PATIENT REPORT

ROSUVASTATIN-INDUCED RHABDOMYOLYSIS PROBABLY VIA CYP2C9 SATURATION

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SUMMARY

A 66 year-old woman with no history of renal or liver disease presented with progressive asthenia and diffuse myalgia. She cited 5 months history of mild hyperlipidemia under treatment with rosuvastatin (10 mg/day). Clinical examination documented both an increase in liver size and proximal muscle weakness, with difficulty in raising arms above the head. Blood tests showed the presence of renal, liver and muscle failure, with no evidence of virological, immunological or haematological diseases. Rosuvastatin treatment was stopped and blood values normalised within five days; but because of an increase in cholesterol plasma levels, rosuvastatin (10 mg/day) was restarted. Two days later, the patient returned to our observation due to the development of asthenia and muscle weakness, with an increase in creatine phosphokinase, 12,165 U/l. Rosuvastatin was discontinued and replaced with pravastatin (40 mg/day) with a complete resolution of clinical and laboratory findings in about six days. Our patient was

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taking rosuvastatin, warfarin and telmisartan, which are metabolised by CYP2C9; we therefore hypothesised that the rosuvastatin-induced rhabdomyolysis was probably by CYP2C9 enzyme saturation.

KEY WORDS

woman, rosuvastatin, creatine phosphokinase, rhabdomyolysis, CYP2C9

INTRODUCTION

Hydroxymethylglutaryl coenzyme A-reductase inhibitors, statins, are the most common pharmacological treatment for hyperlipidemia /1/. The most important adverse effects recording with statin treatment are asymptomatic increase in liver transaminase and myopathy /2,3/. We report a case of rhabdomyolysis during rosuvastatin treatment.

PATIENT REPORT

A 66 year-old woman with no history of renal or liver disease was admitted in May 2006 to the Internal Medicine Department of San Giovanni in Fiore Hospital with progressive asthenia and diffuse myalgia. Her medical anamnesis showed an 8-year history of hypertension and chronic atrial fibrillation treated with warfarin (2.5 mg/day), telmisartan (80 mg/day), ranitidine (150 mg/day os), furosemide (25 mg/day, os) and carvedilol (6.25 mg twice daily). In addition she cited 5 months of mild hyperlipidemia under treatment with rosuvastatin (10 mg/day). Clinical examination documented both an increase in liver size and proximal muscle weakness, with difficulty in raising her arms above her head. Blood tests showed the presence of renal, liver and muscle failure (creatinine 1.8 mg/dl, aspartate aminotransferase 389 U/l, alanine aminotransferase 225 U/l, bilirubin 4.15 mg/dl, creatine phosphokinase 15,189 U/l; lactate dehydrogenase 3,512 U/l), with no evidence of virological, immunological or haematological disease. Rosuvastatin was discontinued with the normalisation of blood values within five days, and the patient was discharged. Three weeks later, a new laboratory test showed normalisation of hepatic and renal function indices with a significant increase in plasma cholesterol levels (total cholesterol 260 mg/dl).

Rosuvastatin (10 mg/day) was restarted. Two days later, the patient returned to our observation due to the development of asthenia and muscle weakness. A laboratory test revealed signs of rhabdomyolysis (creatine phosphokinase 12,165 U/l; lactate dehydrogenase 2,250 U/l). Pharmacological evaluation, using the Naranjo probability scale /4/, indicated a probable relationship between rosuvastatin and rhabdomyolysis, so rosuvastatin was discontinued and replaced with pravastatin (40 mg/day) with a complete resolution of clinical and laboratory findings in about 6 days. During 3 and 6 months follow-up, when the patient was being treated with pravastatin (40 mg/day), warfarin (2.5 mg/day), telmisartan (80 mg/day), ranitidine (150 mg/day os), furosemide (25 mg/day, os) and carvedilol (6.25 mg twice daily), clinical and laboratory tests appeared normal without any requirement for dose adjustment or drug substitution.

DISCUSSION

Statins are the 'gold standard' of lipid lowering drugs and their side effects involving muscle injury can range from muscular pain to rhabdomyolysis /2/. Rosuvastatin is a new statin with a hydrophilic structure, a low incidence of side effects, and liver metabolism predominantly induced by CYP2C9 /5,6/.

Alsheikh-Ali *et al.* /7/ documented a dose-related occurrence of rhabdomyolysis within 12 weeks after statin initiation. We report a woman who developed rhabdomyolysis 5 months after beginning treatment with rosuvastatin 10 mg/day.

It has been previously shown that the incidence of rhabdomyolysis increases with increasing dosage of statin monotherapy or with the intake of concurrent drugs or foods able to inhibit statin metabolism /8/. Ireland *et al.* /9/ reported a case of rhabdomyolysis in a patient taking rosuvastatin and fenofibrate. Fenofibrate is a CYP2C9 inhibitor and increases rosuvastatin plasma levels, thus enhancing rosuvastatin toxicity. Our patient did not take food or drugs able to inhibit cytochrome metabolism which would increase the plasma levels of the statin.

It has been documented that rosuvastatin is able to enhance the anticoagulant effects of warfarin through displacement of the warfarin from protein binding sites with a significant increase in the international normalised ratio (INR) /10/. However, Jindal *et al.* /11/

showed in 12 healthy male volunteers that treatment with rosuvastatin (40 mg/day) did not significantly alter the anticoagulant effects of warfarin (5 mg/day). In agreement with this study, which was performed over 14 days, in our patient INR was maintained at 2.0-2.5, presumably because the patient was taking a low dose of warfarin.

Warfarin as well as telmisartan were being taken by our patient, and both are metabolised by CYP2C9. Therefore, we hypothesise that the rosuvastatin induced rhabdomyolysis by CYP2C9 enzyme saturation. The relationship between rosuvastatin and rhabdomyolysis has been confirmed by the Naranjo Adverse Probability Scale /4/, that indicated a probable relationship between rhabdomyolysis symptoms and drug treatment. We took into consideration the development of rhabdomyolysis after rosuvastatin treatment, the improvement of the adverse reaction after rosuvastatin cessation, the positive re-challenge, and the absence of known alternative causes.

Scordo *et al.* /12/ showed that CYP2C9 genetic polymorphisms markedly influence warfarin dose requirements and metabolic clearance of *S*-warfarin. Moreover, it has also been reported that CYP2C9*2 and CYP2C9*3 allelic variants induce low enzyme activity in 10-20% of the Caucasian population /13,14/. We cannot exclude that one or both of these polymorphisms was present in our Caucasian female patient.

In conclusion, further investigations are needed to study genetic variability and pharmacokinetic interactions during concomitant polytherapy. Moreover, additional data are necessary to clarify rosuvastatin involvement with a possible increased risk of rhabdomyolysis.

REFERENCES

1. Pearson TA. The epidemiologic basis for population-wide cholesterol reduction in the primary prevention of coronary artery disease. Am J Cardiol 2004; 94. 4F-8F.
2. Molokhia M, McKeigue P, Curcin V, Majeed A. Statin induced myopathy and myalgia: time trend analysis and comparison of risk associated with statin class from 1991-2006. PLoS ONE 2008; 3: e2522.
3. Armitage J. The safety of statins in clinical practice. Lancet 2007; 370: 1781-1790.
4. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981; 30: 239-245.

5. Maroo BP, Lavie CJ, Milani RV. Secondary prevention of coronary heart disease in elderly patients following myocardial infarction: are all HMG-CoA reductase inhibitors alike? Drugs Aging 2008; 25: 649-664.
6. McAfee AT, Ming EE, Walker AM. The comparative safety of rosuvastatin: a retrospective matched cohort study in over 48,000 initiators of statin therapy. Pharmacoepidemiol Drug Saf 2004; 15: 444-453.
7. Alsheikh-Ali AA, Ambrose MS, Karas RH. The safety of rosuvastatin as used in common clinical practice. Circulation 2005; 111: 3051-3057.
8. Sorokin AV, Duncan B, Panetta R, Thompson PD. Rhabdomyolysis associated with pomegranate juice consumption. Am J Cardiol 2006; 98: 705-706.
9. Ireland JH, Eggert CH, Arendt CJ, Williams AW. Rhabdomyolysis with cardiac involvement and acute renal failure in a patient taking rosuvastatin and fenofibrate. Ann Intern Med 2005; 142: 949-950.
10. Simonson SG, Martin PD, Mitchell PD, Lasseter K, Gibson G, Schneck DW. Effect of rosuvastatin on warfarin pharmacodynamics and pharmacokinetics. J Clin Pharmacol 2005; 45: 927-934.
11. Jindal D, Tandon M, Sharma S, Pillai KK. Pharmacodynamic evaluation of warfarin and rosuvastatin co-administration in healthy subjects. Eur J Clin Pharmacol 2005; 61: 621-625.
12. Scordo MG, Pengo V, Spina E, Dahl ML, Gusella M, Padrini R. Influence of CYP2C9 and CYP2C19 genetic polymorphisms on warfarin maintenance dose and metabolic clearance. Clin Pharmacol Ther 2002; 72: 702-710.
13. Aithal GP, Day CP, Kesteven PJ, Daly AK. Association of polymorphisms in the cytochrome P450 CYP2C9 with warfarin dose requirement and risk of bleeding complications. Lancet 1999; 353: 717-719.
14. Higashi MK, Veenstra DL, Kondo LM, Wittkowsky AK, Srinouanprachanh SL, Farin FM, Rettie AE. Association between CYP2C9 genetic variants and anticoagulation-related outcomes during warfarin therapy JAMA 2002; 287: 1690-1698.