Rhabdomyolysis Associated with Concurrent Use of Simvastatin and Nefazodone: Case Report and Review of the Literature

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ABSTRACT

Recent clinical studies have demonstrated that life-threatening rhabdomyolysis can occur in patients who receive 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors when they are treated concurrently with agents that may inhibit the metabolism of HMG-CoA reductase inhibitors. Simvastatin is metabolized primarily by the cytochrome P450 3A4 (CYP3A4) pathway, and nefazodone is a potent inhibitor of that metabolic pathway. Therefore, significant risk for an adverse drug interaction may exist in patients treated with that combination of medications. In this article, a case of rhabdomyolysis associated with the concurrent use of simvastatin and nefazodone is reported. To our knowledge, this is the third case report of an adverse drug interaction of nefazodone and simvastatin that caused myopathy or rhabdomyolysis. An elderly female patient presented to a university hospital for evaluation of shortness of breath, myalgias, profound muscle weakness that developed after treatment with nefazodone 3 months earlier, tea-colored urine, and elevated serum creatine phosphokinase (CPK) levels. Her medical history indicated coronary artery disease, a transient ischemic attack, hypercholesterolemia, and depression. Her medications included simvastatin 40 mg once daily, clopidogrel 75 mg once daily, and nefazodone 150 mg twice daily. Polymyositis was ruled out by the results of a muscle biopsy, electromyography, and evaluation of the levels of serum CPK and creatinine. The patient's symptoms and the abnormalities indicated by laboratory testing improved as a result of bicarbonate diuresis and the withdrawal of treatment with simvastatin and nefazodone. She did not undergo pharmacologic rechallenge with statins or nefazodone and was asymptomatic at a 6-month follow-up examination. This patient exhibited the adverse effects that can occur from concomitant treatment with statins metabolized via the CYP3A pathway and agents that inhibit that pathway.

with nefazodone for depression 3 months before her presentation at the university hospital. She reported difficulty in rising from a sitting position, although she denied joint pain, rashes, or fever. She did, however, describe soreness in her biceps and thighs. The results of her physical examination indicated profound weakness (graded “2” on a 5-point ordinal scale) in her proximal musculature and preserved distal strength.

The initial laboratory test results for this patient were as follows: sodium, 142 mEq/L; potassium, 4.0 mEq/L; chloride, 105 mEq/L; carbon dioxide, 27 mEq/L; blood urea nitrogen, 17 mg/dL; creatinine, 0.8 mg/dL; total bilirubin, 0.5 mg/dL; aspartate transaminase, 1744 U/L; alanine transaminase, 1029 U/L; alkaline phosphatase, 82 U/L; creatine phosphokinase (CPK), 37,050 U/L (Figure 1); calcium, 8.6 mg/dL; phosphate, 3.2 mg/dL; white blood cell count, 10,200/µL; hemoglobin, 13.2 g/dL; and platelet count, 327,000/µL. The urine dipstick showed large blood and trace protein. Urine microscopy revealed 3 to 5 red blood cells per high power field, 5 to 10 white blood cells per high power field, and transitional epithelial cells; granular and hyaline casts were present. Evaluation of urine myoglobin was qualitatively positive.

Rhabdomyolysis was diagnosed in this patient, and bicarbonate diuresis was initiated. The level of serum creatinine remained relatively unchanged (0.5 to 0.8 mg/dL) as did the calcium concentration (8.1 to 8.6 mg/dL). However, her potassium concentration decreased from 4.0 mmol to 2.8 mmol within 1 day, and she required daily replacement with intravenous potassium chloride thereafter until the conclusion of diuresis. Polymyositis was suspected, and treatment with steroids was initiated empirically pending the outcome of immunologic testing. Treatment with simvastatin and nefazodone was discontinued. Electromyography demonstrated only mild nonlocalized neuropathy without myopathy. The results of immunologic studies, including anti-Jo-1 and anti-Mi-2, were negative. The results of muscle biopsy indicated vacuolation and some dissolution of muscle fibers with rare residual nuclei and organelles (Figure 2). Immunohistochemistry for CD45, a marker for polymyositis, was negative. Polymyositis was ruled out because of the results of the studies listed, and treatment with steroids was discontinued. The interaction of nefazodone and simvastatin was thought to be the cause of the patient's rhabdomyolysis. Her clinical symptoms and abnormal laboratory test results improved gradually throughout her hospitalization, and the patient was discharged to a rehabilitation facility on the eighth day of her hospital stay. Her serum level of CPK at discharge was 1776 U/L (Figure 1). This patient did not undergo rechallenge with a statin for the treatment of hypercholesterolemia. By the time of her 6-month follow-up examination, the patient's symptoms had resolved and her levels of serum CPK and creatinine were normal.

**Figure 1. Serum Creatine Phosphokinase Concentrations in a Patient with Drug-related Rhabdomyolysis**

The level of creatinine phosphokinase was 37,050 U/L on admission and 1776 U/L at discharge.

**Figure 2. Muscle Biopsy of the Effects of Statin-related Rhabdomyolysis**

The trichrome stain shows mildly abnormal muscle atrophy with focal vacuolization representing chronic fiber breakdown. Note the residual nuclei and organelles.
From 1987 to 2001, almost 500 million prescriptions were written for the treatment of hyperlipidemia, a disorder frequently encountered by the primary care physician. Statins used to treat hyperlipidemia are usually well tolerated, but 2 potentially serious adverse effects of statin treatment include the elevation of liver enzymes and the development of skeletal muscle abnormalities: myopathy is encountered in 0.5% to 2.5%, and muscle pain or weakness and a 10-fold elevation in CPK are exhibited by 0.3%. In 0.1% of patients, rhabdomyolysis is defined as a CPK value of more than 5000 U/L in addition to renal failure and/or electrolyte abnormalities, and is characterized by massive muscle necrosis and myoglobinuria.

Myopathy, which is a direct consequence of statin use, is dose dependent. The proposed mechanism of that type of myopathy involves a decrease in the synthesis of ubiquinone and dolichol, both of which require 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase to synthesize precursors (Figure 3). Ubiquinone is a fat-soluble quinone that functions as an electron carrier for oxidative phosphorylation, a stabilizer of cell membranes, and an intracellular scavenger of free radicals to prevent lipid peroxidation. Dolichol is required for cell membrane stability, and its absence leads to leakage of intracellular contents.

Omar and Wilson reported 601 unique cases of statin-induced rhabdomyolysis from postmarketing data supplied by the Food and Drug Administration adverse event reporting system. Those authors concluded that treatment with simvastatin and cerivastatin was implicated in a relatively higher number of reports of that disorder than were other statins. Of all cases of statin-induced rhabdomyolysis in the population studied, simvastatin accounted for 215 (35.8%), cerivastatin for 192 (31.9%), atorvastatin for 73 (12.2%), pravastatin for 71 (11.8%), lovastatin for 40 (6.7%), and fluvastatin for 10 (1.7%). Simvastatin, lovastatin, atorvastatin, and cerivastatin, which are metabolized by sterol hydroxylation via the CYP3A4 enzyme family, are substrates for that pathway. In contrast, fluvastatin is metabolized via several CYP pathways, and pravastatin is not a CYP substrate.

Inhibitors of the CYP3A4 pathway can increase the concentration of the statins metabolized by that pathway by means of direct competition or irreversible inhibition. Certain substrates and potent inhibitors of the CYP3A4 pathway should be administered extremely cautiously.
tration of statins and CYP3A4 inhibitors (cyclosporine, diltiazem, macrolide antibiotics, azole antifungals, ritonavir, nefazodone) in the onset of acute rhabdomyolysis.6-12 A more comprehensive list of both CYP3A4 substrates and inhibitors is featured in Table 1.5

Inhibition of CYP3A4 enzymes leads to a higher intracellular level of the active metabolites of statins that require the 3A4 pathway for metabolism. A higher level of statin metabolites results in greater inhibition of HMG-CoA reductase enzymes and subsequent lower levels of ubiquinone and dolichol. Lower levels of ubiquinone and dolichol could theoretically lead to a greater risk of myopathy and rhabdomyolysis.

This case report has demonstrated a temporal relationship between the administration of nefazodone and the onset of musculoskeletal symptoms and subsequent myopathy. However, the signs and symptoms of rhabdomyolysis resolved when treatment with simvastatin and nefazodone was terminated. In this patient, the initiation of therapy with nefazodone caused the inhibition of simvastatin metabolism, an elevation of the concentration of intracellular simvastatin, and subsequent myopathy and rhabdomyolysis.

The higher potency of simvastatin may have also contributed to the development of rhabdomyolysis. That theory is supported by a linear regression analysis of the reported death rate caused by statin-related rhabdomyolysis and the relative potency of the statins administered (Table 2, Figure 4).1,13 Those data demonstrate a linear relationship between the relative strength of the statins and the associated death rate ($r^2 = 0.995$). While some of the model’s linearity may be accounted for by the extreme values represented by cerivastatin, closer inspection reveals that a linear relationship exists for the weaker statins as well. This analysis, however, should be interpreted cautiously as postmarketing data were used to identify the number of cases of fatal rhabdomyolysis due to the statins. Postmarketing data do not reflect a true incidence rate, since some cases may not have been reported and others may have been attributed to other causes.

### Table 2. Cases of Fatal Statin-Related Rhabdomyolysis, 1987 - 2001*

<table>
<thead>
<tr>
<th>Statin</th>
<th>Year approved for use in the United States</th>
<th>Fatal statin-related cases of rhabdomyolysis (No.)</th>
<th>N. o. of statin prescriptions (millions)</th>
<th>Reported rate (cases per million prescriptions)</th>
<th>Initial statin dose (mg)</th>
<th>Relative potency†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovastatin</td>
<td>1987</td>
<td>19</td>
<td>99.2</td>
<td>0.19</td>
<td>30</td>
<td>2.0</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>1991</td>
<td>3</td>
<td>81.4</td>
<td>0.04</td>
<td>30</td>
<td>2.0</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>1998</td>
<td>19</td>
<td>116.1</td>
<td>0.12</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>1993</td>
<td>19</td>
<td>37.4</td>
<td>0.00</td>
<td>60</td>
<td>1</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>1996</td>
<td>14</td>
<td>140.4</td>
<td>0.04</td>
<td>5</td>
<td>0.3</td>
</tr>
<tr>
<td>Cerivastatin</td>
<td>1997</td>
<td>31</td>
<td>9.8</td>
<td>3.16</td>
<td>0.3</td>
<td></td>
</tr>
</tbody>
</table>

*Data from Staffa, Chang, and Green1 and from Stein.13 According to the Food and Drug Administration (FDA), these data are intended to be used as “a crude measure of the number of reports received by the FDA . . . Rigorous comparisons between drugs based on these data are not recommended, since many factors can affect reporting and an unknown number of cases may not be attributed to the drug or reported to the FDA. Reporting rates are not incidence rates.”

†Relative potency of the statins listed (eg, a 60-mg dose of fluvastatin was assigned a potency value of 1 and the relative potency of each was determined by the equation $60/m$, where $m$ is the initial dose of each statin.

### Conclusion

This case demonstrates the importance of preventing CYP3A4 drug interactions by reviewing all existing medications before treatment with a new drug is initiated. Caution should be used when a CYP3A4 inhibitor is coadministered with a statin (eg, simvastatin, atorvastatin, lovastatin) metabolized by that pathway. If cotherapy with a CYP3A4 inhibitor and a statin is necessary, then the use of statins (eg, pravastatin, fluvastatin) not metabolized by the CYP3A4 pathway may be preferable if those weaker agents can reduce the level of low-density lipoprotein cholesterol to the target level.14 As an alternative to statin use, treatment with a newer
agent that inhibits the intestinal transport of cholesterol and has not been associated with rhabdomyolysis might be considered.\textsuperscript{15,16}

To our knowledge, this is the third case report in which the concomitant use of nefazodone and simvastatin caused myopathy or rhabdomyolysis. It illustrates the risk of administering any CYP3A4 inhibitor with a statin that is metabolized by that pathway. Because statins and CYP3A4 inhibitors are frequently used drugs, the clinician must always be aware of this important drug interaction to prevent morbidity in patients whose therapy requires both types of agents.

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REFERENCES