lethargic with cushingoid facies. He was stable hemodynamically but was noted to have tremors. He had anasarca with evidence of bilateral edema, ascites, and sacral edema. Laboratory tests showed worsening of renal function: Urea 174 mg/dl, serum creatinine 4.5 mg/dl with hyperkalemia, mild neutrophilia, transaminitis (serum AST 403 U/L, ALT 590 U/L), and raised sCK 150000 U/L. His cyclosporin level was above therapeutic level. He was admitted and started on IV ceftriaxone to cover for the possibility of leptospirosis. His cyclosporin, simvastatin, and diltiazem were withheld during admission. He required four sessions of intermittent hemodialysis for his

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acute kidney injury. His blood biochemistry including sCK improved. He remained afebrile, leptospirosis serology was negative, and blood culture had no growth. However, he succumbed to death at day 11 of admission attributed to likely venous thromboembolism event.

Discussion

IgA nephropathy is one of the most common causes of primary glomerulonephritis.[3] Patients may present at any age with a peak prevalence at second and third decades. Although this disorder was initially thought to have benign course, it is now recognized that it can progress slowly over 20 years to end-stage renal disease in up to 50% of the affected patients.

The treatment approach for IgA nephropathy with asymptomatic hematuria or mild level of proteinuria involves angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB) for blood pressure control and protein lowering in order to slow progression of the renal disease. However in this case, patient presented with nephrotic syndrome which warrants immunosuppressive therapy. Treatment is mainly limited to corticosteroid therapy to control the underlying inflammation.[4] However, due to his poor adherence to the prescribed therapy, he required multiple inductions of high-dose steroid which later complicated his metabolic syndrome. A repeat renal biopsy was not considered as he was not considered as steroid dependent or resistant nephrotic syndrome. Simvastin was added when he has persistent hyperlipidemia. He also became cushingoid which led to the decision of switching him to steroid-sparing immunosuppressant, oral cyclosporin. Diltiazem was subsequently added on as an attempt to increase the cyclosporin level based on the favorable synergistic effect of the combination drugs.[5] In this case, the rhabdomyolysis developed from the rare drug interactions due to shared metabolism via the CYP3A4 pathway involving the triple combination of simvastatin, cyclosporin, and diltiazem, which has not been described in the literature.

Statin is an HMG-CoA reductase inhibitor. Although statin-induced myopathy is common, it rarely causes rhabdomyolysis when used as a monotherapy. Simvastatin is metabolized by cytochrome P450 system through the CYP3A4 pathway specifically.[6] Cyclosporin and diltiazem are metabolized by cytochrome p450 but inhibit the CYP3A4 activity which leads to increase level or effect of simvastatin. In patients treated with cyclosporin and a statin, the risk of myositis has been shown to be as high as 13%–30% in studies of lovastatin at a dose of 40–80 mg[7] daily and simvastatin at a dose of 20 mg daily.[8]

The mechanism of statin causing muscle toxicity or statin-associated muscle symptoms (SAMS) is uncertain. It is thought to be related to myotoxin and inhibition of the chloride channels in myocytes, leading to unopposed muscle contractions and resulting in rhabdomyolysis. Individual statins may have different effects on the coenzyme Q10 (CoQ10, ubiquinone) which plays an important role in muscle cell energy production. Mitochondrial dysfunction has been demonstrated in the studies of patients with statin-reduced myopathy which muscle biopsy in such cases has revealed ragged red fibers suggesting a mitochondrial myopathy.[6] A study of Larsen *et al*. found that long-term use of simvastatin (10–40 mg daily >12 months) reduced ubiquinone content in skeletal muscles and decreased maximal mitochondrial oxidative phosphorylation capacity.[9] Not all statins have the same risk of SAMS when co-administered with cyclosporine. The only statin approved by USFDA for combination therapy with cyclosporine is pravastatin as it is not metabolized by the CYP450. However, having said that, there was a reported case of myopathy in a patient on the combination of pravastatin and cyclosporin which suggesting that a drug-drug interaction beyond the P450 metabolism.[10]

Cyclosporin is a calcineurin inhibitor which binds intracellular calcineurin, inhibiting translocation of transcription factor nuclear factor of activated T-cells (NFAT) to the nucleus and subsequently cytokine-induced cell proliferation. Diltiazem is a non-dihydropyridine calcium channel blocker which has anti-proteinuria effect. However, in patient with immunosuppressants, diltiazem is commonly used to increase the immunosuppressant level. Cyclosporine may affect skeletal muscle in two patterns. The first pattern is myopathy without myolysis in which muscle enzymes are usually normal. This type of myopathy is usually dose-dependent and symptoms improved as soon as the drug is stopped. The second pattern is that of rhabdomyolysis most commonly secondary to drug-drug interaction notably with the statin.[11] There have been no cases of cyclosporin-induced rhabdomyolysis reported to date.

The combination therapy of cyclosporine and diltiazem is commonly aimed at reducing the cost of cyclosporin as it can increase the cyclosporine level; however, if it is left unchecked, it can lead to significant toxicity. We acknowledge there may be other confounding factors in this case; however, the timeline of the events have raised a strong suspicion regarding the effect of combination medications.

In this case, we have illustrated that the drug interaction of cyclosporin, diltiazem, and simvastatin can cause life-threatening rhabdomyolysis. Clinicians must be aware of drugs metabolized via cytochrome P450 isoenzymes and a careful examination of the prescribed medications and a high clinical suspicious on potential drug interaction is therefore needed to prevent any adverse event. A risk-versus-benefit analysis should be carried out before prescribing such drugs.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the next of kin has/have given his/her/their consent for patient's images and other clinical information to be reported in the journal. The family understand that the names and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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