Clin Rheumatol (2008) 27:129–131
DOI 10.1007/s10067-007-0696-9

CASE REPORT

Fatal toxic myopathy attributed to propofol, methylprednisolone, and cyclosporine after prior exposure to colchicine and simvastatin

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Received: 4 May 2007 / Revised: 24 June 2007 / Accepted: 25 June 2007 / Published online: 13 July 2007

Abstract We report a fatal case of toxic myopathy in a patient with a transplanted heart for severe ischemic coronary artery disease. He was on long-term cyclosporine, prednisone, and mycofenolate. Four months before the development of proximal muscle weakness, his simvastatin dose was doubled, and he was also started on colchicine for acute exacerbation of gout. He developed progressive muscle weakness leading to shortness of breath and hospitalization for respiratory failure. Colchicine and simvastatin were stopped on admission. He received high-dose methylprednisolone for continued muscle weakness while he was sedated with propofol. These changes led to a marked elevation of creatine kinase, peaking at 33,580 U/ml. The muscle biopsy revealed toxic vacuolization, mitochondrial damage, and no evidence of inflammation. Based on the timing of events, the combination of propofol, high-dose methylprednisolone, and cyclosporine have triggered rhabdomyolysis, which may have been facilitated by prior administration of colchicine and simvastatin.

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Keywords Colchicine · Cyclosporine · Prednisone · Propofol · Rhabdomyolysis · Simvastatin

Case report

A 66-year-old male patient presented with weight loss, weakness, and muscle aches lasting for 4 months. He had a history of severe ischemic heart disease for which he underwent a cardiac transplantation in 1994. He developed steroid-induced diabetes mellitus after he had the transplantation. He also suffered from diabetic neuropathy, hyperlipidemia, gout, congestive heart failure, chronic obstructive pulmonary disease, and sleep apnea.

The patient lost 30 lb over a period of 4 months before admission. He developed increasing difficulty in walking and getting up from the chair. He could not raise his arms above his head. His medications before admission included daily mycophenolate (500 mg), prednisone (7.5 mg), simvastatin (60 mg), colchicine (1.2 mg), cyclosporine (150 mg), and insulin.

Four months before admission, he was treated with allopurinol for a month for gout as an outpatient. He also had a change in immunosuppression from Imuran to mycophenolate because of the addition of allopurinol. His simvastatin dose was increased from 30 to 60 mg daily for better control of his lipid profile. He was admitted to a Community Hospital, where colchicine and simvastatin were discontinued because of muscle weakness and elevated creatine kinase CK of 2,538 U/ml. Although his CK decreased after discontinuation of colchicine and simvastatin, he developed respiratory distress, requiring ventilation. He was started on a propofol infusion at 30 μg/kg per minute for sedation.

When his respiratory status failed to improve, he was transferred to our hospital with a temperature of 37.2°C, respiratory rate of 20/min, blood pressure of 143/70 mmHg, and oxygen saturation of 98% on mechanical ventilation at 0.4 FiO_2. He was able to follow commands. Handgrip was present but weak. He was able to move his toes. His deep tendon reflexes were decreased. He had multiple tophi in both hands. There was no evidence of joint swelling, erythema, or skin rash.

Laboratory investigations at our hospital revealed negative antinuclear antibody, and rheumatoid factor and complements were normal. Uric acid level was 10.5. His electrocardiogram was normal. Urine microscopy showed coarse granular pigmented casts. Two-dimensional echo showed 65% ejection fraction with diastolic dysfunction. Oral prednisone dose was increased to 30 mg, and daily 500 mg of intravenous methyl-prednisolone was begun for treatment of presumed inflammatory polymyositis. Electromyography revealed diffuse myopathy. Muscle biopsy showed evidence of vascular toxic myopathy with extensive myocyte necrosis with minimal muscle fiber regeneration. There was no evidence for inflammation. Electron microscopy showed mitochondrial damage. There were large lysosomes in cells loaded with necrotic debris.

After much debate, it was decided to continue cyclosporine with close monitoring of drug levels because he had cardiac transplantation. His CK levels continued to rise reaching a peak of 33,580 U/ml. The patient developed rhabdomyolysis and oliguria and was started on hemodialysis. He developed septic shock secondary to pneumonia, and he passed away 5 days after admission.

Discussion

This patient was treated with multiple medications, which could cause a toxic myopathy—colchicine, simvastatin, propofol, prednisone, and cyclosporine. In this report, we discuss the possible contributions of each of these medications.

Colchicine is an alkaloid extract of plants that inhibits microtubule polymerization by binding to tubulin [1]. Microtubule disruption leads to accumulation of vacuoles, especially autophagic vacuoles because of their inability to move correctly, which is called “exocytotic constipation” [5].

Proximal muscle weakness is worse in the lower limbs associated with elevated CK levels. Muscle biopsy shows evidence of vacuolar changes. Muscle weakness resolves, and CK levels return to normal few days to weeks after its discontinuation. Vacuoles are of various sizes, contain basophilic material, and stain for acid phosphatase [9]. Numerous autophagic and lysosomal vacuoles, myofibrillar disarray, and perinuclear aggregates of filaments are also seen [9].

Cyclosporine is a lipophilic endecapeptide derived from a fungus [1]. It impairs production of interleukin-2 and other cytokines and thus lymphocyte proliferation and forms a complex with cyclophillin, which binds to and inhibits calcineurin. This prevents the translocation of cytosolic nuclear factor of activated cells to the nucleus, which is required for the transcription of genes for cytokines [1]. There are a few cases of cyclosporine myopathy reported in the literature. In the majority of cases, CK was high, and biopsies showed fiber atrophy. Symptoms occurred within 4 weeks to 24 months after introduction. All patients responded to cessation of therapy. Myopathy recurred in those who were rechallenged [2]. Cyclosporine A also affects the mitochondrial potential and can cause mitochondrial damage [6].

Statins can produce toxic myopathy and rhabdomyolysis [4]. Cerivastatin was withdrawn in August 2001 after it was associated with 100 deaths [7]. Fatal rhabdomyolysis has primarily been seen when a statin is given concurrently with other medications especially cyclosporine [8]. Cholesterol is an important structural component of biological membranes, and its reduction may alter muscle cell membrane function. Accumulation of lipids in myocytes may be another cause of myopathy. Mevalonate is a precursor of ubiquinone, a constituent of the mitochondrial electron transport chain. Therefore, adenosine triphosphate production and energy metabolism of myocytes are impaired [3].

Vacuolization has been reported in both colchicine and statin myopathy [5]. In cell cultures, statins have been shown to fragment filamentous actin and secondarily collapse the microfilament network. Synergistic myopathy occurs through related pharmacokinetic and pharmacodynamic mechanisms [6].

In patients receiving a combination of colchicine and cyclosporine, histology showed vacuolar myopathy [12]. Colchicine withdrawal is associated with clinical improvement [12]. The multidrug resistance gene 1 product, P-glycoprotein, specializes in energy-dependent cellular transport, and it functions as an efflux pump with broad specificity for a variety of drugs including colchicine. It produces a decrease in intracellular concentrations of the drug, conferring resistance. Cyclosporine A is known to block P-glycoprotein and may inhibit colchicine biliary and renal excretion by possibly inhibiting the multidrug transporter [10].

The combination of cyclosporine and statin results in increased serum levels of the statin, with increased risk for myopathy and rhabdomyolysis. Cyclosporine can increase the level of statins from twofold in the case of fluvastatin and up to 20-fold when lovastatin is used [8]. Cyclosporine may induce cholestasis, which may decrease statin excretion in the bile. In rats, decreased biliary clearance of

lovastatin, simvastatin, and pravastatin has been demonstrated, leading to increased levels in muscle tissue.

Propofol is a central nervous system sedative that interacts with gamma amino butyric acid aminotransferase receptors [13]. It has been implicated in the development of rhabdomyolysis in children and adults. The muscle fibers in previously reported cases of propofol-induced rhabdomyolysis showed acute necrotic reaction with swelling, loss of striations, and vacuoles [13]. Steroids are also known to predispose to rhabdomyolysis and CK elevation especially with concomitant use of propofol. Most cases reported in adults were also on long-term steroids for various reasons. Cremer et al. [15] identified seven adult cases of propofol infusion syndrome. They were characterized by increasing need for inotropic support with progressive myocardial failure and rhabdomyolysis, evident 24–48 h after the start of the propofol infusion. The syndrome has high mortality, and the only recoveries have been seen after hemodialysis [14]. Long-term propofol infusion should be used with caution especially if the patient has been on steroids.

Nava et al. [11] have shown acute weakness of respiratory and skeletal muscle weakness after a short course of methylprednisolone given for acute lung rejection after transplantation. Acute corticosteroid myopathy may occur in muscles paralyzed by hypnotic doses of propofol, even in the absence of neuromuscular blocking agents. In the acute form of acute steroid myopathy, weakness is more generalized, and involvement of the respiratory muscles is common. Marked elevation of CK can occur [11]. Muscle biopsy shows typically widespread atrophy of muscle fibers, excess sarcoplasmic glycogen granules, and myofibril disorganization with selective loss of myosin filaments [6].

Based on the timing of events, we conclude that the combination of propofol, methylprednisolone, and cyclosporine have triggered rhabdomyolysis, which may have been facilitated by prior administration of colchicine and simvastatin. There needs to be an increased awareness toward combinations of drugs with potential muscle toxicity. Their prompt recognition may prevent fatal outcomes, as the toxic effects of most of these medications are reversible.

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