Simvastatin-Nelfinavir Interaction Implicated in Rhabdomyolysis and Death

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We report the first death associated with rhabdomyolysis in a patient treated with a statin and a protease inhibitor, which produced a significant drug-drug interaction.

A 70-year-old white man was admitted to San Francisco Veterans Administration Medical Center (San Francisco, CA) with a 1-week history of progressive muscle weakness, myalgias, and diarrhea. He was HIV-1 infected, with an absolute CD4+ T lymphocyte count of 216 cells/mm³ and a serum HIV-1 RNA load of <50 copies/mm³ before admission to the hospital. His antiretroviral therapy regimen consisted of zidovudine (300 mg/day), lamivudine (150 mg b.i.d.), and nelfinavir (750 mg t.i.d.) at the time of admission. This regimen had not been changed in >2 years. The patient also had a history of hyperlipidemia and coronary artery disease, with coronary artery bypass grafting having been performed in 1986. Six months before admission, the patient’s lipid-lowering medication was changed from simvastatin (10 mg/day) to pravastatin (40 mg/day). Because elevated LDL cholesterol levels were noted while the patient was taking pravastatin (40 mg/day), treatment with simvastatin (80 mg/day) was reintroduced 1 month prior to admission. The patient was also taking aspirin (81 mg/day) and atenolol (25 mg/day). He took no herbal or over-the-counter medications, and he did not use alcohol or illicit drugs.

Three weeks after initiation of treatment with the higher simvastatin dosage, the patient noted the development of new progressive muscle weakness, which caused him to fall several times, and an increase in the severity of diarrhea, which had been mild at baseline. He denied having recently exercised strenuously or having sustained trauma, and he had no prior history of HIV myopathy. Laboratory evaluation revealed findings that were consistent with rhabdomyolysis (creatine kinase, 78,000 U/L [the troponin-I level was within normal limits]; alanine aminotransferase, 2301 U/L; aspartate aminotransferase, 659 U/L; and myoglobinuria) and acute renal failure (blood urea nitrogen, 29 mM; and serum creatinine, 5.6 mg/dL). Serum levels of amylase and lipase were within the range considered to be normal by the laboratory. Results of blood cultures, toxicology screening tests, and serological testing for acute hepatitis were negative.

The patient developed worsening renal failure and oliguria that required hemodialysis. When he subsequently developed abdominal pain, laboratory findings demonstrated metabolic acidosis (pH, 7.28; partial pressure of carbon dioxide, 30 mm Hg; and serum bicarbonate, 18 mM) and an elevated troponin-I level of 6.62 ng/mL (normal level, <0.03 ng/mL). The patient died suddenly, and no resuscitation was attempted, in accordance with his previously expressed wishes. Autopsy demonstrated a large acute myocardial infarction of the posterior wall and colonic ischemia.

Rhabdomyolysis is an uncommon but well-recognized dose-related complication of therapy with statins. In a summary of 601 cases of statin-associated rhabdomyolysis reported to the US Food and Drug Administration from November 1997 through March 2000, treatment consisted of simvastatin for 215 cases (35.8%), cerivastatin for 192 cases (31.9%), atorvastatin for 73 cases (12.2%), pravastatin for 71 cases (11.8%), lovastatin for 40 cases (6.7%), and fluvastatin for 10 cases (1.7%) [1]. Skeletal muscle toxicity is a rare side effect of statins used as monotherapy; however, cases of rhabdomyolysis have been reported in association with concurrent use of drugs that inhibit the liver cytochrome P-450 isoenzyme 3A4 (CYP3A4), including mibefradil dihydrochloride, fibrates, cyclosporine, macrolide antibiotics, warfarin, digoxin, and azole antifungals [1, 2].

Simvastatin and lovastatin and, to a lesser extent, atorvastatin and cerivastatin are metabolized by CYP3A4, whereas fluvastatin is metabolized by cytochrome P-450 isoenzyme 2C, and pravastatin is excreted mostly unchanged by the kidney [2]. All currently available protease inhibitors are also metabolized by cytochrome P-450 enzymes; the most important of these enzymes in vitro is CYP3A4 [3]. Like other protease inhibitors, nelfinavir is both a substrate for and an inhibitor of CYP3A4. The inhibitory effect of nelfinavir on the CYP system is less than that of ritonavir and is similar to that of indinavir [4].

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In addition, all protease inhibitors are substrates for P-glycoprotein (P-gp), a bidirectional drug transporter present on the surfaces of many cells, including intestinal epithelial cells, lymphocytes, and macrophages [5, 6]. Inhibition of P-gp may lead to increased intracellular drug concentrations [6]. Statins inhibit P-gp to varying degrees [7–9]; simvastatin (IC_{50} 9 μM) and lovastatin (IC_{50} 26 μM) are the most potent of the statins [7]. Atorvastatin is also an effective P-gp inhibitor, but at higher serum concentrations. Pravastatin, however, is a poor inhibitor of P-gp as a result of its functional groups [7].

Pharmacokinetic studies have shown that protease inhibitors increase statin concentrations. In one study, addition of ritonavir and saquinavir increased simvastatin concentrations 32.2-fold and increased atorvastatin concentrations 1.7-fold, whereas pravastatin concentrations decreased 0.5-fold in the presence of this protease inhibitor combination [10]. Nelfinavir increases simvastatin’s area under the curve by 505% and its maximum concentration by 517% [11]. For atorvastatin, the corresponding increases are 74% and 122%, respectively [11]. Whether these results are caused by the effects on CYP3A4 or P-gp is unclear.

Case reports of rhabdomyolysis precipitated by interaction between statins and protease inhibitors have been presented [12]; however, ours is the first report of such interaction implicated in a fatal outcome. Given that early data suggest that statins infrequently normalize lipid levels in patients with protease inhibitor–related dyslipidemias [13], it is particularly important to balance therapeutic goals with the risk of toxicity. Caution must be exercised when choosing lipid-lowering agents for patients receiving protease inhibitors, giving special attention to potentially dangerous drug-drug interactions [14].

References