Fenofibrate-Induced Acute Renal Failure Due to Massive Rhabdomyolysis after Coadministration of Statin in Two Patients

Aydin Unal¹, Edip Torun², Murat Hayri Sipahioglu¹, Bülent Tokgoz¹, Mehmet Gungor Kaya³, Öktem Oymak¹ and Cengiz Utas¹

Abstract

Fibric acid derivatives and statins have been increasingly recognized as causes of rhabdomyolysis and acute renal failure. We report severe rhabdomyolysis and acute renal failure associated to combination treatment with statin and fenofibrate in two patients with underlying coronary artery disease. Both patients developed rhabdomyolysis-induced acute renal failure after their hyperlipidemia treatment was changed from statin to statin plus fenofibrate. Both patients experienced intense muscle symptoms, hemoglobinuria, oliguria, and elevation of blood urea nitrogen and serum creatinine. Their serum creatine kinase levels were markedly elevated (case 1; 97,392 IU/l and case 2; 96,639 IU/l). Rhabdomyolysis induced acute renal failure was diagnosed in both patients. Both patients were managed with cessation of the statin-fibrate combination, adequate fluid resuscitation and forced alkaline-mannitol diuresis. Although both patients required hemodialysis, their renal function recovered. Fenofibrate initiation is associated with an increased risk for rhabdomyolysis in patients receiving statin therapy. To prevent future events, it is crucial that clinicians recognize the interaction risk associated with concurrent use of statin and fenofibrate. We recommend careful monitoring when fenofibrate is given to patients receiving statin therapy.

Key words: acute renal failure, fenofibrate, rhabdomyolysis, statin

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Introduction

Rhabdomyolysis is a clinical and biochemical syndrome resulting from skeletal muscle injury and the release of muscle cell constituents into the circulation. It may result in myoglobinuria, the filtration of myoglobin into the urine, and it is often associated with acute renal failure (1). Drug-induced rhabdomyolysis occurs rarely and may be asymptomatic. However, life-threatening severe electrolyte disorders and acute renal failure may occur in the more serious cases (2). Rhabdomyolysis results from inherited muscle enzyme deficiencies, toxins such as alcohol abuse and cocaine, trauma, drugs such as statins, muscle overexertion, infections, and other disorders (3). Rhabdomyolysis with the use of fenofibrate alone or statin-fibrate combinations has been reported in a few cases (4-7). Here, we present two patients who developed rhabdomyolysis and acute renal failure after fenofibrate was added to statin monotherapy.

Case Reports

Case 1

A 56-year-old woman patient was admitted to our hospital with complaints of myalgia, nausea, vomiting, decreased urine output, and muscle weakness for the last few days. Also she had red colored urine for 3 days. Her medical history revealed that balloon angioplasty was performed for treatment of coronary artery disease 12 years previously.
She had used aspirin, beta-blocker, angiotensin-converting enzyme (ACE) inhibitor, pravastatin 20 mg a day for treatment of coronary artery disease for 12 years. She had received fenofibrate 200 mg one a day for hypertriglyceridemia for the recent 2 months. Her renal function had been normal two months earlier [blood urea nitrogen (BUN) 17 mg/dl and serum creatinine 0.9 mg/dl]. The physical examination was completely normal except for muscle weakness. The routine laboratory tests revealed a creatine kinase (CK) of 97,392 IU/l (normal range 40-226 IU/l), which was approximately 430 times the upper limit of normal. Further laboratory results showed hemoglobin (Hb) 13.5 g/dl, white blood cell count 11,400/mm³, and platelet count 393,000/mm³. The erythrocyte sedimentation rate was 35 mm/h. BUN was 37 mg/dl, fasting blood glucose 93 mg/dl, serum creatinine 2.6 mg/dl, albumin 3.5 g/dl, serum potassium 5.9 mmol/l, calcium 8.6 mg/dl, phosphorus 6.8 mg/dl, aspartate aminotransferase (AST) 1,589 IU/l, alanine aminotransferase (ALT) 475 IU/l and lactate dehydrogenase (LDH) 1,642 IU/l. Urinalysis showed 3.67 g/d proteinuria but no erythrocyte and cast. Autoantibodies such as antinuclear antibody (ANA), anti-dsDNA antibody, and anti-Jo-1 and the serologies for brucellosis, human immunodeficiency virus (HIV), and hepatitis B and C virus were negative. C₃ and C₄ complement levels were normal. Thyroid function tests and anti-thyroid peroxidase (TPO) antibody titer were normal. There were no urinary obstruction findings and a normal kidney size on abdominal ultrasound. The patient was diagnosed with severe rhabdomyolysis-induced acute renal failure resulted from the use of the pravastatin plus the fenofibrate. The pravastatin and the fenofibrate were discontinued. Although adequate fluid resuscitation and forced alkaline-mannitol diuresis in which the urine pH is increased to above 6.5 were performed, oliguria persisted and serum creatinine increased to 6.1 mg/dl and metabolic acidosis developed. Hemodialysis was performed. During the follow-up period, hemodialysis was performed 5 times, then the patient’s urine outflow increased and serum creatinine and serum CK decreased to 1.4 mg/dl, and 63 IU/l, respectively, at the end of two weeks. Proteinuria decreased to within the normal range (70 mg a day).

Case 2

A 58-year-old man patient presented to our hospital with complaints of myalgia, muscle weakness, fatigue, decreased urine outflow, and a dark brown color of urine for the last few days. His medical history revealed that coronary artery by-pass surgery was performed for treatment of coronary artery disease 4 months previously. He had used aspirin, beta blocker, ACE inhibitor, atorvastatin 10 mg a day for treatment of coronary artery disease for 4 months. He had started to use fenofibrate 200 mg a day for the treatment of hypertriglyceridemia from one month earlier. His renal function had been normal one month earlier (BUN 14.5 mg/dl and serum creatinine 0.8 mg/dl). The physical examination was completely normal except muscle weakness. Laboratory evaluation at admission revealed a marked increase in CK of 96,639 U/l, which was approximately 427 times the upper limit of normal, BUN of 36 mg/dl, serum creatinine of 3.6 mg/dl, serum albumin of 3.2 g/dl, AST of 1,836 IU/l, ALT of 674 IU/l, and LDH 1,836 IU/l. Urinalysis showed 1.4 g/d proteinuria but no erythrocyte and cast. Autoantibodies such as ANA, anti-dsDNA antibody, and anti-Jo-1 and the serologies for brucellosis, HIV, and hepatitis B and C virus were negative. C₃ and C₄ complement levels were normal. Thyroid function tests and anti-TPO antibody titer were normal. Abdominal ultrasound showed the kidneys of normal size without any finding of obstruction. A diagnosis of rhabdomyolysis-induced acute renal failure resulting from the use of the atorvastatin plus the fenofibrate was made. The atorvastatin and the fenofibrate were stopped. Although adequate fluid resuscitation and forced alkaline-mannitol diuresis were performed, oliguria persisted and serum creatinine increased to 8.8 mg/dl and metabolic acidosis developed. Hemodialysis was started. During the follow-up period, hemodialysis was performed 4 times, and then his urine outflow increased. The patient’s creatinine level and CK had reduced to 1.5 mg/dl and 73 IU/l, respectively, at the end of three weeks. Proteinuria decreased to within the normal range (44 mg a day).

Discussion

Fenofibrate is a drug of the fibrate class that reduces very low density lipoprotein (VLDL), triglycerides, and low density lipoprotein (LDL) and increases high density lipoprotein (HDL). Its adverse effects such as skin reactions, blood disturbances (except for muscle and hepatic side effects) are tolerable and reversible (8). The most important side effect of fenofibrate is rhabdomyolysis (9).

In patients who have high serum cholesterol and triglycerides, with only simple statin or fibrate treatment, it is difficult to decrease both serum LDL-cholesterol and triglycerides. In such patients, especially if they have high-risk of coronary artery disease or already have coronary artery disease, with combined treatment with statin and fibrate, recommend target lipid levels are achieved. However, adverse effects such as myopathy, hepatic injury, and rhabdomyolysis of the combination treatment may develop in some patients (7, 10).

In the study of Schech et al., older age (≥65) was a risk factor for rhabdomyolysis among statin users. Also high statin dosage and renal disease were related to an increased risk for rhabdomyolysis (11). However, the present patients were younger than 60 years. Also these patients had not had renal disease before the statin and fibrate combination treatment. The statin and fenofibrate dosages were relatively low in our patients.

In the study of Graham et al, the rhabdomyolysis risk was low and similar for single therapy with atorvastatin and pravastatin (mean incidence per 10,000 person years for monotherapy with these drugs was 0.44) (9). The develop-
ment of rhabdomyolysis is rare with only simple fibrate treatment and has been reported in only a few cases (4-6). However, combination treatment with statin and fibrate increases the rhabdomyolysis risk (9). Similarly, rhabdomyolysis was developed after fenofibrate was added to statin monotherapy in the present patients.

Hypothyroidism is a rare cause of rhabdomyolysis. In hypothyroidism, mitochondrial activity in muscle cells and some metabolic activities including fatty acid catabolism are inhibited (12). Fenofibrate-induced rhabdomyolysis in patients with hypothyroidism has been previously reported (10, 12). In the present patients who developed rhabdomyolysis, the thyroid function tests and anti-TPO antibody titer were normal.

In addition, five patients with polymyositis related to lipid-lowering agents including statin and fenofibrate have been reported (13). We checked for autoantibodies including ANA, anti-dsDNA antibody, and anti-Jo-1 in terms of polymyositis and found the results to be negative.

In patients with coronary artery disease, some agents concomitantly used with statin treatment including amiodarone, digoxin, warfarin, and verapamil increase the risk of development of rhabdomyolysis (14-16). The present two patients had not used any of the above-mentioned agents.

In conclusion, physicians should be aware of potentially lethal adverse effects including rhabdomyolysis and acute renal failure after fenofibrate added to statin therapy. Furthermore, they should carefully follow-up renal, hepatic, thyroid functions, and muscle enzymes in all patients. Also patients should be informed about risks of the drugs and about symptoms of potential adverse effects of the drugs such as myalgia and muscle weakness.

References