

# Rhabdomyolysis and Anuric Myoglobinuric Renal Failure Associated with Cerivastatin and Gemfibrozil

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**R**habdomyolysis, a condition that frequently occurs in hospitalized patients, most often results from alcohol ingestion, seizures, and muscle trauma. Rhabdomyolysis is a potentially life-threatening complication in patients with crush injuries or patients who have fallen on the floor and have remained immobile for several hours. Other etiologies of rhabdomyolysis occasionally encountered in clinical practice include electrolyte derangements (eg, hypokalemia, hypophosphatemia), systemic infections (eg, influenza, coxsackievirus, legionella), extreme exertion, and the use of various medications.<sup>1,2</sup> Several prescription and illicit drugs that have been associated with rhabdomyolysis include cocaine, haloperidol, phenothiazines, gemfibrozil, and hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, also known as statins.<sup>1-3</sup> In fact, a well-described association exists between HMG-CoA reductase inhibitors and rhabdomyolysis.

Cerivastatin is a newer agent that was purported to have a lower incidence of muscle toxicity because of a dual elimination pathway. However, reports implicating cerivastatin as a cause of rhabdomyolysis have recently appeared in the literature.<sup>3-5</sup> Cerivastatin was voluntarily withdrawn from the US market in August of 2001 because of patient safety issues. To further lend support to the potential muscle toxicity associated with cerivastatin, we report the case of a 48-year-old man with diabetes mellitus and hyperlipidemia who received combination therapy with gemfibrozil and cerivastatin and subsequently developed severe rhabdomyolysis, resulting in anuric renal failure that required hemodialysis.

## CASE PRESENTATION

### Initial Presentation and History

A 48-year-old man with hypertension, type 2 diabetes mellitus, and hyperlipidemia came to the emergency department because of a 3-day history of generalized myalgia and brown-colored urine. He reported

no fever, chills, flank pain, dysuria, cough, rash, or arthralgia and denied recent viral illness, muscle injury, or vigorous exertion.

Three weeks previously, the patient had commenced therapy with cerivastatin 0.4 mg for hyperlipidemia, but he reported starting no other new medications since that time and not using alcohol or illicit drugs. His other medications included glyburide 10 mg twice daily, metformin 500 mg twice daily, furosemide 20 mg daily, gemfibrozil 600 mg twice daily, metoprolol 200 mg daily, terazosin 5 mg daily, and candesartan 32 mg daily. He had been taking all of these drugs without difficulty for several months prior to admission.

### Physical Examination and Laboratory Evaluation

Physical examination revealed a morbidly obese man with normal vital signs. Aside from mild muscle tenderness of the trapezius, biceps, and thigh musculature, findings from the remainder of the physical examination were unremarkable. Initial urinalysis revealed brown urine; the dipstick analysis was strongly positive for hemoglobin, but no erythrocytes or casts were present on urine microscopy. The patient's urine myoglobin level was 139,000 µg/L (normal, < 28 µg/L). Laboratory analysis revealed the following serum values: creatine kinase (CK), 111,850 U/L; aspartate aminotransferase (AST, SGOT), 2134 U/L; and alanine aminotransferase (ALT, SGPT), 628 U/L. The bilirubin and alkaline phosphatase levels were within normal limits. Additional laboratory values are shown in [Table 1](#). The anion gap and thyroid stimulating hormone level were within normal limits, and results of a urine drug screen and serum alcohol measurement were negative.

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### Treatment and Outcome

The patient was admitted to the hospital with a diagnosis of acute myoglobinuric renal failure caused by rhabdomyolysis from cerivastatin and gemfibrozil therapy. Vigorous hydration was instituted with dextrose-containing water supplemented with sodium bicarbonate, with the goal of attaining an alkaline urinary pH. Despite administration of more than 10 L of fluid during the first hospital day, the patient remained anuric, with a peak serum creatinine level of 11.1 mg/dL. However, he did not have significant hypocalcemia or hyperkalemia. The patient underwent several sessions of hemodialysis with a gradual decrease in serum creatinine and increased urine output. His CK level returned to normal over the course of several days. Results of subsequent studies for acute or recent infection with legionella, influenza A and B, coxsackieviruses A and B, echoviruses, cytomegalovirus, and Epstein-Barr virus were all negative. At 2-week follow up, the patient felt well and had a serum creatinine level of 1.5 mg/dL.

### DISCUSSION

The case patient developed acute anuric myoglobinuric renal failure resulting from severe rhabdomyolysis induced by combination therapy with cerivastatin and gemfibrozil. There was no evidence of other precipitants of rhabdomyolysis, such as viral infections, alcohol ingestion, trauma, seizures, hypothyroidism, or other medications.<sup>4</sup> In addition, the temporal association of symptom onset shortly following commencement of cerivastatin implicates this drug as the cause of skeletal muscle damage. Rhabdomyolysis is also a known adverse effect of gemfibrozil and bezafibrate when these drugs are used as monotherapy.<sup>3</sup> However, the risk of rhabdomyolysis is likely increased when combination therapy with a statin and a fibrate is used<sup>6</sup> and may be further increased with concurrent chronic renal failure.

Cerivastatin is the latest generation of HMG-CoA reductase inhibitors, with a pharmacologic potency 60 to 200 times greater than that of other agents (eg, lovastatin, pravastatin, simvastatin).<sup>7</sup> Cerivastatin is eliminated by a dual pathway of the cytochrome system, namely hepatic isoenzymes CYP3A4 and CYP2C8.<sup>3</sup> This dual elimination pathway may account for a lower incidence of drug interactions.<sup>4,5,7,8</sup> However, several reports have recently emerged implicating cerivastatin, alone or in combination with a fibrate drug, in the development of rhabdomyolysis.<sup>3-10</sup> (Since this case report was written, cerivastatin has been withdrawn from the US market because of several deaths resulting from rhabdomyolysis.)

**Table 1.** Additional Serum Laboratory Values of the Case Patient

Variable	Result
Bicarbonate	25 mEq/L
Blood urea nitrogen	43 mg/dL
Calcium	8.0 mg/dL
Creatinine	4.1 mg/dL
Magnesium	2.1 mg/dL
Phosphorus	4.1 mg/dL
Potassium	5.1 mEq/L
Sodium	134 mEq/L

The statin drug class effectively lowers serum cholesterol, which may lead to abnormal sarcolemma fluidity from decreased cell membrane cholesterol content, resulting in myocyte damage and subsequent rhabdomyolysis. To our knowledge, the case patient is the second reported in the literature who developed anuric renal failure requiring hemodialysis as a complication of combination therapy with cerivastatin and gemfibrozil. Ozdemir et al<sup>8</sup> reported a patient with diabetes mellitus who developed anuria and rhabdomyolysis and died of shock during urgent hemodialysis. Of the 4 previously reported patients receiving combination cerivastatin and gemfibrozil, 3 had diabetes mellitus and all had hyperlipidemia.<sup>7-10</sup> In addition, the previously reported patients were all older than 50 years.<sup>3-10</sup> It is unclear whether the presence of diabetic nephropathy and the decline in creatinine clearance that occurs with age increases the risk of cerivastatin-gemfibrozil-induced rhabdomyolysis, but this remains a possibility.<sup>8</sup>

Rhabdomyolysis can lead to acute tubular necrosis and subsequent acute renal failure. Myoglobin is directly toxic to the renal tubular epithelium, especially in the presence of acidic urine. Of 4 previously reported cases of rhabdomyolysis associated with cerivastatin and gemfibrozil, 3 patients exhibited an elevated serum creatinine level (range, 4.3–6.6 mg/dL).<sup>8-10</sup> Two patients responded well to conservative therapy with crystalloid and bicarbonate infusion, with normalization of serum creatinine levels<sup>9,10</sup>; however, as noted previously, 1 patient died during hemodialysis.<sup>8</sup> Despite fluid and bicarbonate administration, our patient became anuric shortly after hospital admission and required several sessions of hemodialysis before eventual renal recovery.

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## CONCLUSION

Although statins are safe and often necessary medications for the treatment of hyperlipidemia, clinicians must be aware of the potentially dangerous risk of combination therapy with statins and fibrates, as this case demonstrates. Clinicians should carefully monitor patients taking statins for acute muscle necrosis, especially if gemfibrozil is administered concurrently. Patients should be counseled to discontinue these medications at the first symptom of skeletal muscle pain, decreased urinary output, or brown discoloration of the urine. Additionally, physicians should obtain a serum CK level in any patient who exhibits any of these symptoms while taking a statin drug alone or in combination with gemfibrozil.

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