The THAI Journal of SURGERY 1999; 20:137-138.
Official Publication of the Royal College of Surgeons of Thailand

Rhabdomyolysis in Renal Transplant Patient Treated with Simvastatin and Cyclosporin: A Case Report

Supot Wudhikarn, MD*
Siwat Puriyapan, MD*
Dusit Lumlertkul, MD**

*Division of Urology, Department of Surgery,
**Division of Nephrology, Department of Medicine, Faculty of Medicine, Chiangmai University, Chiangmai, Thailand

Abstract **We describe a patient treated with combination of cyclosporin and simvastatin who had to be hospitalized due to rhabdomyolysis. After cessation of treatment with simvastatin, intensive hydration and plasmaphoresis, the patient recovered in 2 weeks. While rhabdomyolysis had been described in several patients receiving the combination of lovastatin/cyclosporin, so far only one case had been reported in patients treated with simvastatin/cyclosporin. Our case therefore suggested that this combination may be more frequent than previously suspected. In patient treated with cyclosporin HMG-CoA reductase inhibitor should be used cautiously.**

Hyperlipidemia, frequently seen after renal transplantation is an independent risk factor for cardiovascular disease in renal transplant recipients.[1] About 40 per cent of deaths in renal transplant patient are attributed to cardiovascular complication.[2] It has been reported that intensive lipid-lowering therapy can retard the progression of coronary artery disease, thus reducing the incidence of cardiovascular events.[3,4]

The development of hyperlipidemia in renal transplant patient is multifactorial in origin. Conditions such as proteinuria, hyperglycemia, impaired renal function, immunosuppression including cyclosporin and steroid, and antihypertensive therapy with beta blocker and diuretics are associated with abnormal lipid profile in these patients.[5-6]

Simvastatin is a potent competitive inhibitor of 3 hydroxy - 3 - methylglutaryl coenzyme A (HMG-CoA) reductase which has become commercially available in Europe since 1989 as a treatment of primary hypercholesterolemia. Lovastatin, another inhibitor of HMG-CoA reductase has been used in the USA since 1987. Its side effects are better known than those of simvastatin. Some cases of lovastatin related myopathy have been reported, suggesting that myocytes are sensitive to this drug.[7]

Several cases of rhabdomyolysis associated with lovastatin use have been described.[8] This was observed in heart-transplanted patients[9] receiving concomitant drugs which were thought to increase muscular toxicity, such as cyclosporin.[10] Toxic interactions have also been described with erythromycin,[11] and ketoconazole.[12] The mechanism involved in this interaction is not known. Hypothesis includes a decrease in hepatic clearance of lovastatin brought on by microsomial hepatic enzyme activation or albumin transport site.

We present a case of rhabdomyolysis with renal transplant recipient associated with simvastatin and cyclosporin use.

Case Report

A 43 year-old woman was admitted to our university hospital on January 16, 1998 because of severe myalgia, general muscle weakness and unable to walk. She had undergone renal transplant 4 months before

and medication used were simvastatin 20 mg daily due to hypercholesterolemia and cyclosporin 100 mg twice daily for the past 4 months. At the time of admission the patient presented with abdominal pain, ankle edema, functional disability of the lower limb. Physical examination revealed high blood pressure 180/90 mmHg, body temperature 37°C. Muscle pain was worsened on palpation. All deep tendon reflexes were suppressed.

Laboratory data were as follows: BUN 33 mg/dl, creatinine 1.7 mg/dl, glucose 113 mg/dl, Na 140 mg/dl, K 4.4 mg/dl, Cl 113 mg/dl, CO_2 12 mmol/L, Ca 8.5 mg/dl, P 3.5 mg/dl, Mg 1.5 mg/dl, cholesterol 228 mg/dl, AST (GOT) 401 U/L, LDH 1941 U/L, CPK 19,037 U/L (normal 0-195 U/L). Complete blood count was normal. Bacterial and viral serology analyses were also negative. We concluded that this patient developed rhabdomyolysis.

All medications were stopped and the patient underwent a weekly plasmaphoresis for 3 weeks. Within 8 days muscle aching and weakness progressively disappeared, CPK returned to normal and patient was discharged on 4th February 1988.

Discussion

The various etiologies of rhabdomyolysis such as hard physical effort, traumatism, infections, metabolic and muscular ischemia, burns, alcohol abuse and muscle enzymatic deficiencies were excluded in this patient. Although the occurrence of rhabdomyolysis might theoretically be caused only by the received of simvastatin,[13] it is striking that this patient use cyclosporin as well. During the use of lovastatin, a simvastatin-related HMG-CoA reductase inhibitor, the risk of this side effect might be increased when cyclosporin are used concomitantly.[14,15] This might indicate that the concomitant use of simvastatin and cyclosporin constitutes an aditional risk. The mechanism that causes the desctruction of the muscle fibres during the use of HMG-CoA reductase inhibitor or fibrate is not exactly known. HMG-CoA reductase inhibitors, such as simvastatin, inhibit the conversion of HMG-CoA of mevalonic acid. Some of the metabolic products of mevalonic acid play a role in the formation of the cellular membrane.[16] It is posible that the decrease in the concentration of these products may destroy the muscle fibres.

In conclusion, the concomitants use of HMG-CoA reductase inhibitors and cyclosporin may cause and increased risk of rhabdomyolysis. The combination of these drugs seem justified only with closed follow up.

Acknowledgement

The authors thank Mrs. Nareerat Leukakul and Miss Amara Manoyod for their secretarial assistances.

References

1. Kasiske BL, Risk factors for accelerate atherosclerosis in renal transplant recipient. Am J Med 1988; 84:985.
2. Wing AJ. Brunner FP, Brynger H, et al. Cardiovascular related causes of death and the fate of patients with renovascular disease. Contr Nephrol 1984; 41:306.
3. Brown G, Albers J, Fisher LD, et al. Regression of coronary artery disease as a result of intensive lipid lowering therapy in men with high level of apolipoprotein B. N Engl J Med 1990; 323:1289.
4. The lipid research clinic - coronary primary prevention trial result: II the relationship of reduction incidence of coronary heart disease to cholesterol lowering. JAMA 1984; 251:365.
5. Castelao AM, Barbera MJ, Blanco A, et al. Lipid metabolic abnormalities after renal transplantation under cyclosporin and prednisolone immunosuppression. Transplant Proc 1992; 24:96.
6. Bittar AE. Ratchiffe PJ, Richardson AF, et al. The prevalence of hyperlipidemia in renal transplant recipients. Transplantation 1990; 50:987.
7. Maher VMG, Pappu A, Illingworth D, Thompson GR. Plasma mevalonate response in lovastatin related myopathy. Lancet 1989; ii:1098.
8. Torbert JA. Efficacy and long term adverse effect pattern of lovastatin. Am J Cardiol 1988; 62:28J-33J.
9. Corpier CL, Jones PH, Suki WN, et al. Rhabdomyolysis and renal injury with lovastatin use. JAMA 1988; 260:239-41.
10. Norman DJ, Illingworth DR, Munsun JM, Hosenpud J. Myolysis and acute renal failure in heart transplant recipient receiving lovastatin. N Engl J Med 1988; 318:46-7.
11. Ayanian JZ, Fuchs CS, Stone RM. Lovastatin and rhabdomyolysis. Ann Intern Med 1988; 109:682.
12. Corpier CL, Jones PH, Suki WN, Lederer ED. Rhabdomyolysis and renal failure: 2 case reports. J Am Med Assoc 1988; 260:239-41.
13. Deslypere JP, Vermeulen A. Rhabdomyolysis and simvastatin. Am Intern Med 1991; 114:342.
14. Kogan AD, Orenstein S, Lovastatin - induced acute rhabdomyolysis. Postgrad Med J 1990; 66:294-6.
15. Pierce LR, Wysowski DK, Gross TP. Myopathy and rhabdomyolysis associated with lovastatin - gemfibrozil combination therapy. JAMA 1990; 264:715.
16. Grundy SM. HMG-CoA reductase inhibitors for treatment of hypercholesterolaemia. N Engl J Med 1988; 319:24-3.