Alendronate-Associated Rhabdomyolysis in a Patient with Other Risk Factors

Benjamin Basseri, MD and Mary B. White, MD

This elderly patient was taking a statin for hyperlipidemia and regularly consuming moderate quantities of alcohol. Yet the primary cause of his rhabdomyolysis appears to have been initiation of the bisphosphonate alendronate—which has not been associated with the condition previously.

Rhabdomyolysis is a syndrome that involves muscle necrosis with the release of intracellular muscle contents into the circulation. The classic presentation of rhabdomyolysis includes myalgia, pigmenturia secondary to myoglobinuria, and elevations in serum levels of muscle enzymes.[1] Objective muscle weakness also may be present—although it is less common and usually associated with severe muscle damage. A wide spectrum exists in the severity of disease, ranging from asymptomatic, mild elevations in muscle enzyme levels to severe muscle enzyme elevations accompanied by acute, life threatening renal failure and electrolyte disturbances.

While the diagnosis of rhabdomyolysis usually is fairly straightforward, pinpointing the precise cause is not always so clear-cut. Common causes of the condition include trauma; muscle compression; alcohol use; drug interactions; and direct myotoxins, such as 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (commonly known as statins). Frequently, the cause is not singular but rather a complex interaction of factors.

In this article, we present a case of rhabdomyolysis that appears to have been attributable primarily to use of the oral bisphosphonate alendronate—to our knowledge, the first such case to be documented. This elderly patient had a variety of other factors that may have raised his risk of developing the condition, the most notable of which was concurrent use of a statin medication. Nevertheless, the timing of symptom onset and progression implicates alendronate as the chief cause. Following the case presentation, we review the known etiologies of rhabdomyolysis, with a focus on drug-induced cases, and discuss possible mechanisms by which bisphosphonates, particularly in combination with statins, could precipitate the condition.

INITIAL EXAM

A 73-year-old, Hispanic man with a history of hypertension, hyperlipidemia, type 2 diabetes, and stage 3 chronic kidney disease presented to the emergency department (ED) with muscle pain and weakness. The patient had begun taking oral alendronate 35 mg weekly for osteoporosis prophylaxis three weeks prior. Two days after his first dose, he began experiencing constant and crampy muscle pain bilaterally in his biceps and posterior thighs. Weakness accompanied the myalgia and limited the patient's ability to raise his legs to cross them or put socks on. He was able to ambulate, but with a cautious gait. These symptoms intensified after the second dose of alendronate, one week after the first, and continued to progress until ED presentation eight days later, with the concomitant development of dark urine. (The patient skipped his third dose of alendronate due to his worsening symptoms.)

The patient's history included alcohol use—which he described as consumption of a six-pack of beer on most weekends for many years. He reported no recent increase in alcohol intake and said that he had not consumed any alcohol on the previous weekend because of the severity of his symptoms. He had a smoking

Dr. Basseri is a resident physician and **Dr. White** is the director of the Transitional Care Unit, both in the department of internal medicine, VA Greater Los Angeles Healthcare System, Los Angeles, CA.

history of 30 pack-years, although he reported quitting smoking 40 years ago. He reported no history of illicit drug intake.

At ED presentation, the patient's medications included oral simvastatin 80 mg at bedtime daily for hyperlipidemia and oral rosiglitazone 4 mg twice daily and oral repaglinide 2 mg three times daily before meals for type 2 diabetes. His simvastatin therapy had been ongoing for several years, with no recent changes in the dosage, and he was not taking any other cholesterol lowering medications. His last rosiglitazone dosage increase had been 18 months prior. He reported no consumption of grapefruit or grapefruit juice and no use of herbal remedies or over-the-counter dietary supplements.

Physical examination revealed the patient to be afebrile with stable vital signs. His sclera were anicteric, and cardiovascular, pulmonary, and abdominal examinations yielded benign results. There was mild tenderness to palpation of the muscles of his upper and lower extremities. Muscle strength could not be assessed accurately because of pain, and range of motion in the hips was decreased bilaterally secondary to pain.

Results of laboratory testing included a serum creatine kinase (CK) level of 22,188 U/L, a serum creatinine level of 1.6 mg/dL (patient's baseline range over the prior year, 1.3 to 1.5 mg/dL), a blood urea nitrogen level of 58 mg/dL (reference range, 5 to 25 mg/dL), and a serum alanine aminotransferase (ALT) level of 555 U/L (reference range, less than 53 U/L). Serum levels of sodium, potassium, chloride, carbon dioxide, calcium, magnesium, and phosphorus were normal. Urinalysis demonstrated "large" urine occult blood with only 1 red blood cell per high power field, indicative of myoglobinuria. The patient's urine myoglobin level was 480 ng/mL (reference range, 0 to 5 ng/mL). Vitamin D, thiamine, and thyroid stimulating hormone (TSH) levels were not checked during his ED evaluation and subsequent hospitalization.

HOSPITAL COURSE

Aggressive intravenous fluid hydration with normal saline was initiated immediately and the patient was admitted to the hospital. On the second day of hospitalization, his CK level improved to 15,781 U/L and his serum creatinine level dropped to 1.2 mg/dL. Given the down-trending CK level and normalization of his renal function, the patient was discharged with a plan of one-week follow-up with his primary care provider (PCP), with laboratory testing prior to this appointment.

At the one-week follow-up visit, the patient reported amelioration of muscle pain and weakness. Results of laboratory testing included a CK level of 955 U/L, an ALT level of 253 U/L, and an aspartate transaminase level of 88 U/L. His serum creatinine level and electrolytes were normal. He subsequently resumed oral simvastatin 80 mg daily, at the discretion of his PCP, without any adverse effects. Alendronate was not restarted, as the risks of recurrent rhabdomyolysis were considered to outweigh the benefits of osteoporosis prophylaxis.

ABOUT THE CONDITION

In 1941, the first depiction of rhabdomyolysis in modern medicine appeared in a report describing bombing victims of the Battle of Britain who developed acute renal failure and died within one week.[2] Thereafter, many case reports of rhabdomyolysis secondary to trauma, surgical trauma, immobility, exertion, metabolic myopathies, alcohol use, electrolyte disturbances, drug interactions, and direct myotoxins have been described.

Multiple mechanisms exist through which drugs—both therapeutic and illicit—may precipitate rhabdomyolysis.[3,4] Numerous substances (including heroin, colchicine, alcohol, and statins) are known to have direct myotoxic effects. Immobilization and ischemic compression of muscle secondary to coma associated with central nervous system depressants, such as alcohol or opioids, may lead to rhabdomyolysis. Drug-induced seizures, dystonic reactions, agitation states, and hyperthermia (for instance, secondary to cocaine use) can result in excess muscle injury and subsequent rhabdomyolysis.

Electrolyte disturbances—such as hyponatremia, hypernatremia, hyperosmolar states (chiefly, diabetic ketoacidosis), hypokalemia, total body potassium depletion, hypocalcemia, and hypophosphatemia—have been associated with rhabdomyolysis.[5–9] CK levels peak between two and four days after the onset of hyponatremia, and elevated CK levels may occur regardless of whether the initial hyponatremia is corrected. Because there is a release of potassium and phosphate from myocytes in rhabdomyolysis, serum levels of these electrolytes may underestimate their actual total body depletion in hypokalemic and hypophosphatemic rhabdomyolysis. Rhabdomyolysis secondary to electrolyte abnormalities often is associated with muscle weakness and may be associated with painful hypokalemic myopathy.

In the case presented here, the patient consumed a significant amount of alcohol on the weekends, which may have contributed to his osteopenia and placed him at risk for thiamine deficiency—which, in turn, can result in mitochondrial dysfunction. He was also taking a statin when rhabdomyolysis occurred. Given the

onset of symptoms within two days of initiating alendronate therapy and the exacerbation of symptoms after the second oral alendronate dose, however, it seems reasonable to pinpoint alendronate as the primary suspect in this case. While alcohol and statin use may have been additional risk factors for rhabdomyolysis, the lack of increased alcohol consumption or an increase in his statin dose make these etiologies less likely to be the primary inciting factor.

Possible mechanisms for bisphosphonate-induced rhabdomyolysis

Bisphosphonates are approved by the FDA for the treatment and prevention of osteoporosis. Benefits include increased bone mineral density, a decrease in the markers of bone resorption, and a reduction in the risk of osteoporotic fractures.[10]

Severe musculoskeletal adverse effects occur in up to 6% of patients taking oral alendronate, ibandronate, or risedronate.[11,12] Musculoskeletal problems reported, in order of decreasing frequency, include arthralgia, acute back pain, myalgia, bone pain, and, rarely, chest pain and fever. Higher rates of musculoskeletal pain have been reported with intravenous infusions of pamidronate[13] and zoledronic acid.[14] Reversible erosive esophagitis,[15] other upper gastrointestinal adverse effects,[16] and osteonecrosis of the jaws[17,18] also have been described.

Although musculoskeletal problems are relatively common, an exhaustive literature review utilizing PubMed and Micromedex databases did not produce any published cases of rhabdomyolysis associated with bisphosphonate use. Muscle pain associated with this class of drugs, however, has been reported as severe or debilitating in some cases, appearing within one day to several months after initiation of therapy.[19] Discontinuation usually results in resolution of pain, but recurrence has been reported when bisphosphonate therapy is resumed. Given the frequency and potential severity of these musculoskeletal problems,[19] it is possible that previous cases of bisphosphonate-induced rhabdomyolysis may have been overlooked and attributed to the common adverse effect of myalgia.

The mechanism by which bisphosphonates, such as alendronate, might produce rhabdomyolysis is unclear. With regard to musculoskeletal problems in general, nitrogen containing bisphosphonates (nBPs) inhibit farnesyl pyrophosphate (FPP) synthase in the mevalonate pathway,[20] leading to accumulation of isopentenyl pyrophosphate (IPP) (Figure). IPP is a potent activator of human peripheral blood gamma delta T cells.[11] An in vitro study has demonstrated the induction of cardiac myocyte apoptosis by gamma delta T cells,[21] and this mechanism may conceivably produce skeletal myocyte apoptosis.

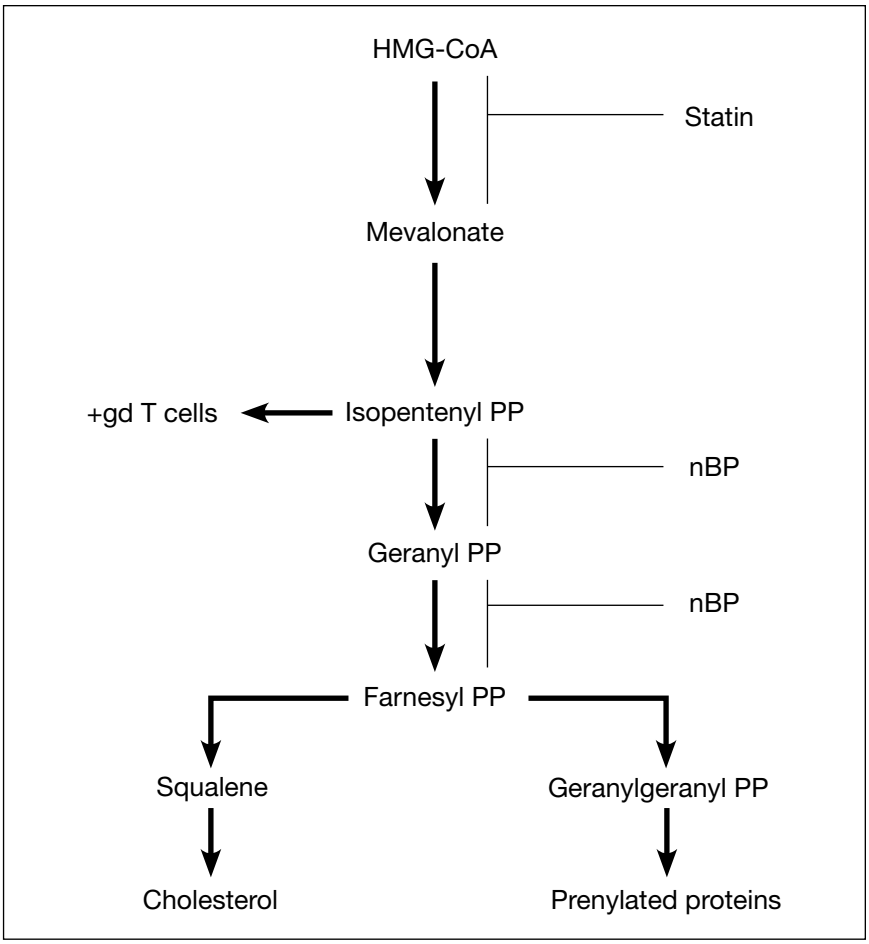

Figure. The mevalonate pathway, which is inhibited by both statins and nitrogen containing bisphosphonates (nBPs). Statins inhibit the first step in the pathway, the conversion of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) to mevalonate. nBPs inhibit farnesyl pyrophosphate (PP) synthase, resulting in accumulation of isopentenyl PP and activation of gamma delta (gd) T cells.

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Alendronate also has been associated with hypocalcemia and hypophosphatemia[22,23]—both of which are electrolyte disturbances capable of producing rhabdomyolysis. For this reason, it is recommended that calcium and vitamin D supplementation be given to patients taking alendronate. In general, it is wise to correct any underlying calcium or phosphorus abnormalities before therapy is started.[24]

For the patient described here, electrolyte values were not obtained before alendronate therapy was started. Although his electrolytes, including calcium and phosphorus, were normal at ED presentation (three weeks after initiation of alendronate), it is possible that they had become abnormal after this therapy was started and subsequently normalized. It is also possible that his serum phosphorus levels may have appeared normal secondary to release of phosphate from damaged myocytes. The presence of muscle weakness at presentation supports the hypothesis of an underlying electrolyte disturbance.

A statin-bisphosphonate interaction?

Statin-induced rhabdomyolysis is relatively rare, occurring in less than 0.1% of patients taking the drugs.[25] Nonetheless, the increasingly widespread use of statins—over 100 million statin prescriptions were filled in 2004[26]—for patients with hyperlipidemia, diabetes, and coronary artery disease should make clinicians cognizant of this potentially life threatening adverse effect and the clinical factors that increase its likelihood in patients receiving statin therapy. These factors include drug interactions, renal and hepatic disease, diabetes, and hypothyroidism.[27] Our patient had a history of stage 3 chronic kidney disease and diabetes which may have placed him at additional risk for rhabdomyolysis.

Multiple interactions between statins and other drugs have been associated with rhabdomyolysis. Gemfibrozil, macrolide antibiotics, cyclosporine, and protease inhibitors used to treat HIV, for instance, may interfere with statin clearance. Other potentially interacting drugs mentioned in a study of statin-associated rhabdomyolysis cases reported to the FDA between November 1997 and March 2000 included mibefradil, fibrates, warfarin, digoxin, and azole antifungals.[28] Overall, an incidence of 0.44 cases of statin-associated rhabdomyolysis per 10,000 patient-years has been reported,[29] as well as a rate of 0.15 rhabdomyolysis deaths per 1 million statin prescriptions.[30]

Alendronate is not known to have any interactions with statins, nor does it alter their clearance. Recent evidence, however, suggests that statins—like nBPs—may induce skeletal muscle injury through mevalonate pathway inhibition.[27] Statins reduce the production of mevalonic acid from HMG-CoA, the first step in the mevalonate pathway. Both statins and nBPs, therefore, inhibit the production of FPP, which is required for the production of ubiquinone, or coenzyme Q10, and small guanosine triphosphate (GTP)–binding proteins.[31] Ubiquinone depletion may contribute to the higher ratio of lactate to pyruvate in patients taking statins, suggesting increased anaerobic metabolism and possible mitochondrial dysfunction.[32] The small GTP-binding proteins—such as Ras, Rho, and Rac—promote cell maintenance and growth and attenuate apoptosis.[33–35] Inhibition of FPP synthesis by both statins and nBPs prevents posttranslational modification (prenylation) of small GTP-binding proteins, thus inhibiting the regulatory actions of these proteins.

Given the frequency and potential severity of musculoskeletal problems associated with bisphosphonate use, previous cases of rhabdomyolysis may have been overlooked.

IN SUMMARY

Rhabdomyolysis is a potentially life threatening condition that may have multiple etiologies. In this case report, we have described the first documented case of rhabdomyolysis associated with alendronate use. Given the frequency and potential severity of musculoskeletal problems associated with bisphosphonate use, previous cases of rhabdomyolysis may have been overlooked.

It is unclear whether other risk factors must exist for the initiation of alendronate therapy to result in rhabdomyolysis, but such factors as statin use, alcohol consumption, diabetes, and renal disease may play a role. Potential mechanisms may involve electrolyte disturbances or downstream inhibition of the mevalonate pathway,

which may be partially inhibited already by a statin. In light of this dual inhibition of the same pathway, as well as the increasing use of both classes of drugs, clinicians should be aware of the potentially increased risk of rhabdomyolysis in patients taking concurrent bisphosphonate and statin therapy.

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

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