

Rosuvastatin Induced Rhabdomyolysis in a Low Risk Patient: A Case Report and Review of the Literature

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Abstract: We report a case of rosuvastatin induced rhabdomyolysis in a low risk patient, who presented with five-day history of generalized muscle pain, weakness and easy fatigability associated with passing dark urine. Initial investigations showed creatinine 140 μ mol/L, creatine kinase (CK) 4566 U/L and serum myoglobin 2694 ng/ml with a significant increase in urine myoglobin. Although there were no obvious risk factors, the patient was diagnosed with rosuvastatin induced rhabdomyolysis. The drug was stopped on the first day of admission and the patient was initiated on intravenous fluid with cautious monitoring of serum electrolytes. On the following days the level of creatine kinase and serum myoglobin returned toward normal and consequently he was discharged without statins but on dietary therapy. On follow-up evaluation, the patient was symptom free his serum creatinine was 106 μ mol/L, whereas his LDL cholesterol was 2.1mmol/L. The rosuvastatin induced rhabdomyolysis is discussed and the danger of its use in low risk patients is emphasized.

Key Words: Cytochrome P450, rhabdomyolysis, rosuvastatin.

INTRODUCTION

Statins are 3-hydroxy-3-methyl coenzyme A (HMG-CoA) reductase inhibitors that have significant effects on the plasma lipid and lipoprotein profile, lowering total and LDL cholesterol and triglyceride levels and raising HDL cholesterol levels; currently they are the mainstay of dyslipidemia management for the primary and secondary prevention of cardiovascular disease.

The use of statins in randomized trials has demonstrated 30% reductions in atherosclerotic end points without serious morbidity [1, 2]. Rosuvastatin is a competitive inhibitor of the enzyme HMG-CoA reductase, having a mechanism of action similar, yet higher efficacy, to other statins [3]. The efficacy of rosuvastatin across its dose range of 10 to 40 mg is superior to that of other statins across their dose range, although the safety is similar [4-8]. There is limited information about the efficacy and safety of rosuvastatin in doses higher than 40 mg/day. This remains speculative and needs further studies. Rosuvastatin 40 mg reduced LDL cholesterol levels by 54%, while it increased HDL cholesterol by 13% after 96 weeks [6]. Like other statins, rosuvastatin is associated with a spectrum of adverse events ranging from mild to life-threatening. The most severe adverse event is severe myopathy (ranges from myalgias to rhabdomyolysis), which can cause acute renal failure; this adverse event usually associated with many risk factors. Rosuvastatin was introduced onto the Qatari market in 2006, since that time no cases of rosuvastatin induced rhabdomyolysis had been reported. In this report we present a case of rhabdomyolysis induced by low dose of rosuvastatin (10 mg daily) in a 57-year-old Qatari man who had no obvious risk factor.

CASE REPORT

A 57-year-old Qatari man admitted to the hospital with five-day history of generalized muscle pain, weakness and easy fatigability associated with passing dark urine. He denied the consumption of grapefruit juice or alcohol abuse and he hadn't had any exercise before this episode. There was no family history of muscle disease. The patient had history of diabetes mellitus (DM) type II, hypertension, hypercholesterolemia, ischemic cerebral stroke and left knee osteoarthritis. He had hypertension and diabetes mellitus since 6 years and had been followed up regularly by his physician in the clinic. Hypercholesterolemia and ischemic stroke were diagnosed three years ago. The patient had no history of renal impairment with a baseline creatinine of 104 μ mol/L. current medications included glimepiride 4 mg once daily orally (PO), valsartan 80 mg once daily PO, amlodipine 10 mg once daily PO and clopidogril 75 mg once daily. His hypercholesterolemia was treated initially by simvastatin 40 mg/day for 2 years, but the patient was shifted to rosuvastatin 10 mg once daily PO during the last 9 months for better control of hypercholesterolemia. For his osteoarthritis, the patient used to take non-steroidal anti-inflammatory drugs when necessary. On examination the pulse was 105/min and the blood pressure 150/95 mmHg. Neurologic examination showed left sided weakness 4/5 as a result of previous ischemic stroke with up-going plantar reflex. His left knee joint was tender with restricted movement. Fundus examination showed background retinopathy. The remaining of the examination was unremarkable.

Initial investigations showed hemoglobin level of 14 g/dL, total leucocyte count 18600/uL and platelets, 451000/uL; urea nitrogen 13.8 mmol/L, creatinine 140 μ mol/L, sodium 132 mEq/L and potassium 4.6 mEq/L, bicarbonate 23 mmol/L, Ca 2.3 mmol/L, blood sugar 11.7 mmol/L. His myoglobin was elevated, 2694 ng/ml with a significant increase in urine myoglobin. The creatine kinase (CK) level was markedly

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elevated (4566 U/L), with normal CK MB fraction and cardiac troponin levels. Aspartate aminotransferases (AST) was 44 IU/L, alanine aminotransferase (ALT) 104 IU/L and alkaline phosphatase 341 IU/L. Total bilirubin was 11 µmol/L, total proteins, 7.5 g/dL, and albumin, 4.0 g/dL, whereas PT and INR were normal. His fasting lipid profile was; total cholesterol, 3.3 mmol/L; LDL cholesterol, 1.7 mmol/L; triglyceride, 1.1 mmol/L. Thyroid function tests were normal. Tests for antinuclear antibodies, circulating immune complexes, ANCA, and cryoglobulinaemia were negative. Serum complements C3 and C4 were normal. Antibodies to hepatitis A, B and C viruses, and human immunodeficiency virus were absent.

Eight weeks before this episode the patient visited his doctor at the medical clinic. Routine laboratory data showed: Urea nitrogen level of 9.4 mmol/L, serum creatinine 104 µmol/L, sodium 136 mEq/L and potassium 4.6 mEq/L, bicarbonate 20 mmol/L, Ca 2.2 mmol/L, random blood sugar 11.8 mmol/L. AST level was 29 IU/L, ALT 31 IU/L, alkaline phosphatase 66 IU/L, total bilirubin 8 µmol/L, total proteins 6.9 g/dL and albumin 3.6 g/dL. His fasting lipid profile was; total cholesterol 4.1 mmol/L; LDL cholesterol 2.0 mmol/L and triglyceride, 1.8 mmol/L. His creatine kinase (CK) level was 198 U/L.

Rhabdomyolysis secondary to rosuvastatin now seemed the most likely diagnosis; accordingly this drug was stopped at time of admission and intravenous fluids (normal saline) given at 150 cc/hour with cautious monitoring of serum electrolytes. Other medications were resumed.

On the following days the level of creatine kinase and serum myoglobin declined toward the normal value and consequently he was discharged 7 days after hospitalization without statins but on diet therapy. At the time of discharge, the serum AST level was 34 IU/L, ALT 47 IU/L, alkaline phosphatase 73 IU/L, total bilirubin 8 µmol/L, CK 484 U/L. On follow-up evaluation two months after discharge the patient was symptom free; laboratory evaluation yielded CK of 212 U/L, serum creatinine of 106 µmol/L and LDL cholesterol of 2.1 mmol/L.

DISCUSSION

Rosuvastatin is a relatively new cholesterol-lowering drug in Qatar as well as in other gulf countries; although highly efficacious, this new statin has generated considerable controversy regarding its safety. In Canada as well as United States, many cases of rosuvastatin induced rhabdomyolysis had been reported [9, 10]. Like other statins, rosuvastatin can cause life threatening rhabdomyolysis (defined as muscle symptoms with marked creatine kinase elevation typically substantially greater than 10 times the upper limit of normal, with a creatinine elevation consistent with pigment nephropathy and usually with brown urine with myoglobinuria) [2, 11]. Our patient presented with muscle pain, weakness, fatigue and passing dark urine. His serum creatinine was higher than the baseline and his CK was greater than 10 times the upper limit of normal. The incidence of rosuvastatin-induced rhabdomyolysis is not known exactly but it was presumed to be low [6, 7], and similar to atorvastatin, pravastatin, and simvastatin [7]; to our knowledge this is the

first reported case in Qatar. Although statin induced rhabdomyolysis had been reported at rates of 1 death per 6.6 million prescriptions [12], no deaths related to rosuvastatin induced rhabdomyolysis were reported in the literature [7].

Heerey *et al.* [13] estimated that approximately 30% of all users of statins have concomitant prescribed drugs that can inhibit statin metabolism by hepatic cytochrome P450 (CYP) system, potentially leading to rhabdomyolysis. Rosuvastatin is not metabolized by means of cytochrome P450 (CYP) 3A4, but it is minimally metabolized in the CYP2C9 isoenzyme pathway and to lesser extent in the CYP2C19 isoenzyme pathway [14, 15]. In addition, rosuvastatin does not have any inhibitory or inducing effects on the CYP system. Thus, CYP isoenzyme inhibitors, including erythromycin, itraconazole, Amiodarone and ketoconazole, do not substantially affect rosuvastatin metabolism.

The most common drug interactions of rosuvastatin are with the following drugs: cyclosporine [16], Gemfibrozil [17-19], warfarin [20], oral contraceptives [21] and antacid containing magnesium or aluminum hydroxide [22]; these interactions are not related to the CYP system. Thus, concurrent use of these drugs with rosuvastatin should be with caution. None of these medications were used by our patient.

The factors that increase the risk of rosuvastatin induced myopathy or rhabdomyolysis include increased age, renal impairment, hypothyroidism, personal or family history of hereditary muscular disorders, previous history of muscular toxicity with another statin or fibrate, consumption of grapefruit juice (more than 1 L per day), alcohol abuse, being of Chinese or Japanese descent, concomitant use of fibrates. This group of patients should be given rosuvastatin with caution [10].

Our patient had no obvious risk factor; he was 57 years old and non alcoholic with normal thyroid function test; his baseline creatinine was normal and the calculated creatinine clearance was 68 ml/min. How could rosuvastatin cause rhabdomyolysis without obvious precipitating factor?

It is probable that muscle weakness which resulted from a previous stroke, was the precipitating factor of rhabdomyolysis in this patient.

Rosuvastatin should be discontinued in patients with a creatine kinase level of more than 10 times the ULN with or without muscle symptoms [10].

Rosuvastatin is contraindicated in individuals with a known hypersensitivity to the drug and in those with active liver disease or unexplained persistent elevations in liver transaminases levels (> 3 times the upper normal limit (ULN) on two consecutive visits). Liver transaminase levels should be assessed at baseline, at 12 weeks after the start of therapy or an increase in dose, and at 6-month intervals thereafter. The dosage should be reduced or therapy withdrawn if liver transaminase levels exceed 3 times the ULN. Because of the potential for rosuvastatin to increase liver transaminase levels, it should be used with caution in patients with a history of liver disease or alcohol abuse [22]. Overall, persistent elevations in liver transaminase levels are reported in 0.1-0.4% of patients taking rosuvastatin 5-40 mg

[22]. Similarly, our patient showed high transaminase level which was returned to normal after discontinuation of the drug.

Like all statins, rosuvastatin is in pregnancy category X. Its safety in pregnant women has not been established, and its use should be avoided in women who are pregnant or may become pregnant. Information on the excretion of rosuvastatin in breast milk is not available [23].

Although the exact mechanism of statin-induced rhabdomyolysis is unknown, the implicated mechanisms include the followings: first, the cholesterol synthesis blockage; which makes the skeletal muscle-cell membranes unstable due to low cholesterol content [11]. Second, prenylated protein abnormalities causing imbalances in intracellular protein messaging [24]. Third, coenzyme Q10 deficiency causing abnormal mitochondrial respiratory function [25-27].

Rosuvastatin induced rhabdomyolysis in this patient is supported by the following: first, among the drugs used by the patient, there was no drug that known to cause rhabdomyolysis; second: myoglobin and CK were washed out from the blood and returned towards normal within few days after discontinuation of rosuvastatin.

In conclusion, although highly efficacious, rosuvastatin has generated considerable controversy regarding its safety; clinicians should maintain an increased level of awareness of the potential for muscle toxicity and rhabdomyolysis, which associated with this new drug. Accordingly, Emergent myalgias in patients under rosuvastatin necessitate immediate testing of creatine kinase and myoglobin to exclude life-threatening rhabdomyolysis.

REFERENCES

- [1] Nissen SE, Nicholls SJ, Sipahi I, *et al.* Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. *JAMA* 2006; 295: 1556-65.
- [2] Antons KA, Williams CD, Baker SK, Phillips PS. Clinical perspectives of statin-induced rhabdomyolysis. *Am J Med* 2006; 119: 400-9.
- [3] Cannon CP, Braunwald E, McCabe CH, *et al.* Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004; 350: 1495-1504.
- [4] Jones PH, Davidson MH, Stein EA, *et al.* Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR Trial). *Am J Cardiol* 2003; 92: 152-160.
- [5] Schuster H, Barter PJ, Stender S, *et al.* Effects of switching statins on achievement of lipid goal: Measuring Effective Reductions In Cholesterol Using Rosuvastatin therapY (MERCURY I) study. *Am Heart J* 2004; 147: 705-712.
- [6] Stein EA, Amerena J, Ballantyne CM, *et al.* Long-term efficacy and safety of rosuvastatin 40 mg in patients with severe hypercholesterolemia. *Am J Cardiol* 2007; 100: 1387-96.
- [7] Shepherd J, Vidt DG, Miller E, Harris S, Blasetto J. Safety of rosuvastatin: Update on 16,876 rosuvastatin-treated patients in a multinational clinical trial program. *Cardiology* 2007; 107: 433-43.
- [8] Brewer HB Jr. Benefit-risk assessment of rosuvastatin 10 to 40 milligrams. *Am J Cardiol* 2003; 92: 23-29.
- [9] Woollorton E. Rosuvastatin (Crestor) and rhabdomyolysis. *CMAJ* 2004; 171: 129.
- [10] Association of Crestor (rosuvastatin) with rhabdomyolysis [Dear Health Care Professional letter]. Mississauga (ON): Astra Zeneca Canada Inc.; 2004 June 15. Available: <http://napra.ca/pdfs/advisories/crestorhc.pdf> [accessed 2008 July 28].
- [11] Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. *JAMA* 2003; 289: 1681-90.
- [12] Staffa JA, Chang J, Green L. Cerivastatin and reports of fatal rhabdomyolysis. *N Engl J Med* 2002; 346: 539-40.
- [13] Heerey A, Barry M, Ryan M, Kelly A. the potential for drug interactions with statin therapy in Ireland. *Ir J Med Sci* 2000; 169: 176-9.
- [14] McTaggart F. Comparative pharmacology of rosuvastatin. *Atheroscler Suppl* 2003; 4: 9-14.
- [15] White CM. A review of the pharmacologic and pharmaco-kinetic aspects of rosuvastatin. *J Clin Pharmacol* 2002; 42: 963-70.
- [16] Simonson SG, Raza A, Martin PD, *et al.* Rosuvastatin pharmacokinetics in heart transplant recipients administered an antirejection regimen including cyclosporine. *Clin Pharmacol Ther* 2004; 76: 167-77.
- [17] Prueksaritanont T, Zhao JJ, Bennett MA, *et al.* Mechanistic studies on metabolic interactions between gemfibrozil and statins. *J Pharmacol Exp Ther* 2002; 301: 1042-51.
- [18] Prueksaritanont T, Tang C, Qui Y, Mu L, Subramanian R, Lin JH. Effects of fibrates on metabolism of statins in human hepatocytes. *Drug Metab Dispos* 2002; 30: 1280-7.
- [19] Schneck DW, Birmingham BK, Zalikowski JA, *et al.* The effect of gemfibrozil on the pharmacokinetics of rosuvastatin. *Clin Pharmacol Ther* 2004; 75: 455-63.
- [20] Barry M. Rosuvastatin-warfarin drug interaction [comment]. *Lancet* 2004; 363: 328.
- [21] Simonson SG, Martin PD, Warwick MJ, Mitchell PD, Schneck DW. The effect on estrogen and progestin pharmacokinetics in healthy women taking an oral contraceptive. *Br J Clin Pharmacol* 2004; 57: 279-86.
- [22] Astra Zeneca Pharmaceuticals LP. Crestor (rosuvastatin calcium) prescribing information: Wilmington, DE; 2003.
- [23] Culhane NS, Lettieri SL, Skae JR. Rosuvastatin for the treatment of hypercholesterolemia. *Pharmacotherapy* 2005; 25: 990-1000.
- [24] Flint OP, Masters BA, Gregg RE, Durham SK. Inhibition of cholesterol synthesis by squalene synthase inhibitors does not induce myotoxicity *in vitro*. *Toxicol Appl Pharmacol* 1997; 145: 91-98.
- [25] De Pinieux G, Chariot P, Ammi-Said M, *et al.* Lipid lowering drugs and mitochondrial function: Effects of HMG-CoA reductase inhibitors on serum ubiquinone and blood lactate/ pyruvate ratio. *Br J Clin Pharmacol* 1996; 42: 333-337.
- [26] Evans M, Rees A. Effects of HMG-CoA reductase inhibitors on skeletal muscle: are all statins the same?. *Drug Saf* 2002; 25: 649-63.
- [27] Phillips PS, Haas RH, Bannykh S, *et al.* for the Scripps Mercy Clinical Research Center. Statin-associated myopathy with normal creatine kinase levels. *Ann Intern Med* 2002; 137: 581-5.