Simvastatin-Induced Rhabdomyolysis and Acute Renal Injury

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Key Words

Simvastatin • Rhabdomyolysis • Acute renal failure • Hemodialysis • Diabetes mellitus

Abstract

Simvastatin is one of the most commonly prescribed CoA reductase inhibitors. The safety profile of this drug has been widely discussed in the medical and consumer advocacy communities. Like other statins, simvastatin can cause a serious and potentially life-threatening complication: rhabdomyolysis. We describe a case of simvastatin-induced rhabdomyolysis complicated by acute renal failure requiring urgent hemodialysis. The relative safety of simvastatin compared to other HMG-CoA reductase inhibitors and the conditions that can potentiate its toxicity are discussed. The clinical features of rhabdomyolysis, and subsequent acute renal failure, and their treatment modalities are presented.

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Introduction

HMG-CoA reductase inhibitors (statins) are the cornerstone of modern therapy for dyslipidemias and ischemic heart disease. Since the approval of the first one, lovastatin (Mevacor®), in 1987 [1], statins have been increasing in number, effectiveness and market share. This evolution, however, brought with it a number of complications and controversies. Among the most worrisome

complications of statins are the increase in liver transaminases level and myopathy. The latter can range from simple diffuse muscle soreness to a more severe, and even fatal, rhabdomyolysis.

Rhabdomyolysis is defined by the breakdown of striated muscle fibers with release of toxic intracellular components into the systemic circulation. Beside the clinical picture of severe diffuse muscular pain, rhabdomyolysis is diagnosed with tenfold elevation or more in the serum creatine kinase (CK) level. Many other hemodynamic and metabolic derangements might follow this muscular injury. Hypovolemia, fluid sequestration, hyperkalemia, cardiac arrhythmia, hypocalcemia, metabolic acidosis, disseminated intravascular coagulation, acute renal failure, and other disturbances can occur with rhabdomyolysis [2]. Many predisposing factors for rhabdomyolysis have been identified: some of them are well known like female gender, small body frame, elderly people, presence of multiple co-morbidities, perioperative periods, crush injury, overexertion, seizures, alcohol abuse, certain medications, and some industrial toxins [3, 4]. Other etiologies are less known or rare, e.g. fire ant bites [5], pomegranate juice [6] and lightning [7].

All statins are well known to cause a variable degree of myopathies, from simple muscular soreness to more serious myositis and even fatal rhabdomyolysis. This dreaded complication is worse when any statin is combined with other medications like fibric acid derivatives, niacin, amiodarone, cyclosporine, macrolides, azole antifungal agents, diltiazem, verapamil, HIV protease inhibitors,

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etc. There are medical conditions that predispose to muscular statin toxicity, like diabetes mellitus, renal impairment, familial muscular disorders, hypothyroidism, and the consumption of grapefruit juice [8].

Cervastatin (Baycol®) was withdrawn from the US market in August 2001 after many reported cases of severe rhabdomyolysis, acute renal failure and death. Lovastatin, simvastatin and atorvastatin can also cause rhabdomyolysis, but to a much lesser degree [9].

Rosuvastatin (Crestor®) was the last HMG-CoA reductase inhibitor to be approved by the Food and Drug Administration (FDA, USA) in August 2003 [1]. Since the first step of its approval, rosuvastatin has been causing more controversy than other statins. A good number of trials were conducted to look at the safety of rosuvastatin. Many investigators came up with a favorable conclusion, stating rosuvastatin has a similar adverse effect profile compared to other HMG-CoA reductase inhibitors [10–15]. Other authors took a more cautious attitude with regard to the spectrum of its possible adverse effects [16–19].

The first simvastatin, Zocor®, was approved by the FDA in 1991. Since then, it has been one of the most prescribed HMG-CoA reductase inhibitors. In 2005, the total sales for statins were estimated at USD 16 billion. Zocor® ranked No. 2 after atorvastatin [1]. In 2006, the FDA approved generic simvastatin, which competes with Zocor® and other products for the lucrative statins market.

In anticipation of the patent expiration of Zocor®, Merck, the maker of the drug, launched Vytorin® in 2004. It contains both simvastatin and ezetimibe.

The risk of simvastatin-induced rhabdomyolysis is thought to be low [20, 22]. Its myotoxicity can occur either as monotherapy [21–23] or in combination therapy [24–27]. Compared to other statins, simvastatin is thought to be in the middle of the statin muscular adverse effect scale. It can potentially cause more rhabdomyolysis than pravastatin and fluvastatin [28]. One study found that simvastatin is more toxic to the muscle than atorvastatin [29].

Case Report

A 63-year-old female, with multiple medical conditions, presented to King Abdulaziz University Hospital Emergency Room on April 28, 2007, with the chief complaint of severe generalized myalgia. The patient is legally blind and is known to have had a history of type 2 diabetes mellitus for the past 20 years, hypertension for 5 years, dyslipidemia for 1 year, and a poorly documented ischemic heart disease. The patient was taking metformin, aspi-

rin, atenolol, perindopril, clopidogrel, furosemide, and simvastatin. Since the patient was new to our institution, it was related that she started taking simvastatin 10 mg daily for the past 1 year. The dose was increased to 40 mg daily, 10 days prior to her initial first visit at our institution. After a few days, she started experiencing fatigue, malaise, poor appetite and vomiting. Subsequently, she developed severe muscle pain in her extremities and abdomen, followed by urine discoloration (red urine noted by relatives) and oliguria (twice per day). She was brought to our Department of Emergency Medicine where she was evaluated and subsequently admitted.

Physical Examination

On physical examination, the patient was a middle-aged female who was drowsy but arousable, complaining of diffuse pain. BP 137/74 mmHg; pulse 70 bpm; RR 24/min; temperature 36.4°C; weight 59 kg. She had a 2/6 ejection systolic murmur at the left sternal border, and diffuse abdominal tenderness without guarding or organomegaly. Her neuromuscular examination showed severe muscular tenderness on palpation of the four extremities with diffuse decreased motor strength to 3/5, otherwise there was no focal motor deficit, the cranial nerves were intact, no swelling or erythema of her extremities, and no involvement of her joints. The rest of her examination was unremarkable.

Laboratory Findings on Admission

A preliminary laboratory evaluation was done after her arrival to the department of Emergency Medicine (April 28, 2007), which shows the following findings: WBC $20.3 \times 10^3/\mu\text{l} \times 10^3$ (87% neutrophils); hemoglobin 11.7 g/dl; hematocrit 33.8%; platelets $332 \times 10^3/\mu\text{l}$; sodium 110 mmol/l; potassium 5.8 mmol/l; magnesium 0.88 mmol/l; chloride 7 mmol/l; random glucose 8.0 mmol/l; BUN 36.3 mmol/l; serum creatinine 384 $\mu\text{mol/l}$; serum calcium 1.72 mmol/l; serum phosphate 2.71 mmol/l; creatine kinase (CK): 31,207 U/l (CK-MB 320 IU/l); troponin-I 0.07 $\mu\text{g/l}$; lactate dehydrogenase 1,715 U/l; aspartate aminotransferase (AST) 549 U/l; alanine aminotransferase (ALT) 576 U/l; γ -glutamyl transferase (GGT) 284 U/l, and alkaline phosphatase (ALP) 164 U/l.

The rest of her laboratory findings, including thyroid function testing, were unremarkable.

Treatment

Based on the clinical presentation and laboratory findings, the diagnosis of rhabdomyolysis complicated by acute renal injury was established. Looking back at the fact that her dose of simvastatin was increased from 10 to 40 mg/day, we can conclude that this drug was the most likely etiology behind her rhabdomyolysis. This high probability is further confirmed by the elevation noticed in her liver enzymes, a well-known complication of all statins.

The patient was admitted to the medical ward, simvastatin was stopped and urgent treatment with hemodialysis was started. Her first session was on April 29, 2007, with little clinical improvement; the patient was still oliguric, complaining of diffuse myalgia. Her blood test that day showed mild improvement in the CK level 28,108 IU/l, potassium level 5.5 mmol/l, phosphate level 2.43 mmol/l, and WBC to $18.1 \times 10^3/\mu\text{l}$. Her serum creatinine level rose, however, to 462 $\mu\text{mol/l}$, and the serum calcium worsened to 1.35 mmol/l. Furthermore, blood and urine cultures were done and were negative. The patient did not receive any antibiotic therapy.

Fig. 1. Serum creatine kinase levels.

Table 1. Main laboratory findings by date

	4/28/07	4/29/07	4/30/07	5/1/07	5/2/07	5/3/07	5/7/07	5/8/07	5/12/07	5/16/06
Creatine kinase	31,207	28,108		8,407		1,975		95		
Serum creatinine	384	462	393	264	275	343	703		251	171
Potassium	5.8	5.5		3.1		3.6	3.7		3.8	5.0
Sodium	110	110	122	125	127	122		136	129	134
Calcium	1.72	1.35	1.40	1.60		1.80	1.90			
Phosphate	2.71	2.43	2.07	1.17		1.12				
WBC	20.9	18.1					12.3		11.7	

Subsequently, this patient underwent four more hemodialysis sessions on the following days: April 30, May 1, 5, and 7, 2007. She felt progressively better afterwards. Her severe muscle pain resolved and she started having better urine output. Table 1 summarizes her successive important laboratory findings. The serum CK level showed a sharp and steady decline after stopping simvastatin. It completely normalized within 10 days of the patient's admission to our institution (fig. 1). The serum electrolytes, including potassium, sodium, calcium and phosphate, also progressively improved. The kidney function, however, worsened after initial treatment, requiring therefore further hemodialysis. After the fifth and last dialysis episode, the patient was on her way to complete renal function recovery (fig. 2).

Follow-Up

After a 21-day stay at King Abdulaziz University Hospital, the patient was discharged home, on May 19, 2007, following complete clinical recovery and normalization of her laboratory data. She received the following medications: metformin 500 mg p.o. t.i.d., nifedipine 20 mg p.o. b.i.d., isosorbide dinitrate 10 mg p.o. b.i.d., pantoprazole 40 mg p.o. q.d., with iron and vitamin D replacements.

The patient was seen at the outpatient clinic on May 30, 2007 for a follow-up appointment. She was doing well overall, denied further muscular pain, and was urinating in a satisfactory fashion. A repeat serum creatinine level was done that day and it was 80 $\mu\text{mol/l}$. She also had a liver function testing done on May 8, 2007 that showed major improvement with AST 28 U/l and ALT 100 U/l.

Discussion

Our 63-year-old female patient, with diabetes mellitus, hypertension, dyslipidemia, and ischemic heart disease, represents a good example of the usual 'bread and butter' of many physician practices around the world. These diabetic, hypertensive, dyslipidemic, vasculopathies are treated by family practitioners, internists, endocrinologists, cardiologists, nephrologists, and even by pharmacists and nurses in some countries. Polypharmacy usually accompanies these co-morbid conditions, which

Fig. 2. Serum creatinine level.

can add insult to injury. That was the case at the initial presentation of our patient, who was taking simvastatin with many other medications. The dose of simvastatin was increased from 10 to 40 mg daily, 10 days prior to this presentation. She developed severe diffuse muscular pain, urine discoloration and poor urinary output. The diagnosis of rhabdomyolysis, complicated by acute renal injury, hyperkalemia, hyponatremia, hypocalcemia, and hyperphosphatemia, was established.

Simvastatin was thought to be the culprit of this severe complication. It was stopped immediately after her admission. The patient was urgently started on hemodialysis, requiring a total of five sessions, with successful clinical outcome. Most of her laboratory findings, especially serum CK, potassium, sodium, calcium and phosphate levels, normalized within 10 days of treatment. Her kidney function worsened initially despite treatment. It took the full five sessions of hemodialysis to see a steady improvement in renal function. It fully recuperated within 1 month of the initial insult.

Our patient did present several features putting her at a higher risk for rhabdomyolysis. She was a thin female, relatively old, with a long-standing history of diabetes mellitus. What is interesting about her presentation though is the fact that she had been on simvastatin for 1 year prior to this event. It is the increase of the statin dose that led to the cascade of rhabdomyolysis, acute renal failure and electrolyte derangements. The comprehensive history and physical done for our patient, followed by the exactly-needed laboratory work, were key to establishing a precise diagnosis, followed by a successful treatment.

Conclusion

Rhabdomyolysis remains a dreadful condition for both patients and physicians. Indeed, its symptoms of severe myalgia, urine discoloration, decreased urine output, acute renal failure, and other complications are not easily forgotten by any patient who experiences this potentially fatal condition. Physicians in general are challenged in making the exact diagnosis, then by the treatment of this condition and its potential complications. This is more pertinent for doctors who will probably deal directly with it at the emergency room, outpatient clinic, inpatient setting, or in the dialysis unit.

Acute renal injury secondary to rhabdomyolysis is well established. It is usually associated with potentially dangerous metabolic and mineral derangements. Hemodialysis is usually needed to treat the renal insult and some of the dangerous electrolyte abnormalities.

Simvastatin, among other HMG-CoA reductase inhibitors, is known to cause rhabdomyolysis. Physicians should always keep in mind the possibility of this complication occurring, while either starting their patients on statins for the first time, or while attempting to increase the dose of a previously prescribed one. This statin side-effect alertness should be even higher when doctors are treating frail elderly patients with other co-morbid conditions, like diabetes mellitus, and polypharmacy.

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