Rhabdomyolysis Secondary to Lovastatin Therapy

Anthony A. Manoulan,1 Nadhipuram V. Bhagavan,2 Takuji Hayashi,3 Thomas A. Nestor,4 Carlos Rios,5 and Alfred G. Scottolini6,7

We report a case of lovastatin-induced rhabdomyolysis and resulting life-threatening renal failure. Lovastatin, a hypocholesterolemic agent, decreases endogenous cholesterol synthesis by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase (EC 1.1.1.88). This agent has been implicated in causing rare serious side effects in various clinical settings; however, the mechanism of these adverse reactions is not understood. The clinical course of our patient was characterized by profound muscle weakness with marked increases in serum creatine kinase and myoglobin. Light- and electron-microscopic studies of skeletal muscle of our patient demonstrated a noninflammatory myopathy suggestive of ongoing rhabdomyolysis with vacuolization and focal degeneration of myocytes. The patient's symptoms and the laboratory values referable to rhabdomyolysis resolved after discontinuation of the drug. We speculate that the rhabdomyolysis was due to mitochondrial damage secondary to inadequate synthesis of coenzyme Q and heme A, members of the electron-transport system of the inner mitochondrial membrane.

Additional Keyphrases: nephrotoxicity • mitochondria

Lovastatin decreases endogenous cholesterol synthesis by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase; EC 1.1.1.88). This enzyme catalyzes an early and major rate-limiting reaction in the biosynthesis of cholesterol. Lovastatin blocks the reduction of HMG-CoA to mevalonate. As such, lovastatin is efficacious pharmacologically in decreasing the concentration of cholesterol in serum because ~66% of total body cholesterol is endogenously produced. However, lovastatin has been implicated in rare serious side effects, including rhabdomyolysis in various clinical settings. Initial reports (1, 2) involved organ-transplant recipients who were receiving concomitant cyclosporin therapy. Subsequent reports (3) have cited gemfibrozil, nicotinic acid, and erythromycin as other drugs that enhance lovastatin's rhabdomyolysis-producing potential. The mechanism by which this adverse reaction is produced is not known. Compromised hepatic function appears to be a common denominator in many cases. Lovastatin may also possess inherent hepatotoxic activity. Additional clinical correlation may elucidate this mechanism and thus identify that population in whom lovastatin should not be used. Here we present a case report of lovastatin-induced rhabdomyolysis and resulting life-threatening renal failure in a patient presenting with congestive heart failure.

Case Report

A 59-year-old Caucasian woman was admitted with a two-day history of shortness of breath and difficulty walking. She had been discharged two weeks earlier from hospitalization for congestive heart failure and, since discharge, had experienced progressive weight gain and pedal edema such that walking had become difficult.

Nine months before this admission, she had suffered an anterior wall myocardial infarct with subsequent echocardiography demonstrating left ventricular dilatation and residual fractionate shortening of 9%. She had a 15-year history of non-insulin-dependent diabetes mellitus but required insulin for euglycemia. She was obese and had a 76-pack-year smoking history. She was diagnosed as hypothyroid at age 11 years.

For 13 days before admission she had been taking lovastatin, 20 mg orally twice a day, for hypercholesterolemia (varying from 8.82 to 9.78 mmol/L). Her medications also included diltiazem, captopril, furosemide, L-thyroxin, and gemfibrozil for control of serum triglycerides. She had multiple drug allergies, including allergies to salicylate, penicillin, iodine, and sulfa drugs. On physical examination she was afebrile with a pulse of 102/min, respiratory rate of 20/min, and blood pressure of 110/70 mm Hg. There was no skin rash. Scattered rales were noted at the lung bases bilaterally. Heart rate and rhythm were regular with an S3 gallop. There was 2+ pretilial edema. Femoral and popliteal pulses were 2+ bilaterally.

Chest roentgenography revealed cardiomegaly and fluid within the pulmonary fissures. Her electrocardiogram showed anterior Q waves consistent with remote myocardial infarction. The hemato logical indices were unremarkable. The urine was clear and straw-colored, with glucosuria at 2.5 mg/L and 2+ for blood. Results for serum chemical analytes were unremarkable except for glucose (17.3 mmol/L) and potassium (5.4 mmol/L).

Symptoms referable to congestive failure resolved over 48 h after diuresis of 8.1 L. However, on the second hospital day, she complained of profound muscle weakness in her lower extremities, which progressed over several hours to include the upper extremities, in addition to pain on palpation so that she could no longer walk spontaneously. Neurological examination revealed intact cranial nerves. Pain and vibration sense were decreased bilaterally in the lower extremities. Profound muscle weakness was noted proximally, including the biceps, triceps, brachioradialis, iliopsoas, gluteals, hamstrings, and quadriceps femori bilaterally. Interossei, hand grip, gastrocnemii, and anterior tibials showed normal strength bilaterally. Deep tendon
reflexes were 1+ and symmetrical.

The hematological indices showed increases in leukocytes to 17.0 \times 10^9/L, a prothrombin time of 31.8 s, an activated partial thromboplastin time of 40.4 s, and a sedimentation rate of 130 mm/h. Her urine suddenly became red and turbid, with 3+ blood and 4+ protein. Serum glucose remained above normal, with sodium 130 mmol/L, potassium 7.2 mmol/L, chloride 88 mmol/L, and total carbon dioxide 20 mmol/L.

Serum creatine kinase (CK) increased from a baseline of 157 U/L two weeks before admission to 1800 U/L on the second hospital day, eventually peaking at 176500 U/L on the twelfth hospital day. The CK-MB isoenzyme was detected only after total CK exceeded 100000 U/L, with the MB isoenzyme fraction peaking at 42.6%. Lactate dehydrogenase (LD) increased to 319 U/L and showed a prominent LD-5 isoenzyme pattern.

The antinuclear antibody titer was positive at 1:800 with a homogeneous and speckled pattern by the immunofluorescence technique. Total complement, C3, and C4 were essentially within the normal range. Serum protein electrophoresis showed a decreased albumin of 28 g/L and a slight increase of the alpha1 and alpha2 regions, consistent with an acute inflammatory pattern. Serum myoglobin was markedly increased to 1250 \mu g/L by radioimmunoassay.

These findings supported a differential diagnosis of typical adult polymyositis vs rhabdomyolysis induced by lovastatin. This, in turn, raised the therapeutic question of whether to treat the patient with prednisone, the drug of choice in the management of polymyositis. However, steroid therapy can lead to immunosuppression, which has been implicated in enhancing the toxicity of lovastatin.

Examination of a muscle biopsy by light microscopy revealed a noninflammatory myopathy suggestive of ongoing rhabdomyolysis characterized by skeletal muscle degeneration and vacuolization but without features specific to this form of toxic myopathy. Periodic acid–Schiff stains showed numerous fibers devoid of glycogen. Only rare mononuclear cells were present.

Lovastatin was discontinued and steroids were withheld. CK (t½ = 13 h) activities returned to baseline 14 days after termination of lovastatin therapy.

The diagnosis of lovastatin-induced rhabdomyolysis was further supported by the patient's subsequent clinical course of marked acute renal failure, with serum creatinine 30 \mu mol/L, blood urea 67.1 mmol/L, potassium 7.2 mmol/L, phosphate 3.7 mmol/L, urine creatinine 1591 \mu mol/L, and urine sodium 119 mmol/L. These urinary indices implied acute tubular necrosis, probably secondary to myoglobinuria. The patient became profoundly anuric and required hemodialysis for 18 days, after which renal function progressively resolved.

Coinciding with the onset of renal failure, serum studies showed increases in aspartate aminotransferase to 2090 U/L and alanine aminotransferase to 287 U/L; however, \gamma-glutamyltransferase, alkaline phosphatase, and total bilirubin remained within the normal range.

The patient's rhabdomyolysis and subsequent acute renal failure eventually resolved. However, she had a myocardial infarct on the 46th hospital day and was transferred to the critical care unit. She stabilized without further congestive failure and was transferred to a skilled nursing facility on the 61st hospital day, where she died as a consequence of "cardiopulmonary arrest." Autopsy was denied.

Discussion

The recent clinical trials in the prevention of coronary atherosclerosis through therapeutic control of hyperlipidemia have been reviewed by Bilheimer (4). These studies support the hypothesis that reducing serum cholesterol reduces cardiovascular risk. The efficacy of lovastatin in decreasing serum cholesterol in multicenter studies involving >1000 patients has been reviewed by Tobert (5). Although lovastatin is generally a well-tolerated drug, he noted the occurrence of "rare cases of myopathy usually occurring in a complicated clinical setting and asymptomatic increases in transaminases." Garg and Grundy (6) reported that reduction of the concentrations of plasma lipids in patients with non-insulin-dependent diabetes mellitus could decrease the risk of development of coronary artery disease, the leading cause of death in these patients.

Norman et al. (1) and East et al. (2) reported a total of five cases of rhabdomyolysis in patients taking lovastatin. All cases occurred in heart-transplant recipients receiving concomitant cyclosporin therapy. Three patients were also taking other lipid-lowering agents: two gemfibrozil and one nicotinic acid. Two of the five patients developed subsequent renal failure. Ayanian et al. (3) reported rhabdomyolysis in a patient takingLovastatin and erythromycin.

The mechanism of lovastatin-induced rhabdomyolysis is not understood. The co-administration of other drugs such as gemfibrozil, niacin acid, and erythromycin may increase the risk for rhabdomyolysis in patients taking lovastatin. In fact, the lovastatin package insert now warns that "the possible benefits of combined therapy withLovastatin and gemfibrozil do not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure." Several authors have underscored the importance of monitoring transaminases in patients onLovastatin.

Lovastatin may inhibit mitochondrial production of ATP. HMG-CoA reductase converts HMG CoA to mevalonate; mevalonate, in turn, is an important precursor for several biologically essential compounds in addition to cholesterol. Two such compounds are the polyisoprenes sideways-of coenzyme Q (CoQ) and the farnesyl residue of heme A, which are important components of the electron-transport chain and oxidative phosphorylation. The inhibition of mevalonate production could interfere in the biosynthesis of CoQ and heme A. Mabuchi et al. (7) hypothesize that whileLovastatin suppresses HMG-CoA reductase, a small amount of mevalonate ordinarily is preferentially diverted to CoQ and heme A, because serum values for CoQ remain within the normal range despite inhibition of cholesterol synthesis. InLovastatin-induced rhabdomyolysis secondary to toxic concentrations in blood, the preferential diversion of mevalonate to CoQ and heme A may be either absent or inadequate.

Electron-microscopic studies of skeletal muscle in our case revealed extensive mitochondrial damage (unpublished observations). We speculate that this may be due to inadequate synthesis of CoQ and heme A in the inner mitochondrial membrane with subsequent derangement of cellular energy production and cell death.

References