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Case Report

Simvastatin Induced Acute Rhabdomyolysis in a Renal Transplant Patient

Böbrek Nakilli Hastada Simvastatin Kullanımına Bağlı Gelişen Akut Rabdomyoliz

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ABSTRACT

The risk of development of rhabdomyolysis and myoglobinuric acute graft failure is higher than the general population in renal transplant recipients with concomitant use of cyclosporine A and statin. A 64-year-old female patient, who underwent renal transplantation from a living donor in Germany 14 years ago, had diabetes mellitus, hyperlipidemia and hypertension in her past medical history. During her follow up in this country, simvastatin 80 mg/day was added to her therapy due to hyperlipidemia. Her biochemical analysis revealed serum creatine phosphokinase (CPK) of 27336 u/L, cretine kinase –MB (CK-MB): >300 ng/mL, myoglobin >4000 ng/mL, urea: 284 mg/dL, creatinine: 5.1 mg/dL and cyclosporine level: 145.6. Although her serum CPK, CK-MB, myoglobin levels returned to normal levels during her 25-day follow-up, her renal function test levels did not improve and she was accepted to have chronic renal failure. An AV fistula was opened and she was entered into a routine hemodialysis program. In conclusion, simvastatin may cause serious adverse effects in renal transplant patients. One should be very careful and the patient should be followed very closely when it is used.

KEYWORDS: Renal transplant, Rhabdomyolysis, Simvastatin

ÖZ

Uzun dönemde renal transplant alıcılarında mortalite ve morbiditeyi etkileyen en sık sebep kardiyovasküler hastalıklardır. Canlı donörden Almanya'da 14 yıl önce böbrek nakli yapılan 63 yaşındaki kadın hastanın diabetes mellitus, hiperlipidemi ve hipertansiyon tanıları vardı. Hastaya bu ülkedeki takiplerinde hiperlipidemisi nedeniyle de simvastatin 80 mg eklenmişti. Hastanın biyokimyasal parametrelerinde serum CPK: 27336 u/L, CK-MB: >300 ng/mL, myoglobin >4000 ng/mL, üre: 284 mg/dL, kreatinin: 5,1 mg/dL, siklosporin düzeyi:145,6 saptandı. Yaklaşık 25 günlük takibinde serum CPK, CK-MB, myoglobin değerleri normal seviyelere gelmesine rağmen böbrek fonksiyon testleri yüksek seyretmesi üzerine kronik rejeksiyon kabul edildi. AV fistül açılarak kronik hemodiyaliz programına alındı. Sonuç olarak; böbrek nakilli hastalarda simvastatin ciddi yan etkilere neden olabilir; kullanılacağı zaman doz ayarlamasında çok dikkatli olunmalı ve rabdomyoliz açısından yakından izlenmelidir.

ANAHTAR SÖZCÜKLER: Böbrek nakli, Rabdomyoliz, Simvastatin

INTRODUCTION

Cardiovascular diseases are the most common cause of mortality and morbidity in long-term renal transplant recipients (1,2). The most important risk factor in the development of cardiovascular and peripheral vascular diseases is hyperlipidemia. The prevalence of post-transplantation hyperlipidemia ranges between 16% and 78% (2).

The main reason of post-renal transplantation hyperlipidemia is administration of immunosuppressive agents such as corticosteroids and cyclosporine A (3). The other risk factors are genetic predisposition, hypertension, obesity, diabetes mellitus and smoking (4).

Statins used as a lipid lowering strategy decrease the cardiovascular risk by improvement in hyperlipidemia through inhibition of 3-hydroxy-3-methylglutaryl

coenzyme A (HMG-CoA) reductase (5). The most commonly known adverse effect is gastrointestinal symptoms. However, the most important adverse effect of this therapy is rhabdomyolysis, although it develops rarely (6). The risk of development of rhabdomyolysis and myoglobinuric acute graft failure is higher than general population in renal transplant recipients with concomitant use of cyclosporine A and statin (7).

Serious adverse effects may develop in cases using statin. We report a case of rhabdomyolysis due to simvastatin usage in a renal transplant patient.

CASE REPORT

A 64-year-old female patient, who underwent renal transplantation from living donor in Germany 14 years ago, had diabetes mellitus, hyperlipidemia and hypertension in her past medical history. During her follow up in this country, simvastatin 80 mg/day was added to her therapy due to hyperlipidemia while she was receiving antihypertensive and cyclosporine therapy. No data showing the initial lipid and creatinine levels of the patient was present while we evaluated her. She was admitted to the physical therapy and rehabilitation clinic after 15 days of simvastatin therapy due to complaints of severe leg muscle and back pain. Both lower extremities showed 3/5 muscle power loss and diffuse sensitivity in her physical examination. Biochemical analysis revealed serum creatine phosphokinase (CPK) of 27336 u/L, creatine kinase –MB (CK-MB): >300 ng/mL, troponin I: 0.09 ng/mL, myoglobin >4000 ng/mL, urea: 284 mg/dL, creatinine: 5.1 mg/dL, uric acid: 7.0 mg/dL, aspartate aminotransferase (AST): 688 u/L, alanine aminotransferase (ALT): 338 u/L, lactate dehydrogenase (LDH): 1905 u/L, glucose: 221 mg/dL, sodium: 135.0 mEq/L, potassium: 5.25 mEq/L, calcium: 8.7 mg/dL, phosphorus: 9.8 mg/dL, albumin: 2.7 g/dL, hemoglobin: 10.2 g/dL, and cyclosporine level: 145.6. The patient was admitted to nephrology clinic and her urine benzidine was positive. No erythrocyte was observed in the sediment. The amount of urine in 24 hours was 300 cc. Her viral markers were negative and she had no drug history. Thyroid function tests were normal. Simvastatin therapy was stopped. She received emergent hemodialysis. Intravenous fluid supplementation was provided and fluids with mannitol+bicarbonate were given. Diuretic therapy was started. Her renal function test levels did not improve during her follow-up of nearly 25 days although her serum CPK, CK-MB, LDH, AST and ALT levels returned to normal levels. She was therefore accepted to have chronic renal failure. An AV fistula was opened and she was entered into the routine hemodialysis program.

DISCUSSION

Recommendations about aggressive lipid therapy are currently increasing, together with suspicions about the safety of statins. The adverse effects of statins mainly concentrate on liver and muscle. However, these adverse effects are dose-dependent and reversible.

Myalgia and fatigue are seen in 2% to 7% of cases and tenderness of muscles, weakness and myopathy with more than 10 fold increase of creatine kinase are seen in 0.01% to 0.5% of cases (8). Rhabdomyolysis characterized with severe CPK increase, muscle necrosis and renal failure due to myoglobinuria may develop very rarely (0.15 fatal case in 1 million uses). Atorvastatin, lovastatin and simvastatin are primarily metabolized through the cytochrome P 450 3 A4 pathway. The risk of adverse effects increases and important drug reactions may develop when they are used together with drugs metabolized through this pathway such as fibrates, cyclosporine, macrolite antibiotics, digoxin and warfarin (9). As rosuvastatin does not use this pathway, it has fewer side effects. Rhabdomyolysis cases developing after administration of simvastatin in renal transplant cases have been reported in literature.

Weise et al. reported the development of rhabdomyolysis in a 55-year-old diabetic renal transplant case after simvastatin 20 mg/day for hyperlipidemia therapy (10).

Rhabdomyolysis in a 53-year-old renal transplant case following administration of simvastatin 20 mg/day due to hyperlipidemia therapy was reported by Gumprecht et al (11). Another rhabdomyolysis case developed in a renal transplant patient while receiving mycophenolate, cyclosporine, prednisone, furosemide, diltiazem, aspirin, simvastatin, an angiotensin receptor blocker and insulin as reported by Najafian et al (12).

The dose of the simvastatin should be adjusted in renal transplant or chronic renal failure cases, especially if they are receiving medicines metabolized through the cytochrome P 450 3 A4 pathway. Otherwise, another statin not metabolized through this pathway should be selected in hyperlipidemia therapy of these cases. An antilipidemic diet should also be encouraged in such cases.

In conclusion, simvastatin may cause serious adverse effects in renal transplant patients. One should be very careful and the patient should be followed very closely when it is used.

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