Statin-associated rhabdomyolysis triggered by grapefruit consumption

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Case report. A 40-year-old woman was admitted to the emergency room for bilateral lower extremity weakness. She had been exercising regularly in a gym, including workout and aerobics, and skydived regularly. She had felt perfectly healthy until 10 days earlier when she noticed slight muscle weakness and myalgia that increased gradually. Examination revealed bilateral proximal leg weakness, although muscle strength in the face, neck, arms, and distal legs was normal. Walking distance was <20 meters. Initial laboratory studies revealed dramatically increased serum levels of creatine kinase (12,640 U/L), myoglobin (6,453 μg/L), aspartate aminotransferase (623 U/L), and alanine aminotransferase (700 U/L), suggesting rhabdomyolysis. Serum electrolytes and renal function were normal. The patient was taking simvastatin (80 mg/d taken at bedtime) for hypercholesterolemia related to a heterozygous familial defective apolipoprotein B100 mutation. Statin-associated rhabdomyolysis was assumed, and simvastatin was discontinued. Treatment with vigorous fluid replacement (250 mL/h) and alkalinization of the urine with addition of sodium bicarbonate prevented renal failure. During the next 2 days, the weakness disappeared completely, and serum levels of creatine phosphokinase and myoglobin decreased dramatically (figure). EMG of the quadriceps muscle was completely normal, including normal motor unit morphology and regular recruitment pattern. The patient was discharged in excellent physical condition 6 days after admission. The case puzzled us because the patient had tolerated simvastatin well for >2 years. The dose was increased from 40 to 80 mg six months prior without any side effects. We questioned the patient for a possible trigger of rhabdomyolysis. Fourteen days before admission (i.e., 4 days before the first symptoms appeared) she had begun to eat one fresh grapefruit a day (but not the peel or additional juice) for breakfast following the advice of a wellness magazine. She had not taken any other medication that could have increased myotoxicity. Cholestyramine was started for cholesterol-lowering therapy. Because of gastrointestinal side effects, however, cholestyramine was later replaced with ezetimibe, a selective inhibitor of intestinal cholesterol absorption. Cholesterol levels are well controlled currently under this medication without any side effects.

Discussion. We report a case of statin-associated rhabdomyolysis triggered apparently by the consumption of grapefruits. This pathogenesis is strongly suggested by the close temporal relationship between grapefruit intake and appearance of first muscular symptoms. Discontinuation of the statin medication resulted in a fast and complete recovery without any relapses. Moreover, our patient had no myalgia or other side effects during 2 years of high-dose simvastatin medication, and there were no EMG signs of chronic myopathy. Rhabdomyolysis is a rare but serious adverse event following statin therapy.[1-3] Cerivastatin (Lipobay, Bayer Pharmaceuticals, West Haven, CT) was withdrawn recently from the market because of >50 lethal cases of rhabdomyolysis and shortly after a high-dose regimen was introduced to the US market. Importantly, skeletal muscle toxicity of statins is dose dependent. The inhibition of mevalonate production in the striated muscle leads to a depletion of isoprenoids, such as ubiquinone (coenzyme Q10), that are involved in several important cellular functions, including glycosylation of cell surface proteins, electron transfer in mitochondria, and post-translational modification of regulatory proteins.[1] In addition, decreased cholesterol content in the muscle membrane may increase susceptibility of the fiber to rhabdomyolysis.[4] Although all statins share inhibition of 3-hydroxy-3-methylglutaryl coenzyme (HMG-Co) A-reductase as their common mechanism of action, they differ in pharmacokinetic properties. Simvastatin, like atorvastatin, lovastatin, and cerivastatin, is metabolized by the microsomal cytochrome P450 (CYP) 3A isoenzyme species CYP3A4. Grapefruit juice contains a furanocoumarin that causes inactivation and subsequent accelerated degradation of CYP3A4.[5-7] Thereby, grapefruit juice considerably increases the systemic bioavailability of simvastatin similar to other CYP3A4 inhibitors, such as macrolides, protease inhibitors, imidazoles, or cyclosporin A. In conclusion, patients treated with simvastatin have to be advised not to eat grapefruits. In case of increased creatine kinase levels or myalgia, patients have to be asked specifically for grapefruit consumption. The same precautions apply to several other statins, such as lovastatin, atorvastatin (and formerly cerivastatin), but not pravastatin, and other drugs metabolized by CYP3A4, such as cyclosporins.[5,7]

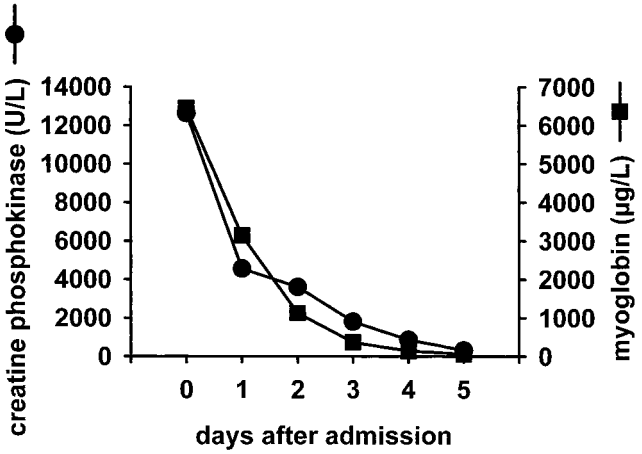

Figure. Time course of creatine kinase and myoglobin serum levels after discontinuation of simvastatin.

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