Rhabdomyolysis with Simvastatin Use

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Dear Sir,

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 primitive 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 [1].

Several cases of rhabdomyolysis associated with lovastatin use have been described [2]. This was observed in heart-transplanted patients [3] receiving concomitant drugs which are thought to increase muscular toxicity, such as ciclosporin [4]. Toxic interactions have also been described with erythromycin [5], ketoconazole [6], nicotinic acid [7], levothyroxine [8] and gemfibrozil [9]. The mechanisms involved in these interactions are unknown; hypotheses include a decrease in hepatic clearance of lovastatin brought on by microsomal hepatic enzyme inactivation, or a displacement of the albumin transport sites.

We present a case of rhabdomyolysis with acute renal failure, acute pancreatitis and increase in hepatic enzymes, associated with simvastatin use.

A 67-year-old woman was admitted to our hospital on September 1, 1989, because of severe myalgia, which kept her from standing upright. Onset occurred 3 days prior to admission and was associated with asthenia, anorexia and anuria. She had been cholecystectomized 40 years before, and presented with memory troubles (treated by nicergoline) and hypercholesterolemia for 10 years. The latter was first treated by cholestyramine, which was replaced in 1987 by gemfibrozil because of cholestyramine digestive intolerance. Finally, simvastatin was administered 10 mg/day on June 3, 1989, 3 months prior to admission.

At the time of admission the patient presented with abdominal pain, ankle edema, functional disability of the lower limbs with diffuse myalgia and anuria. Physical examination revealed high blood pressure (200/90 mm Hg), body temperature was 37°C. Muscle pain worsened on palpation. All deep tendon reflexes were suppressed.

Laboratory data were as follows: creatinemia, 592 $\mu\text{mol/l}$; uremia, 34.8 mmol/l ; glycemia, 7.8 mmol/l ; natremia, 132 mmol/l ; kalemia, 6.3 mmol/l ; chloremia, 104 mmol/l ; bicarbonate, 23 mmol/l ; calcium, 2.11 mmol/l ; phosphorus, 1.92 mmol/l ; magnesium, 1.2 mmol/l ; transaminases: ASAT, 1,070 U/l ; ALAT 621, U/l , γ -glutamyltranspetidase 50 U/l ; bilirubin, 9 $\mu\text{mol/l}$; lactic dehydrogenase, 3,840 U/l ; creatine kinase (CPK), 20,000 U/l (normal 10–50); alkaline phosphatases, 221 U/l ; amylasemia, 719 U/l ; red blood count, $4.64 \times 10^6/\text{l}$; white blood count, $28.9 \times 10^6/\text{l}$ with 95% polynuclear; platelets $295 \times 10^6/\text{l}$; myoglobin-emia, $> 800 \text{ ng/ml}$ ($n < 80 \text{ ng/ml}$). All autoimmunization tests were negative. Bacterial and viral serology analyses were also negative. Thyroid hormone level was within normal limits. Biochemistry analysis of a muscle biopsy sample revealed normal enzymatic activity. Abdominal CT scan showed an enlarged pancreas with several hypodense zones and infiltration in the left perirenal fascia. We concluded that this patient developed rhabdomyolysis with renal insufficiency and acute pancreatitis with hepatic cytolysis.

All medication was stopped and the patient underwent 11 sessions of hemodialysis during 3 weeks. Within 10 days, muscle aching and abdominal pain progressively disappeared, CPK and amylasemia returned to normal. On September 14, 1989, abdominal CT scan showed that pancreatic and mesenteric infiltration had disappeared. Diuresis reappeared after 3 weeks of treatment and renal function was normal when the patient was discharged in October 1989. The different etiologies of rhabdomyolysis were considered: hard physical effort, traumatism, infections, metabolic and muscular ischemia, burns, alcohol abuse, and muscle enzymatic deficiencies were eliminated.

Lithiasic pancreatitis was eliminated because chole-cystectomy had been done 40 years earlier and because main bile duct was normal at retrograde cholangiography. Endoscopic retrograde pancreatography was nor-

366

Berland/VacherCaponat/Durand/Baz/Laugier/Musso

mal, ruling out congenital malformation known to be associated with acute pancreatitis such as pancreas divi-sum. Only toxic rhabdomyolysis and acute pancreatitis were retained. Nicergoline, widely used for several years, has never been incriminated in this type of pathology. Only simvastatin may have some responsibility. To date, several cases of rhabdomyolysis have been reported with lovastatin use but none with simvastatin.

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