Rhabdomyolysis Developing Secondary to Atorvastatin Therapy in a Patient with Liver Cirrhosis

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Abstract

Atorvastatin is a lipid lowering agent that is widely used worldwide. Rhabdomyolysis is a rare but serious side effect that may lead to renal failure and dangerous electrolyte abnormalities in patients with decreased hepatic clearance of atorvastatin. We herein report the case of a patient with liver cirrhosis receiving atorvastatin therapy for ischemic heart disease and hyperlipidemia who developed rhabdomyolysis and acute renal failure.

Key words: rhabdomyolysis, liver cirrhosis, atorvastatin

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Introduction

The benefits of statins in lowering the cholesterol levels, reducing inflammatory responses and preventing heart disease can be considered a revolution in cardiovascular medicine (1). However, adverse drug reactions are inevitable when using statins, as with any other medications. Atorvastatin is one of the most popular statins and is safely used and tolerated by the vast majority of patients without any major side effects. Hepatitis, headaches, gastrointestinal discomfort and arthralgia are among the side effects of atorvastatin (2). Although it occurs rarely, rhabdomyolysis is the most serious adverse effect and has been reported with catastrophic events and even death in some patients (3).

We herein describe the case of a patient receiving long-term use of atorvastatin for hyperlipidemia and ischemic heart disease who continued to use the medication after receiving a diagnosis of liver cirrhosis and developed rhabdomyolysis.

Case Report

The patient was a 65-year-old obese woman with a long-term past history of type 2 diabetes, hyperlipidemia and ischemic heart disease who presented to our emergency room with a four-day history of progressive muscle pain and weakness in both lower extremities. She also complained of dark urine. She had no history of weight loss, abdominal pain, fever, headache, nausea or vomiting. She had also been diagnosed as having cryptogenic cirrhosis after developing ascites six months prior to her current problems. Her medications included neutral protamine Hagedorn (NPH) insulin, aspirin (80 mg daily), atorvastatin (40 mg daily) and nitrate (6.4 mg PO three times daily), which she had continued to use after receiving a diagnosis of cirrhosis. A physical examination revealed a blood pressure of 130/70 mmHg, a pulse rate of 80 beats/min, a respiratory rate of 14 breaths/min and a normal temperature. The findings of chest and abdominal examinations were normal, except for ascites. The patient was absolutely alert and had pain, tenderness and weakness that were more prominent in the lower than the upper extremities. Her deep tendon reflexes were normal, her plantar reflexes were bilaterally downward and no lateralizing signs were detected on the physical examination. Preliminary laboratory tests showed acute renal failure, mild hyperkalemia and increased serum levels of creatine phosphokinase (CPK) and lactate dehydrogenase (LDH) (Table). Arterial blood gases (ABGs) showed mild metabolic acidosis and a urinalysis revealed evidence of myoglobinuria. The patient was admitted under suspicion of a diagnosis of rhabdomyolysis secondary to atorvastatin therapy. Atorvastatin

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was discontinued, and she was treated with intravenous (IV) hydration and bicarbonate. A few days after stopping atorvastatin, her general condition improved, the renal failure resolved, the laboratory tests became normal and she was discharged in relatively good health.

Discussion

The liver is an organ that is thoroughly involved in the metabolism of several drugs, including statins. Atorvastatin, simvastatin and lovastatin are all metabolized in the liver by the cytochrome P450 3A system (CYP3A) (4). Atorvastatin and other statins have been reported to induce elevations in the levels of liver enzymes, and conducting liver function tests is recommended prior to and at 12 months after the initiation of therapy (5). Although atorvastatin exerts beneficial effects in protecting against hepatic fibrosis in rats (6) and attenuating steatohepatitis in patients with nonalcoholic fatty liver disease (NAFLD) (7), it is contraindicated in patients with active liver disease or unexplained elevations in liver enzymes, and conducting liver function tests is recommended prior to and at 12 months after the initiation of therapy (5). Although atorvastatin exerts beneficial effects in protecting against hepatic fibrosis in rats (6) and attenuating steatohepatitis in patients with nonalcoholic fatty liver disease (NAFLD) (7), it is contraindicated in patients with active liver disease or unexplained elevations in the level of aminotransferase (5). Liver cirrhosis is associated with a 10-20-fold increase in the serum concentrations of statins (8). Furthermore, the activity of CYP3A is significantly diminished in patients with liver cirrhosis, thereby contributing to a lower clearance of drugs compared to that observed in healthy controls (9). Therefore, discontinuing or reducing the dose of drugs processed via hepatic metabolism such as atorvastatin is necessary to minimize side effects.

Rhabdomyolysis is a serious side effect of statins, including atorvastatin. This complication rarely occurs in patients on atorvastatin therapy, with a substantially greater risk observed in patients receiving combined treatment with fibrates or other drugs such as ketoconazole, cyclosporine or erythromycin that competitively inhibit CYP3A (10). This leads to blockade of oxidation in the liver and subsequently higher serum concentrations of statins and an increased probability of rhabdomyolysis (10). In a large cohort of patients receiving lipid lowering agents, including 130,865 individuals on atorvastatin therapy, only eight patients developed rhabdomyolysis requiring hospitalization (11). Rhabdomyolysis occurring following combination therapy with atorvastatin and fibrates (12), fusidic acid (13), warfarin (14), azithromycin (15) and cyclosporine (16) has also been reported.

In addition to atorvastatin, the patient used aspirin, insulin and nitrate derivatives. Aspirin seems to have minimal effects on CYP450, and insulin not only inhibits the CYP450 function, but also increases the activity of CYP450 3A (17). However, the administration of organic nitrates is accompanied by decreased CYP450 activity in rats (18) and may lead to increased serum levels of drugs with CYP450-dependent metabolism. Atorvastatin had been used by our patient for several years. In this case, liver cirrhosis most likely caused by nonalcoholic steatohepatitis was an additive disease that was diagnosed since six months earlier; however, the patient continued to use atorvastatin at its previous dose. Diminished activity of P450 secondary to cirrhosis and probably nitrate use led to reduced atorvastatin clearance and subsequent rhabdomyolysis. Therefore, atorvastatin therapy may be disadvantageous in patients with liver cirrhosis and should be prescribed cautiously in these patients and in patients receiving nitrate derivatives.

The authors state that they have no Conflict of Interest (COI).

References