

Pregabalin and Simvastatin

First Report of a Case of Rhabdomyolysis

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ABSTRACT

Purpose: We sought to determine whether a case of rhabdomyolysis was a probable adverse reaction associated with pregabalin (Lyrica) and simvastatin (Zocor). Pregabalin is not recognized as a cause of rhabdomyolysis, but statins are known to cause it.

Patient Summary: A 70-year-old man with a history of fibromyalgia, type-2 diabetes, hypercholesterolemia, and chronic back pain presented to the emergency department with altered mental status, limb weakness, twitching, and slurred speech. He was taking multiple pain and neuropathic medications and had recently started taking lisinopril (e.g., Zestril) and simvastatin. His pregabalin dose was also increased from 50 mg to 100 mg three times daily.

On admission, serum creatinine (SCr) and creatine phosphokinase (CPK) levels were 1.5 mg/dL (normal, 0.7–1.5 mg/dL) and 1,391 units/L (normal, 30–170 units/L), respectively. Metformin (Glucophage) was discontinued, and insulin was started. He was alert and oriented. The review of symptoms was normal except for leg weakness. He had no seizure activity.

Simvastatin was discontinued, and the patient was aggressively hydrated. The following day, the SCr level was 1.6 mg/dL and the CPK level was 14,191 units/L. Pregabalin was then discontinued. The rhabdomyolysis resulted from simvastatin and perhaps also pregabalin. The Naranjo Causality Algorithm indicates a probable relationship between rhabdomyolysis and combined therapy. Three days later, the patient had significantly improved, and CPK began to decline. His discharge plan included all prior medications except simvastatin and pregabalin.

Conclusion: It is not well known that pregabalin can cause rhabdomyolysis, and there is only one published report on pregabalin-induced hepatotoxicity. When different therapies are combined, the risk of rhabdomyolysis may be increased. The cause of rhabdomyolysis in our patient might be related to decreased renal elimination of both pregabalin and simvastatin

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(e.g., renal tubular reabsorption). It is important to be aware of this potentially serious and possibly life-threatening reaction especially when medication doses are increased or combined with other agents with similar safety issues.

INTRODUCTION

Rhabdomyolysis has been defined by the American College of Cardiology, the American Heart Association, and the National Heart, Lung, and Blood Institute as muscle symptoms with marked creatine phosphokinase (CPK) elevations of more than 10 times the upper limit of normal (ULN) with creatinine elevation, usually with brown urine and urinary myoglobin.¹ Myoglobinuria is the most significant consequence in patients with rhabdomyolysis, leading to acute renal failure in 15% to 33% of patients, as a result of muscle necrosis.² The mortality rate is approximately 5%.³

Rhabdomyolysis can be caused by various drugs and toxins⁴ as well as by mechanical, viral, bacterial, metabolic, and environmental factors.³ Statins (3-hydroxy-3-methylglutaryl-CoA reductase inhibitors) are associated with higher rates of rhabdomyolysis outside of the clinical trial setting and with higher rates of myopathy or rhabdomyolysis when used either alone or in combination with fibrates.⁴

Pregabalin (Lyrica, Pfizer) is similar in structure to gamma-aminobutyric acid (GABA); it is also similar structurally and chemically to gabapentin (Neurontin, Pfizer). Pregabalin exhibits analgesic, anxiolytic, and antiepileptic properties.⁵ Although it is similar to GABA, pregabalin does not exhibit GABA-mimetic effects; however, it does result in increased neuronal GABA levels and generates dose-dependent glutamic acid decarboxylase activity.

The drug's effect on neuropathic pain, anxiety, and other pain syndromes probably results from a reduction in neuronal calcium trafficking in α_2 -delta calcium channels and/or by reducing calcium currents. Pregabalin does not bind to benzodiazepine or opiate receptors or to GABA_A or GABA_B receptors, and it has no effect on cyclooxygenase activity. It does not inhibit serotonin, norepinephrine, or dopamine reuptake, and it is inactive at these receptors.

The FDA has approved pregabalin for the treatment of diabetic peripheral neuropathic pain (DPN), postherpetic neuralgia (PHN), as adjunctive therapy for adults with partial-onset seizures, fibromyalgia, and neuropathic pain associated with spinal cord injury.⁶ The recommended dosage of pregabalin for DPN is 50 mg three times daily. This dose can be increased to 100 mg three times daily within a week according to its effectiveness and the patient's tolerability.

Pregabalin has negligible hepatic metabolism and does not bind to plasma proteins. It is excreted primarily unchanged

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in the urine (90%–98%) with its renal clearance proportional to the creatinine clearance (CrCl) in patients not receiving hemodialysis. A dose reduction may be required in patients with renal dysfunction or failure.

The drug's oral bioavailability is about 90% independent of the dose, and the elimination half-life is about 6 hours.⁶ Common adverse reactions include central nervous system (CNS) depression, dizziness and drowsiness.

Pregabalin is classified as a federally controlled substance (C-V) and therefore may cause some physical or psychological dependence. Suicidal ideation in association with this agent was the topic of an initial FDA alert in January 2008.⁷ Angioedema, peripheral edema, dry mouth, blurred vision, weight gain, difficulty in concentration, and hypersensitivity reactions have also been reported.

Case Report

A 70-year-old male patient presented to the emergency department (ED) with generalized extremity weakness. He was mentally disoriented and unable to stand up, and his legs were atonic. His right side and all four extremities were twitching, and he had slurred speech. The patient had experienced these symptoms when he was at home, and emergency medical services was called. In the ED, his medical history was significant for type-2 diabetes mellitus, peripheral neuropathy, hypercholesterolemia, and chronic low back pain (a disc had been removed in the early 1980s). He had no family history of stroke or coronary artery disease. In addition, he stated that he is functional and walks his dog four or five blocks every day.

According to the patient's medication reconciliation file, his home regimen included the following oral medications: lisinopril (e.g., Zestril, AstraZeneca) 5 mg daily, amitriptyline 25 mg in the morning, amitriptyline 50 mg at bedtime, simvastatin (Zocor, Merck) 20 mg daily (started 4 days earlier), pregabalin (Lyrica) 100 mg three times daily, oxycodone HCl controlled-release (OxyContin, Purdue Pharma) 80 mg every 8 hours, oxycodone HCl immediate-release (generic) 30 mg every 4 hours as needed, and metformin (Glucophage, Bristol-Myers Squibb) 500 mg twice daily.

The only recent modifications to the regimen were the additions of lisinopril 5 mg and simvastatin 20 mg and an increase in the pregabalin dose from 50 mg three times daily 4 days earlier; it was not known how long the patient had used the lower pregabalin dose. He denied smoking, drinking alcohol, or using recreational drugs, and he had no known drug allergies or a history of trauma.

The patient's initial vital signs were as follows: temperature, 97.6 °F; heart rate, 71 beats/minute; blood pressure, 110/60 mm Hg; and respiratory rate, 14 breaths/minute. Oxygen saturation was recorded at 99% on room air. The physical examination findings were normal except for the musculoskeletal system, which showed more weakness in the legs than in the arms. Upper-limb strength was 5/5 (normal), but lower-limb strength was 3/5 (movement possible against gravity but not against resistance by the examiner). A muscle twitch was also observed in the right lower and upper extremities.

Laboratory test results were significant for elevated CPK levels of 1,391 IU/L, a creatine phosphokinase–muscle band (CPK–MB) of 234 ng/mL (MB 1%), serum creatinine (SCr) of 1.5 mg/dL, and a fingerstick glucose reading of 117 mg/dL. The patient was

awake, alert, and oriented to person, place, and time, although he stated that he felt very tired.

The patient displayed no slurred speech or acute distress. According to his wife, he was back to his baseline mental status, which included being mentally oriented to person, place, and time. The stroke team was activated. A neurologist stated that the patient's history did not suggest a cerebrovascular accident. Computed tomography (CT) of the head was negative for an infarct or a hemorrhage.

Additional laboratory tests were within normal limits. Total bilirubin was 0.5 mg/dL, direct bilirubin was zero, alkaline phosphatase was 78 units/L, aspartate aminotransferase (AST) was 39 units/L, and alanine aminotransferase (ALT) was 24 units/L. The prothrombin time was 10 seconds, the activated partial thromboplastin time was 28.7 seconds, the International Normalized Ratio (INR) was 1, and glycosylated hemoglobin (HbA_{1c}) was 6.2%. His lipid panel was also within normal limits. It was not evident whether he had received previous treatment for hypercholesterolemia or, if so, which agent or agents had been previously prescribed. Additional laboratory tests throughout his hospitalization are presented in Table 1.

The patient was admitted with a diagnosis of rhabdomyolysis, which was probably a result of statin therapy. It was also thought that he might have had a seizure disorder, but this was ruled out following a normal electroencephalogram. Simvastatin was discontinued. The patient was initially given a 1-liter normal saline (NS) bolus, followed by intravenous (IV) NS at 100 mL/hour. His acute renal failure was monitored, and the fluids were changed to bicarbonate (0.45% NS with 75 mEq of bicarbonate at a rate of 150 mL/hour) to keep the urine pH at approximately 7. Serial troponin levels were used to rule out acute coronary syndromes.

On the second hospital day, CPK peaked at 14,191 units/L and SCr peaked at 1.6 mg/dL. The patient had received one dose of pregabalin and lisinopril that morning but not simvastatin. His mental status had improved, and he was able to follow commands. Pregabalin, lisinopril, and metformin were discontinued in the afternoon. The patient received 5,000 units of heparin sodium subcutaneously every 12 hours for deep vein thrombosis prophylaxis, sliding-scale (short-acting) insulin, and 10 units of insulin glargine (Lantus, Sanofi) at bedtime for diabetes.

The next day, leg pain and chronic low back pain were the same as at baseline; he was able to take slow walks and bear weight. His strength, balance, and coordination improved, and his mental status continued to improve. His CPK and SCr values began to fall; CPK was 4,605 units/L, and SCr was 1.0.

It was recommended that the patient restart lisinopril and metformin upon discharge. However, the safety of pregabalin was questioned by the medical resident, and pregabalin and simvastatin were not restarted. The patient has not been readmitted to New York Downtown Hospital.

DISCUSSION

One report of hepatotoxicity occurring with pregabalin use has been published.⁸ In the package labeling for pregabalin, three cases of rhabdomyolysis are noted in premarketing clinical trials; however, no further details are provided.⁶ Other reports mention CPK elevations in premarketing clinical trials.⁹

In premarketing trials in patients with DPN, there was a 0.8% incidence of CPK elevations in pregabalin-treated patients com-

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Table 1 Patient Laboratory Values*

Test Date	WBC (4–11 x 10 ³)	RBC (3.8– 5.4x10 ⁶)	Hb (14– 18 g/dL)	Hct (40%– 54%)	CPK (30–170 IU/L)	AST (14–59 U/L)	ALT (9–72 U/L)	ALK-P (38–126 U/L)	Cr (0.7–1.5 mg/dL)	BUN (7–20 mg/dL)
12/21†	18.7	3.78	12.1	35	1,391	39	24	78	1.5	28
12/22‡	15.7	3.46	10.8	32.5	14,191	240	44	67	1.6	30
12/23	10.3	3.13	9.9	29.6	4,605	118	41	72	1.0	26
12/24	10.1	3.2	10.2	30.5	3,437	94	44	76	0.9	16

ALK-P = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CPK = creatine phosphokinase; Cr = creatinine; Hb = hemoglobin; Hct = hematocrit; NR = not reported; RBC = red blood cells; WBC = white blood cells.
 *Parentheses represent normal values.
 †Simvastatin was discontinued.
 ‡Pregabalin was discontinued.

pared with 0.4% of placebo-treated patients (range, 0.3%–1.4%). In the clinical studies of PHN, there was a 0% incidence of CPK elevations for placebo-treated patients and a 0.6% incidence for pregabalin-treated patients (range, 0.3%–1.6%).⁹

In the epilepsy trials, there was also a 0% incidence of CPK elevations for placebo-treated patients and a 0.4% overall incidence of CPK elevations in pregabalin-treated patients (range, 0.4%–0.8%).⁹ In the fibromyalgia studies, there was a 0.6% incidence of CPK elevations for placebo-treated patients and an overall 0.5% incidence of CPK elevations in pregabalin-treated patients (range, 0.0%–0.8%).

When all the controlled trials of pregabalin were combined, 12 placebo-treated patients and 62 pregabalin-treated patients experienced increased CPK levels exceeding three times the upper limit of normal (ULN).⁹ In addition, very high CPK levels (1,000 units/L or higher) were observed in 0.3% of placebo-treated patients and in 0.7% of pregabalin-treated patients. This represents at least double the risk in active-treatment patients. High CPK levels (340 units/L or above in men; 180 units/L or above in women) were documented in 8.1% of placebo patients and in 10.5% of pregabalin patients.

In one case, Einarsdottir and Björnsson suggested that pregabalin was the cause of acute liver injury.⁸ A healthy 61-year-old man with herpes zoster received pregabalin 75 mg twice daily for 12 days from his physician. He presented to the hospital with a 1- to 2-week history of sickness (e.g., nausea, vomiting, itching). Four days before hospitalization, the physician discontinued the pregabalin due to the patient's nausea, which had occurred after he started taking pregabalin.

In the hospital, the AST was 50 times the ULN, the ALT was 35 times the ULN, the bilirubin was 354 μ M/L (normal, below 21 μ M/L), and the INR was 3.8. Serologic values for hepatitis were negative, as were serologic findings for Epstein-Barr virus and cytomegalovirus. Autoantibodies were also negative, and an abdominal CT scan showed no signs of hepatic vein thrombosis. The INR increased to 4.2 after 2 days and then began to decrease. On follow-up 6 weeks later, the ALT and AST had returned to normal, the INR was 1.2, and bilirubin was 75 μ M/L.

Einarsdottir and Björnsson noted that this liver injury was of the hepatocellular type.⁸ Because pregabalin does not undergo significant hepatic metabolism, it is not usually sought as a potential hepatotoxin. These authors describe another case in

which a different drug caused significant hepatotoxicity, even though it is not metabolized by the hepatic route. Because of the limited number of patients studied before a drug is approved, rare adverse reactions would not be likely to occur.¹⁰ Therefore, uncommon reactions such as hepatotoxicity tend to occur in the postmarketing period, when a greater number of patients receiving a medication would be more likely to have complications.

Sendra et al. reported a case of pregabalin-induced hepatotoxicity.¹¹ A 59-year-old man with a history of mantle-cell lymphoma was treated for neuropathic pain with pregabalin 25 mg twice daily. After 14 days of pregabalin therapy, edema of the left ankle was reported along with a significant elevation in liver enzymes (AST, 907 U/L; ALT 1582 U/L; and total bilirubin, 1.1 mg/dL). Pregabalin was thought to be the offending agent. It was discontinued, because it was the only new agent administered. Two days after the drug was discontinued, ankle edema and liver enzymes decreased. A follow-up visit 4 months later reflected normal liver-function test results.

Our patient and the other two patients described by Einarsdottir and Björnsson⁸ and Sendra et al.¹¹ showed elevated liver enzymes, which appeared to be caused (at least in part) by pregabalin therapy. Discontinuing pregabalin therapy resulted in resolution of symptoms. Our patient was also taking simvastatin concurrently, and this might have led to an increased risk of rhabdomyolysis.

The exact mechanism of statin-induced myopathy is not well understood, but numerous theories exist.¹² There are no reports of early-onset (of less than 1 week) statin-induced myopathy in the literature. Potential sites of statin–drug interactions included the cytochrome P450 3A4 pathway and a decrease in renal elimination of hydrophilic metabolites.¹³ It is possible that pregabalin inhibited the elimination of simvastatin, leading to myopathy; alternatively, the pregabalin dose needed to be decreased because of impaired renal function. In addition, after impaired renal function was identified, metformin was also discontinued. Either way, the pregabalin dose might have been too high for our patient. It is generally recommended that multiple medication adjustments not be made at the same time. Doing so makes it very difficult to determine the cause of untoward effects, as in this case.

No known interactions have been published to date between simvastatin and pregabalin, and no other causes were sought

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