Massive Rhabdomyolysis and Simvastatin

To the Editor:

Simvastatin, a new 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitor used in the treatment of hypercholesterolemia, blocks the reduction of HMG-CoA to mevalonate, like lovastatin, and leads to a decrease in the synthesis of endogenous cholesterol. The most common clinical adverse effects are mild gastrointestinal reactions and headache (1); elevations of transaminase and of creatine-phosphokinase (CPK) to more than three times the upper limit of normal also have been described in 3–5% of patients (2, 3). These elevations are usually transient and asymptomatic and do not require withdrawal of therapy. The mechanism by which compromised hepatic function and myopathy occur is not known. HMG-CoA reductase inhibitors may inhibit mitochondrial production of ATP, leading to inadequate synthesis of CoQ and heme A in the inner mitochondrial membrane, with subsequent derangement of cellular energy production and cell death (4).

There currently exists a single report of severe myopathy with rhabdomyolysis secondary to the use of simvastatin, with elevations in CPK values to 10 times the upper limit of normal (5). We present the case of a 68-year-old obese woman with a history of cholecystectomy and hysterectomy, who was admitted for evaluation of profound muscle pain and weakness in the legs of 3 d duration. Her symptoms had intensified progressively and had spread to involve shoulder and back muscles, such that her movement and walking were impeded. Three months before, she had experienced paroxysmal episodes of atrial fibrillation, for which digitalis and oral diacoumarol anticoagulant therapy were prescribed. On that occasion, high concentrations of cholesterol (8.92 mmol/L) and low-density lipoprotein (LDL) cholesterol (6.33 mmol/L) were found, and daily treatment with simvastatin at 10 mg (Sinvacor, Merck Sharp & Dohme Italia, Rome) was begun. All other analyses, including those for CPK, alanine amino transferase (ALT), and aspartate amino transferase (AST), gave normal results.

At the patient’s admission, results of laboratory analyses disclosed extremely high CPK values (26 010 U/L; normal range: 24–190 U/L) exclusively involving the isoenzymatic MM component, with an increase equivalent to 137 times the upper limit of normal. ALT and AST values were 419 U/L (normal range: 10–38 U/L) and 2070 U/L (normal range: 7–35 U/L), respectively. Serum myoglobin was markedly elevated to 5580 µg/L (normal range: 10–90 µg/L), and myoglobinuria was present. Myosine, a new marker of muscular damage, was 10 078 µU/L (normal range: 10–400 µU/L). There were slight signs of renal insufficiency (creatinine 217 mmol/L). Antinuclear and anti-smooth-muscle autoantibody titers were negative. Erythrocyte sedimentation rate, rheumatoid factor, and C-reactive protein were normal.

On her third hospital day, treatment of the patient with simvastatin was suspended. Her presenting symptoms of intense muscle pain and generalized muscle weakness continued unvaried for 5–6 d, and CPK concentrations remained high, ranging from 25 600 to 23 900 U/L over the next 15 d. Thirty days later, CPK values (7466 U/L) and ALT (209 U/L) and AST (157 U/L, respectively), were still high but were progressively falling; creatinine concentrations had normalized (102 mmol/L), and the patient had completely recovered her strength and usual lifestyle. We considered a muscle biopsy nonessential; it was not necessary for diagnosis and it would have required suspension of the anticoagulant therapy in course. Moreover, given the severity of the clinical picture, we did not rechallenge with simvastatin. Ninety days after admission, the patient’s heart and hepatic enzyme values had returned to the normal range.

Although simvastatin is highly effective in treating hypercholesterolemia, the possible onset of important side effects should not be overlooked. In our case, these were manifested as life-threatening massive rhabdomyolysis.

References

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Salivary Homocyst(e)ine Concentrations

To the Editor:

The ease of saliva sampling makes homocyst(e)ine an attractive alternative to blood plasma for diagnostic use. Mild hyperhomocyst(e)inemia has been reported in patients with premature vascular disease, many of whom could be heterozygous for homocystinuria (1, 2). On the basis of the incidence of the homocystinuric condition at birth, the estimated prevalence of the heterozygous state is 1–2% of the population.

We undertook to ascertain the possibility of using measurement of homocyst(e)ine in saliva as a screening method for the diagnosis of hyperhomocyst(e)inemia. We obtained saliva by the most common technique of saliva collection, having the patient spit into a container and then freezing (5000 × g for 10 min), thawing, and centrifuging the sample. We determined salivary and plasma total homocyst(e)ine concentrations by a previously described radioisotopic method (3). We measured the sum of homocyst(e)ine bound to protein, free homocysteine, and homocysteine. The precision of the method was determined by run-