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CASE REPORT

Rhabdomyolysis And Hepatitis Associated With Pravastatin Therapy

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ABSTRACT

A 65-year-old woman with diabetes mellitus type II, hypercholesterolemia and depressive disorder, admitted to the hospital with one-week history of generalized weakness and fatigability. Her medications included gliclazide, pravastatin, fluoxetine hydrochloride (Prozac), Hydroxyzine hydrochloride and Lorazepam. Clinical examination was unremarkable. Both myoglobin and creatine kinase (CK) level were elevated as well as liver enzymes. The urine myoglobin test result was positive. The patient was diagnosed with pravastatin induced rhabdomyolysis and hepatitis. Pravastatin was stopped and rhabdomyolysis was managed with vigorous hydration and urine alkalinization. On the following days the level of creatine kinase, liver enzymes and s.creatinine returned to normal and consequently she was discharged.

Key words: Hepatitis; myopathy; pravastatin; rhabdomyolysis

Introduction

Pravastatin is a 3-hydroxy-3-methyl coenzyme A (HMG-CoA) reductase inhibitor that has significant effects on the plasma lipid and lipoprotein profile, lowering total and LDL cholesterol and triglyceride levels and raising HDL cholesterol levels**.** [1],[2],[3] The long-term safety profile of pravastatin, established over many years of clinical use, is excellent. Although rhabdomyolysis and hepatitis are recognized toxic effects of this medication, the occurrence of both rhabdomyolysis and hepatitis at the same time is extremely rare. A PubMed search of the same time is extremely rare. A PubMed search of the literature revealed no cases of pravastatin induced rhabdomyolysis and hepatitis have been reported in the same patient. We report here an extremely rare case of a 65-year-old woman with rhabdomyolysis and hepatitis associated with pravastatin therapy.

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Case History

A 65-year-old woman admitted to the hospital with one-week history of generalized weakness and fatigability. Past medical history was remarkable for diabetes mellitus (DM) type II, hypercholesterolemia and depressive disorder. The patient had never received a blood transfusion and she denied the use of alcohol or intravenous drugs. She had a depressive disorder since 6 years and had been followed up regularly at a psychiatric clinic. DM and

hypercholesterolemia were diagnosed three years ago. Her medications included gliclazide 80mg twice daily orally (PO), pravastatin 40 mg once daily PO, prozac 20 mg once daily PO, Hydroxyzine hydrochloride 25 mg once daily PO and Lorazepam 1 mg PO at night.

On examination the pulse was 110/min and the blood pressure 115/75 mmHg. Fundus examination showed background retinopathy. The remaining of the examination was unremarkable.

Initial investigations showed hemoglobin level of 12 g/dL, total leucocyte count 9500/uL and platelets, 467000/uL; urea nitrogen 10 mmol/L, creatinine 160µmol/L, sodium 135 mEq/L and potassium 5.6 mEq/L, bicarbonate 20 mmol/L, Ca 2.2 mmol/L, blood sugar 20.6 mmol/L. asparate aminotransferase level of 343 IU/L, alanine amino-transferase 967 IU/L, alkaline phosphatase 540 IU/L, total bilirubin 58 µmol/L, total proteins 7.4 g/dL, albumin 3.8 g/dL, PT and INR were normal. Arterial blood gas analysis on room air showed pH 7.30, PaO_2 of 99 mm Hg, $PaCO_2$ of 22 mm Hg, and HCO_3^- of 18 mEq/L. Her fasting lipid profile showed; total cholesterol, 4.1 mmol/L; LDL cholesterol, 2 mmol/L; triglyceride, 3.2 mmol/L. Her myoglobin was elevated, 1319 ng/ml and the creatine kinase (CK) level was markedly elevated (3957 U/L), with normal CK MB fraction and cardiac troponin levels. The urine myoglobin test result was positive. But there was no hematuria, pyuria, or ketonuria. Thyroid function test was normal. Hepatitis A Ig M anibodies, hepatitis C antibody and hepatitis B markers were negative. Ultrasound of the abdomen showed a normal liver and with normal gallbladder and nondilated intrahepatic and extrahepatic biliary ducts.

One month before admission the patient visited her doctor at the medical clinic. Routine laboratory data showed: hemoglobin level of 11.2 g/dL, total leucocyte count 7300/mm3, platelets, 180,000/mm3. Urea nitrogen 9.2 mmol/L, creatinine 102µmol/L, sodium 139 mEq/L and potassium 4.3 mEq/L, bicarbonate 20 mmol/L, Ca 2.4 mmol/L, random blood sugar 12.2 mmol/L.aspartate aminotransferase level of 20 IU/L, Alanine amino-transferase 12 IU/L, alkaline phosphatase 66 IU/L, total bilirubin 14 µmol/L, total proteins 7.4 g/dL, albumin 3.8 g/dL, PT and INR were normal. Her fasting lipid profile was; total cholesterol, 4.7 mmol/L; LDL cholesterol, 2.4 mmol/L; triglyceride, 3.8 mmol/L. Her creatine kinase (CK) level was 34 U/L. In view of the above findings, a diagnosis of pravastatin induced rhabdomyolysis and hepatitis was made; pravastatin was stopped on the first hospital day and rhabdomyolysis was managed with vigorous hydration and urine alkalinization, as well as cautious monitoring of serum potassium and other electrolytes levels. The patient was kept on his antidepressive medication and the blood sugar was controlled by Insulin and gliclazide. On the following days the level of creatine kinase, liver enzymes and s.creatinine returned toward normal. In order to control her hypercholesterolemia the patient was kept on atorvastatin 10 mg once daily PO. The patient was discharged after 20 days of hospitalization with stable condition. At the time of discharge, the serum AST level of 120 IU/L, ALT 177 IU/L, alkaline phosphatase 110 IU/L, total bilirubin 43 µmol/L, CK 334 U/L.

On follow-up evaluation approximately 2 months after the patient's discharge from the hospital, the patient was symptom free. Laboratory evaluation yielded serum AST level of 40 IU/L, ALT 35 IU/L, alkaline phosphatase 105 IU/L, total bilirubin 28 µmol/L, total proteins 6.8 g/dL, albumin 3.6 g/dL, CK 110 U/L and normal PT and INR.

Discussion

The 3-hydroxy-3-methyl coenzyme A (HMG-CoA) reductase inhibitors or statins, specifically inhibit the enzyme HMG-CoA reductase in the liver, thereby inhibiting the rate limiting step in cholesterol biosynthesis and so reducing plasma cholesterol levels. Myopathy, myositis, rhabdomyolysis and hepatitis are the well known side effects of HMG-CoA reductase inhibitors. Most available HMG-CoA reductase inhibitors, the "statins," have been implicated in causing rhabdomyolysis, either as monotherapy or in combination with such agents as cyclosporine, erythromycins, niacin, and antifungal drugs.[4],[5],[6],[7].

A recent study in Ireland estimated that approximately 30% of all users of statins have concomitant drugs prescribed that can inhibit statin metabolism, potentially leading to rhabdomyolysis.[8] . Hydrophilic statins such as pravastatin are considered to have the best safety profile in this class of drugs and are frequently recommended as a firstline choice for the prevention of coronary transplant vasculopathy. [9],[10],[11], [12] .They have little potential to induce myopathy or interact adversely with other drugs because, unlike lipophilic statins, hydrophilic statins are not

metabolized through the hepatic cytochrome P450 (CYP) 3A4 pathway. [13],[14] In addition to it's effect on lipid, pravastatin has been shown to have a range of other antiatherothrombotic effects, including the restoration of endothelial function [15] and anti-inflammatory effects.[16] Pravastatin therapy has been shown unequivocally to reduce cardiovascular risk in a series of large-scale, randomized, controlled clinical trials.[1],[2],[3]

The potential mechanisms underlying statin-induced myotoxicity are complex with no clear consensus of opinion. One theory suggests that blocking the synthesis of cholesterol reduces the cholesterol content in skeletal muscle-cell membranes by making them unstable. [17] Another theory attributes muscle injury to reduced levels of regulatory proteins or isoprenoids, such as ubiquinone. [18] A higher lactate:pyruvate ratio has been observed in patients receiving statins, suggesting that anaerobic metabolism and, possibly, mitochondrial dysfunction may have a role in muscle injury. [19],[20] One study reported that mitochondrial dysfunction was observed in biopsy specimens from individuals presenting with muscle complaints, but no elevations in serum CK concentration. [21]

The mechanism of hepatitis in this case is unclear since the risk for interactions is very low. It may be due to direct liver toxicity by a mechanism, as yet, unknown.

The muscle and liver injury affecting our patient can be attributed to pravastatin because:

[1] there was no history of liver or biliary tract disease and the patient had documented normal liver enzymes one month before admission; [2] there was no alcohol abuse and no serological or circumstantial evidence for viral hepatitis; [3] obstruction of the common bile duct and sclerosing cholangitis were eliminated by abdomen ultrasound.

The temporary evolution also implicates pravastatin as the offending drug, as its withdrawal was followed by permanent improvement of laboratory findings

The differential diagnosis of rhabdomyolysis and hepatitis in this patient includes; neuroleptic malignant syndrome (NMS) and pravastatin induced rhabdomyolysis and hepatitis.

Although the patient is under anti depressive drugs, which might cause NMS and rhabdomyolysis and hepatitis, the absence of stiffness and hyperthermia exclude the diagnosis. Other causes of rhabdomyolysis and hepatitis, such as hyperthermia, prolonged seizures, trauma, physical muscle damage or stress, dehydration, burns, alcohol abuse, and infections with human immunodeficiency virus, influenza virus, or herpesvirus were not evident in this patient.

In conclusion, although the risk of drug-drug interaction is very low with pravastatin, clinicians should be aware of the potential for serious muscle and liver injury, which associated with pravastatin. Accordingly, Emergent myalgias, with or without jaundice in patients under pravastatin necessitate immediate testing of creatine kinase, myoglobin and liver enzymes to exclude life-threatening rhabdomyolysis and drug induced hepatitis.

Conflict of Interest: None declared

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