

Severe Rhabdomyolysis from Pharmacokinetic Interaction of Statin in Patient with Diabetic Nephropathy: A Case Report

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ABSTRACT

Rhabdomyolysis is a potentially life-threatening syndrome characterized by muscle necrosis and the release of intracellular muscle contents into systemic circulation. The authors report a rhabdomyolytic patient with chronic kidney disease who had reduction of renal function owing to undiagnosed hypothyroidism, from drug interaction of simvastatin with gemfibrozil and amlodipine.

Keywords: Rhabdomyolysis, acute renal failure, drug interaction, statins

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INTRODUCTION

Rhabdomyolysis is a potentially life-threatening syndrome characterized by the breakdown of skeletal muscle resulting in the subsequent release of intracellular contents into the circulatory system. These cell contents include enzymes such as creatine kinase (CK), lactate dehydrogenase, aldolase and haeme pigment myoglobin. Electrolytes such as potassium, phosphates and purines are also released from the intracellular tissues.^{1,2} The development of rhabdomyolysis may be associated with a wide variety of diseases, injuries, medications and toxins.³ It ranges in severity from an asymptomatic elevation of CK levels in blood to severe life-threatening cases associated with very high CK levels, myoglo-

binuria and acute renal failure. The classical findings of this abnormality such as muscle pain, weakness and tea-colored urine are non-specific and may not always be present.⁴ We hereby report an elderly female patient who proved to be a case of rhabdomyolytic acute renal failure precipitated by undiagnosed hypothyroidism, from the combination use of simvastatin, gemfibrozil and amlodipine.

CASE REPORT

A sixty year-old female was diagnosed with hypertension and diabetic mellitus for the past ten years, dyslipidemia for the past four years and diabetic nephropathy or chronic kidney disease for the past two years. She has an average body weight of thirty kilograms. Her baseline serum creatinine and estimated glomerular filtration rate (eGFR) were an average 1.72 mg/dl and 16.47 ml/min, respectively. The medication included Mixtard[®] (RI 30/NPH70) 30 units/day SC, amlodipine 10 mg/day and gemfibrozil 1,200

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mg/day which she used for many years. A month before presenting to the hospital, a physician prescribed simvastatin 20 mg/day additional to her medication including previous treatment. Her lipid profile including total cholesterol, triglyceride, LDL-C and HDL-C before starting simvastatin was 271, 210, 192 and 37 mg/dL, respectively. She presented with severe generalized weakness, diffuse muscle pain at both legs and difficulty in walking without assistance for 1 week duration. She also complained of severe vomiting and noticed decreased urine output. There was no fever, history of any trauma, viral exanthema, severe exercise, seizure, uncontrolled blood glucose, or use of any herbal medication preceding the illness. On admission, she was well-nourished. There was anicterus, no clubbing, and no lymphadenopathy. She was afebrile with body temperature 36.6°C, pulse rate of 90 beats per minute and blood pressure of 120/80 mm/Hg. Neurological examination revealed proximal muscle weakness with score 1/5 power in all four limbs, absent deep tendon reflexes with no sensory involvement. Other examination was unremarkable. All laboratory investigations have been presented in Table 1. The Anti-HIV, HBsAg and anti-HCV antibodies were negative. The patient was initially treated with intravenous normal saline plus high dose of N-acetylcysteine and dexamethasone without hemodialysis. Urinalysis and urine myoglobin were not investigated. According to clinical presentation and laboratory examination, myalgia (severe muscle pain and proximal muscle weakness), reddish discoloration to urine, deterioration

of renal function, elevated aspartate transaminase, creatine kinase more than 10 times of normal limit proved a diagnosis of rhabdomyolysis. All lipid lowering agents were stopped. Amlodipine was continued to control her blood pressure. At day 5 of admission, she developed severe hyperkalemia, hyperphosphatemia and metabolic acidosis. The patient was treated for hyperkalemia with furosemide, calcium polystyrene sulfonate, regular insulin plus glucose and 10% calcium gluconate, respectively for resolution of serum potassium level. Sodium bicarbonate injection was also prescribed for treatment of metabolic acidosis complication. After day 17 of admission, the urine output and urine discoloration were improved. Her serum creatinine stabilized at 1.57 mg/dL. Total creatine kinase and aspartate transaminase levels trended to normal. She improved power in all limbs and deep tendon reflexes appeared again. During hospitalization, all clinical signs and symptoms were improved without hemodialysis.

DISCUSSION

Rhabdomyolysis is a rare but clinically important adverse event of statin monotherapy or combination therapy. The common risk factors for the development of statin-induced myopathy included high dosages, polypharmacy, increasing age, low body weight, female sex, renal and hepatic insufficiency, diabetes mellitus, concomitant therapy with fibrates and amlodipine.^{5,6} Also, it would probably be from genetic polymorphism of cytochrome P450 (CYP); CYP3A4 (poor meta-

TABLE 1. Laboratory investigations during hospitalization.

Investigation	Day 0	Day 5	Day 7	Day 13	Day 15	Day 17
BUN (mg/dL)	84	93	127	22	18	12
Serum creatinine (mg/dL)	1.72	2.17	3.66	1.88	1.70	1.57
Serum potassium (mEq/L)	4.3	7.2	6.5	3.6	3.4	4.4
Serum phosphate (mEq/L)	4.6	10	-	4.4	-	-
AST (U/L)	292	915	862	59	-	29
ALT (U/L)	119	265	397	140	-	59
ALP (U/L)	125	119	159	66	-	83
Free T4 (ng/L)	0.51	-	-	-	-	-
TSH (μIU/L)	9.46	-	-	-	-	-
LDH (U/L)	2,476	-	-	-	-	-
Creatine kinase (IU/L)	10,863	39,729	43,226	465	-	344

bolizer) which most common occurs in asian population.

Each statin is different in their risk of inducing rhabdomyolysis, with some patients developing this syndrome when switching from one statin to another.⁷ Generally, statins are classified into hydrophilic and lipophilic groups based on tissue selectivity. Hydrophilic statins, such as pravastatin and rosuvastatin have less tissue absorption except for the liver, fewer side effects and less drug interaction due to lower dependence on the CYP enzyme than lipophilic statins (simvastatin, atorvastatin).^{8,9} The specific risk factors presented in this patient have been widely reported.^{5,6,9} Four risk factors for the onset of rhabdomyolysis in this patient were identified including use of simvastatin, undiagnosed hypothyroidism, co-administration of simvastatin with gemfibrozil and co-administration of simvastatin with amlodipine.

Statin-induced rhabdomyolysis incidence is about 1.5 to 5.0%.^{6,7,9} It may result from a variety of mechanisms. Firstly an unstable skeletal muscle cell membrane due to a blockage in the synthetic pathway for cholesterol, which results subsequently in a low intra-membranous cholesterol content. Secondly, the presence of abnormal prenylated protein causes an imbalance in intracellular protein messenger. Thirdly, abnormal mitochondrial respiratory function occurs which is caused by coenzyme Q10 deficiency.^{9,10} From several studies, a patient develops muscle symptoms after 2 or 3 weeks (median of 1 month) after initiation of statin therapy, ranging up to 12 months similar to this patient.¹¹ Once a patient's muscle symptoms have occurred after taking statin during the onset period, all medication must be discontinued. Possible other risk factors for causing of muscle pain must be considered and excluded. If clinical intervention is needed to treat dyslipidemia for prevention of cardiovascular diseases, clinicians have several options, including the use of a different statin with low incidence of rhabdomyolysis such as hydrophilic statin. Also low dose second efficacious statin and efficacious statin with alternate day (weekly dosing regimen) have been recommended. The utilization of non-statin lipid-lowering agents such as ezetimibe and

bile-acid binding resins could also be considered. Hypothyroidism was reported as a predictor of statin-associated myopathy. Hypothyroidism could itself be a risk factor for renal impairment.¹³ The likely mechanisms of renal impairment in hypothyroidism are the reduction in GFR due to the lower cardiac output and renal blood flow, and thyroxine hormone may mediate tubular secretion of creatinine, so hypothyroidism may increase creatinine release from muscle and cause rhabdomyolysis.¹⁴

Simvastatin is metabolized through the hepatic CYP3A4 pathway. Concomitant use of CYP3A4 inhibitors have the potential to increase exposure to simvastatin and increase risk of myopathy or rhabdomyolysis.^{5,7,8} Gemfibrozil is a substrate and potent inhibitor of CYP3A4 via glucuronidation reaction. Other possible mechanisms of gemfibrozil and simvastatin interaction could result from inhibition of organic anion transporter (OAT2). In humans, OATP2 (also known as OATP-C) is expressed in the liver and makes a substantial contribution to the hepatic uptake of statins. Gemfibrozil inhibition of OATP2-mediated statin hepatic uptake may explain, at least partly explain, the drug-drug interactions reported between gemfibrozil and statins.^{15,16} Concurrent administration of these two medications is contraindicated.

Amlodipine is a substrate and potent inhibitor of CYP3A4 and therefore increases the plasma concentration and maximum plasma concentration (C_{max}) of simvastatin when they are co-administered. Concurrent administration of amlodipine and simvastatin increased area under the curve and C_{max} of simvastatin by 1.77 and 1.47 folds, respectively.¹⁷ Pharmacokinetic interaction of simvastatin and amlodipine is classified as a majority of severe with rapid onset of interaction. Several guidelines have recommended that if it is necessary to co-administer, the dose of simvastatin should not exceed 20 mg/day applied with amlodipine at doses of both 5 and 10 mg.^{17,18}

This presented case suggested a caution that hypothyroidism and interaction with other drugs should be considered when patients were going to be initiated on statins particularly patients with many risk factors.

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