

# Suspected pravastatin-induced rhabdomyolysis in a patient experiencing a myocardial infarction

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HMG-CoA reductase inhibitors have become the first-line agents for treating hyperlipidemia associated with increased LDL. While they have been proven to be effective in reducing LDL and total cholesterol, and increasing HDL cholesterol, potentially serious adverse effects may occur in some patients. Rhabdomyolysis is one such adverse effect observed in patients treated with this class of medications. The purpose of this paper is to report a case of a patient presenting with severe ischemic-type chest pain in whom the timing and magnitude of serum enzyme changes are strongly suggestive of pravastatin-induced rhabdomyolysis.

## CASE

A 67-year-old obese male presented to the emergency room in May 1997 with shortness of breath and severe retrosternal pain radiating to his left arm. During the previous 48–72 hours, he had experienced chills, sweating, rigors, and he had complained of a nonproductive cough over the preceding week. His cardiac history was significant for 3 previous myocardial infarctions (2 in 1996 and 1 in 1979), coronary artery bypass surgery in 1982, congestive heart failure and hypercholesterolemia. His medications just prior to admission were amlodipine 10 mg daily, furosemide 80 mg in the morning and 120 mg in the afternoon, isosorbide dinitrate 10 mg 3 times daily, ASA 80 mg daily, losartan 50 mg daily, digoxin 0.25 mg daily, pravastatin 20 mg nightly for the last 9 months, warfarin 5 mg daily, and cisapride 10 mg 3 times daily.

On examination, the patient's temperature was 39°C, his blood pressure was 130/70, his heart rate was 80 beats per minutes and his respiratory rate 20 breaths per minute. He had an elevated venous pressure and palpable cardiomegaly. His ECG revealed a normal sinus rhythm, with a first degree heart block, and no ST segment changes. Blood tests showed an elevated leukocyte count of 13.1 (normal 4–10 x 10<sup>9</sup>/L) as well as an elevated myoglobin at 5500 U/L (normally negative), creatine phosphokinase (CK) at 7405 U/L (35–230 U/L), troponin I at 13.1 µg/L (0–1 µg/L), and LDH at 444 U/L (88–177 U/L). The admitting diagnosis was a new acute myocardial infarction, though rhabdomyolysis secondary to pravastatin was considered and this drug was withheld.

By the third day after admission, the patient's serum creatinine and blood urea nitrogen (BUN) had risen from 182 µmol/L (70–120 µmol/L) and 7 mmol/L (3.5–7 mmol/L) to 268 and 19.4 respectively, with a decreased urine output. Serial cardiac enzymes revealed a continued increase in total CK despite decreasing troponin I levels. By the sixth day following admission, the serum troponin had nearly normalized despite the total CK peaking at 9150 IU/L. Concurrently, the serum creatinine and BUN were 324 µmol/L and 33.2 mmol/L respectively.

The patient received a furosemide infusion in combination with oral metolazone to enhance diuresis. The total CK, serum creatinine and BUN began to decrease, and were at levels of 335 IU/L, 174 µmol/L, and 35.2 mmol/L respectively by the tenth day post admission. At this point, the patient was feeling well with his only complaint being fatigue.

The patient's laboratory results in June 1997 revealed a total CK of 90 U/L, a serum creatinine of 119 µmol/L, and a BUN of 7.9 µmol/L.

## DISCUSSION

The marked and persistent elevation in total CK measured in this patient is strongly suggestive of extra-cardiac origin, specifically rhabdomyolysis secondary to pravastatin.<sup>1</sup> However, since there was also an elevation of troponin I (considered of higher specificity for cardiac origin) and severe ischemic-type

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chest pain was present on admission, it is likely that the patient also had a non-Q wave myocardial infarction.<sup>2,3</sup> The elevated blood urea and creatinine may have been the result of rhabdomyolysis-related renal failure as they decreased with continuation of furosemide diuresis. A review of the product monographs of the patients concomitant medications did not reveal elevation of CK or rhabdomyolysis as a potential adverse effect.<sup>4</sup>

The HMG-CoA reductase inhibitors, and the fibric acid derivatives have been implicated in causing rhabdomyolysis in the literature.<sup>5-10</sup>

In 2 large pravastatin trials involving over 10,000 subjects, there were no reports of rhabdomyolysis in the safety analysis.<sup>10,11</sup> In the WOSCOP trial, 20 of the 3302 patients receiving pravastatin (0.6%) reported myalgias, 97 subjects (2.9%) reported muscle aches and 3 patients (0.09%) presented with an asymptomatic elevation in CK (>10 times the upper limits of normal). None of these incidences were significantly different from placebo.<sup>11</sup> In the CARE trial, there were 12 cases (0.6%) of CK elevation in the 2081 pravastatin patients (incidence not significantly different from placebo), with no reports of myalgia or muscle aches.<sup>12</sup>

According to manufacturer data, myalgia was associated with pravastatin therapy in 2.7% (n=900) compared to 1% in placebo-treated individuals (n=411). Again, these differences were not statistically significant.<sup>10</sup>

Myopathy without renal sequelae has been demonstrated in case reports. Although serious myopathy is considered rare, one report revealed a severe myopathy in a 69-year-old male taking pravastatin for 5 months for hypercholesterolemia. The patient, who was also suffering from non-insulin-dependent diabetes mellitus, was unable to stand, and his skin showed an erythematous rash on his thighs. The patient also had extreme pain and tenderness in his lower limbs. The patient's CK peaked at 1892 U/L, and a biopsy of the patient's gastrocnemius (calf muscle) showed an inflammatory infiltrate of lymphocytes, macrophages, and eosinophils. Phagocytosis and degenerative changes of the muscle were evident.<sup>6</sup>

Despite the lack of rhabdomyolysis reported in clinical trials, there have been case reports of pravastatin-associated rhabdomyolysis. One case involves 61-year-old female who had been taking clofibrate, and was switched to pravastatin. Three weeks later she developed severe pain in her subscapular region, and her CK levels attained a peak level of 682 U/L. The drug was removed, and the myalgia disappeared completely 10 days later.<sup>5</sup>

Another case in the literature reported a 63-year-old female using pravastatin 10 mg per day for her cholesterol, as well as famotidine and prednisilone (for a mixed connective tissue disorder). Four months after starting pravastatin, she presented with muscle pain and weakness, fever and dark urine. Her peak CK was 8280 U/L, and her urine myoglobin level was 1227 µg/L. Pravastatin was discontinued, and her CK decreased to 39 U/L within 7 days. Her renal function, and myalgias improved over the ensuing month, without an increase in her prednisilone dosage.<sup>7</sup>

Although this adverse event is rare, it is not surprising. Both myopathy and rhabdomyolysis have been associated with hypercholesterolemia treatment. This reaction was initially described with the fibric-acid derivatives, but has been demonstrated by the HMG-CoA reductase inhibitors. Lipid lowering medication-associated rhabdomyolysis characteristically occurs within the first 2-5 months of treatment; however, the patient described in this case had been taking his lipid-lowering agent for approximately 9 months.<sup>5</sup> Factors associated with its development include moderate to severe renal insufficiency, nephrotic syndrome associated hypoalbuminemia, combining HMG-CoA reductase inhibitors with fibric-acid derivatives, and hypothyroidism.<sup>5,8</sup> As well, the frequency is increased in the presence of other drugs such as cyclosporine, erythromycin, nicotinic acid, and fibric acid derivatives.<sup>5</sup>

The actual cause of the rhabdomyolysis is complex and not completely understood. The acute muscle damage that occurs often leads to renal damage, which is thought to occur via 3 proposed mechanisms.<sup>13</sup> The first is impairment of renal vascular flow due to sympathetic nervous overactivity, followed by activation of the renin-angiotensin system, alteration of prostaglandin synthesis, high circulating levels of antidiuretic hormone and the deposition of microthrombi. The second mechanism includes tubular obstruction by myoglobin casts or crystals of uric acid, with passive diffusion of glomerular filtrate. Myoglobin and uric acid are filtered through the kidneys and give the urine a reddish-brown colour. Lastly, it is thought that ferrihemate (a product of the dissociation of myoglobin at pH<5.6) causes direct toxicity. Ferrihemate has been shown in animals to produce a dose-dependent deterioration in renal function, with depression of renal transport mechanisms, cell swelling and death.

As was evident in the patient described in this case, renal failure can follow myoglobinuria. Other sequelae include hyperphosphatemia, marked hyperuricemia,

severe hypocalcemia, metabolic acidosis and disseminated intravascular coagulopathy (DIC).<sup>13</sup> Our patient presented with an anion gap of 16 (normal 8–14) on admission, and a calcium of 1.95 mmol/L (2.12–2.62 mmol/L), and albumin of 32 g/L (35–50) and a phosphate of 2.20 mmol/L (0.8–1.45 mmol/L) measured on the third day of admission.

Aside from furosemide, other diuretics have been used in the treatment of rhabdomyolysis. Mannitol has been used to promote diuresis. The increase in glomerular filtration leads to an increased intratubular flow, followed by a decrease in the tubular obstruction. As well, the increased flow flushes out the nephrotoxic substances. Mannitol itself has the disadvantage of being nephrotoxic at doses greater than 200 grams per day.<sup>13,14,15</sup> Sodium bicarbonate infusions can also be used, as myoglobin and urate crystals are more soluble in alkalinized urine, and alkalinization prevents the dissociation of myoglobin to its nephrotoxic metabolite ferrihemate. Using a sodium bicarbonate infusion however, can lead to metabolic alkalosis.

Once the offending agent is withdrawn, the signs and symptoms of myalgia normally disappear. Normalization of the CK can, however, take 1–2 weeks.<sup>5</sup> In our case, the patient did not have any overt muscle pain; however, he did complain of extreme weakness both during and after the episode. It is difficult to determine whether this weakness was a result of an adverse reaction or secondary to the myocardial infarction. As can be expected, this patient's CK levels did not fall until the patient recovered from the acute renal effects. The patient experienced oliguria, treated by a combination of high-dose furosemide plus metolazone.

Patients who develop rhabdomyolysis may benefit from lipid-lowering therapy from another class of agents. In a case of simvastatin-induced rhabdomyolysis, the drug was discontinued and, at least 6 months later, gemfibrozil was instituted with no adverse effects by 7 months.<sup>16</sup>

The literature suggests that any patients starting lipid-lowering therapy with either an HMG-CoA reductase inhibitor or a fibric-acid derivative should be evaluated for baseline CK levels and thyroid function.<sup>8,10</sup> If not identified early, rhabdomyolysis can be a serious adverse effect. Therefore, patients taking HMG-CoA reductase inhibitors who present with complaints of muscle weakness or pain, with elevated CK levels (approximately 10 or more times their baseline value) should be suspected of having a drug-induced myopathy, and have the medication discontinued.

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