Rhabdomyolysis and HMG-CoA Reductase Inhibitors

Mohamed A Omar, James P Wilson, and Tamara S Cox

OBJECTIVE: To review rhabdomyolysis and discuss the role of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) and their interactions with other agents in precipitating this condition, and to present case reports of statin-induced rhabdomyolysis.

DATA SOURCE: Relevant clinical literature was accessed using MEDLINE (January 1985–October 2000). The following search terms were used: rhabdomyolysis, adverse events, drug interactions, statins, and HMG-CoA reductase inhibitors.

DISCUSSION: Rhabdomyolysis occurs when extensive muscle damage results in the release of cellular contents into systemic circulation. Major complications include acute renal failure, cardiac abnormalities, and compartment syndrome. Treatment of rhabdomyolysis is supportive, with the primary aim of preventing renal and cardiac complications. Statin monotherapy or combination therapy may result in myopathy, which rarely progresses to rhabdomyolysis. The mechanism for drug interactions with the statins involves their property of lipid or water solubility. This characteristic determines the degree of hepatoenteric or renal metabolism of the statins. All statins except pravastatin undergo metabolism via the cytochrome P450 enzyme system. Other pharmacologic agents that are also metabolized via this pathway may interact with the statins and cause rhabdomyolysis. The risk of statin-induced rhabdomyolysis is increased significantly when statins are used concomitantly with such drugs as fibrates, cyclosporine, macrolide antibiotics, and azole antifungals.

CONCLUSIONS: Rhabdomyolysis is a rare but clinically important adverse event of statin monotherapy or combination therapy. Thorough understanding of this condition may help prevent or minimize adverse health outcomes in patients receiving statin therapy.

KEY WORDS: fibrate, hyperlipidemia, myopathy, rhabdomyolysis, statins, HMG-CoA reductase inhibitors.

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The hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are well established as pharmacologic agents that improve the lipid profile of dyslipidemic patients as well as decrease cardiovascular-related morbidity and mortality.[1-5] These drugs decrease cholesterol synthesis by competitively inhibiting HMG-CoA reductase. This enzyme is responsible for catalyzing the conversion of HMG-CoA to mevalonate, a precursor of cholesterol. Currently, there are five statins on the market in the US: lovastatin, pravastatin, simvastatin, atorvastatin, and fluvastatin. Cerivastatin was pulled from the US market on August 8, 2001. As a class, the statins are well tolerated[6,7] and rarely have severe adverse effects. Common adverse events include gastrointestinal disturbances, dyspepsia, headache, myalgia, central nervous system disturbances, and sleep disorders.[8,9] Hepatotoxicity[10] and skeletal muscle abnormalities[11] are the most clinically important adverse effects. Increases of hepatic enzyme and creatine kinase (CK) concentrations to more than three times the upper limit of normal have been reported[12,13] in 3–5% of patients; however, the elevation of these enzymes is usually transient and patients generally remain asymptomatic. Thus, in most cases, withdrawal of therapy is not necessary. Skeletal muscle abnormalities can range from benign myalgia to myopathy, which is defined as a tenfold elevation of the CK concentration.[11] When statins are prescribed as monotherapy, the incidence of myopathy is approximately 0.1–0.5% and is dose-related.[14,15] If myopathy is

Author information provided at the end of the text.

not recognized and statin therapy is continued, necrosis of muscle cells and subsequent myoglobinuria may occur. This may result in life-threatening rhabdomyolysis. The incidence of rhabdomyolysis when statins are used alone has been reported[16] to be 0.04–0.2%. The interaction of statins with certain pharmacologic agents that are metabolized via common pathways increases the risk of myopathy and rhabdomyolysis up to tenfold.[11] However, the true incidence of this condition among the statins when they are prescribed alone or in combination with other agents is not completely clear. This may be due to the rarity of this condition, the relative lack of experience with some of the newer agents in this class, and the inherent problem of underreporting during the drugs' postmarketing period.

The statins are used widely in clinical practice today to improve the health outcomes of patients who are at risk of or have coronary heart disease. Therefore, issues of safety and drug tolerance with the statins and ways to optimize these are of particular importance to clinicians. Even though rhabdomyolysis is a rare adverse event of the statins, the prevalent use of these drugs makes it increasingly important for clinicians to understand the nature of this condition. It is also important to understand the role of statins and their interactions with other agents in precipitating rhabdomyolysis.

This article reviews the pathophysiology, etiology, clinical presentation, diagnosis, treatment, and prognosis of rhabdomyolysis. It also discusses rhabdomyolysis as it pertains to statin therapy and reviews the mechanism of drug interactions of the statins with other pharmacologic agents that may result in this condition. Finally, this article presents published case reports of rhabdomyolysis associated with statin monotherapy or combination therapy.

Overview of Rhabdomyolysis

Rhabdomyolysis is a potentially fatal consequence of any cause of extensive muscle necrosis. Thus, it is not considered a disease but rather a clinical and biochemical syndrome that results from injury to the sarcolemma of skeletal muscle and the subsequent release (lysis) of skeletal muscle contents into systemic circulation.[17,18] There are a large number of causes of rhabdomyolysis. The majority of cases occur in healthy individuals as a result of acquired causes such as trauma (e.g., excessive exercise, crush injury), bacterial and viral infections (e.g., *Staphylococcus*, influenza), medications (e.g., statins), and toxins (e.g., recreational drugs). Some cases are attributed to hereditary metabolic abnormalities or structural abnormalities of the skeletal muscle cell.[17,19,20]

The clinical presentation of rhabdomyolysis varies greatly, due mainly to the large number of causes of this condition. Muscular signs and symptoms include pain, weakness, tenderness, and contractures. The muscle groups that are usually involved include the calves and lower back. However, the majority of patients with mild rhabdomyolysis do not present with signs that are referable to muscle.[19] Patients typically experience nonspecific symptoms such as unintentional weight gain, fatigue, malaise, fever, tachycardia, nausea, and dark red or "cola"-colored urine that results from excretion of myoglobin.[21]

The skeletal muscle contents that are released into systemic circulation include CK, creatinine, potassium, uric acid, myoglobin, calcium, and phosphate, among others. When some of these products exceed certain concentrations, complications can occur. The three major clinical sequelae of rhabdomyolysis include acute renal failure secondary to myoglobinuria, cardiac arrest or arrhythmias due to hyperkalemia and hypocalcemia, and compartment syndrome, which results from muscle swelling and subsequent compression of nerves and blood vessels.[17]

The diagnosis of rhabdomyolysis is made primarily from serum measurement of CK (normal 0–150 U/L), an enzyme present in skeletal muscle, and from the history of illness. In addition, skeletal muscle biopsy can be used to confirm diagnosis. CK is the most sensitive indicator of damage to muscles, and measuring serum concentrations of CK can help determine both the extent and timing of the damage to muscle. In rhabdomyolysis, the CK-MM subtype of the enzyme predominates.[19] The concentration of serum CK is considered significantly elevated if it is at least 10 times the upper limit of normal,[20] although the magnitude of elevation is rather arbitrary. At its peak, the concentration of CK can be elevated 100- or 1000-fold.[22] A rise in serum CK concentrations is usually observed about two to 12 hours after the muscle injury. Peak concentrations are seen within one to three days and decline after three to five days of the injury.[19] It is important to note the lack of correlation between the level of CK elevation and the intensity of symptoms reported by the patient.[23]

Myoglobinuria is also expected in rhabdomyolysis. The role of myoglobin is to store and carry oxygen and thus maintain the ability of muscles to contract. If the concentration of myoglobin in the urine is >1 g/L,[17] the urine may take on a red-brown hue or cola-colored appearance. In the absence of microscopic hematuria or hemolysis, the presence of myoglobin in the urine can be confirmed by a positive reaction with the orthotolidine and benzidine tests. Serum myoglobin (normal 0.3–8 µg/dL) usually increases before a rise in CK to a concentration of 20 times normal. It also drops more rapidly than does the decline in CK concentration.[19] Myoglobinuria accompanied by dehydration can lead to acute renal failure and thus should be treated aggressively. Approximately one-half of patients with rhabdomyolysis will develop oliguria.[20]

Other biochemical findings include raised concentrations of muscle enzymes such as lactic dehydrogenase, aminotransferases, serum aldolase, and carbonic anhydrase III.[20] Potassium, phosphorus, uric acid, and blood urea nitrogen generally increase with accompanying renal insufficiency and failure but may be normal until the onset of kidney failure.[19] Serum creatinine (normal 50–110 µmol/L) also increases due to release from muscle cells, with high concentrations resulting in patients who develop renal failure or have preexisting renal insufficiency. Calcium concentrations vary during the course of rhabdomyolysis. Patients are commonly hypocalcemic in early renal failure, then transi-

tion to hypercalcemia as more calcium is released from lysed muscle cells.[20]

The early recognition of rhabdomyolysis is critical to minimize adverse outcomes. Patients who may be at risk for this condition should be informed about the warning signs and urged to report their symptoms to their healthcare provider immediately. The mainstay of treatment of rhabdomyolysis is essentially to correct hypotension, hypovolemia, and dehydration, as well as to prevent the complications of acute renal failure. Therapy includes removal of the offending cause, if known (e.g., drug, infection), and measurement of CK concentration. It is also important to induce diuresis with large volumes of fluid to prevent renal failure in the early stages of oliguria, since many patients are volume depleted at the time of admission. Mannitol is an osmotic diuretic that is commonly used to force diuresis. This agent improves renal perfusion by expanding intra- and extracellular fluid volume and by improving blood viscosity. Bicarbonate is used to alkalinize the urine and thus increase the solubility of myoglobin, since precipitation of myoglobin in renal tissues can cause or exacerbate renal failure.

A good urine output may eliminate the need for dialysis. A potential therapeutic regimen could include infusion of hypotonic NaCl (110 mEq/L) and bicarbonate (40 mEq/L) in dextrose 5% to which 10 g/L of mannitol has been added. Hydration should be conducted cautiously in elderly patients, with loop diuretics preferred to induce diuresis.[13] If acute renal failure occurs, peritoneal dialysis or hemodialysis should be implemented.[19] Dialysis is usually temporary, as most patients recover renal function when adequately treated. Infusion of calcium is not advised despite the presence of hypocalcemia, since calcium may deposit in the affected muscle and worsen the rhabdomyolysis.[13] Finally, potassium concentrations must be monitored carefully to prevent cardiac complications.[18]

The outcome of rhabdomyolysis varies, depending on the extent of muscle injury and renal damage. Mild forms of this condition may be self-limiting and patients may recover with no noticeable sequelae. Hyperkalemia and acute renal failure are the two potentially life-threatening complications. It is important to correct these conditions early and adequately to prevent fatal outcomes. The incidence of acute renal failure in patients with rhabdomyolysis is not well defined. One report[24] indicates that approximately one-third of patients with rhabdomyolysis may develop acute renal failure. The morbidity and mortality of patients with acute renal failure due to rhabdomyolysis is also unclear. Another study[24] found no difference in morbidity and mortality in patients with acute renal failure between patients with and without rhabdomyolysis. Another study[25] reported that the mortality rate in patients with acute renal failure caused by rhabdomyolysis was between 5% and 30%.

For additional information on rhabdomyolysis, the reader is referred to review articles by Poels and Gabreels,[17] Dayer-Berenson,[18] Grob,[19] and Knochel.[26]

The Role of Statins in Rhabdomyolysis

The mechanism by which statins cause myopathy and rhabdomyolysis is not precisely known. Two theories have been suggested. The first includes alteration in the stability of cell membrane permeability of the myocyte as a result of decreased cholesterol synthesis.[27] The second theory proposes decreases in mitochondrial concentrations of ubiquinone, a facilitator of electron transport, thus causing disturbances in cellular energy production and subsequent cell death.[28,29]

Myopathy and its possible progression to rhabdomyolysis is dose-dependent. Cases of myopathy have been associated with increased drug concentrations of statins.[30] Thus, when statins are administered concomitantly with other drugs that may also be toxic to the myocyte or that increase the plasma concentration of the statin drug to a toxic concentration, the likelihood of myopathy increases. Since statins are prescribed on a long-term basis, it is likely that a patient may receive a drug during the course of statin therapy that may interact with the statin. A report[31] based on data from two clinical trials found that approximately half of patients undergoing statin therapy also received drugs metabolized via the same metabolic pathway as the statins.

The mechanism by which drug interactions with statins may precipitate rhabdomyolysis involves their physicochemical property of lipid or water solubility.[32] Table 1[29,33,34] presents a comparison of the pharmacokinetic properties of the six statins currently available in the US. Pravastatin is the most water-soluble of the six statins. Even though it undergoes some hepatic and enteric metabolism, its main route of excretion is via the kidneys.[31] On the other hand, atorvastatin, cerivastatin, fluvastatin, lovastatin, and simvastatin are more lipophilic agents,[35] thus crossing the renal tubule walls readily. Consequently, they undergo hepatic and enteric metabolism via the cytochrome P450 enzyme system.[31] Within this system, the CYP3A4 isoenzyme, the metabolic pathway for most drugs currently available in clinical practice,[36] is responsible for the metabolism of the statins. The pharmacokinetic interaction of four of the statin drugs (atorvastatin, cerivastatin, lovastatin, simvastatin) with other agents is the result of inhibition of this isoenzyme, which consequently leads to increased concentrations of the statins and greater risk of myopathy and rhabdomyolysis. Several case reports of myopathy and rhabdomyolysis have appeared in the literature, with lovastatin[37-63] and simvastatin[16,64-83] used either as monotherapy or in combination with other inhibitors of the CYP3A4 system. Relatively fewer reports of myopathy or rhabdomyolysis have appeared for combination therapy with atorvastatin[84,85] or cerivastatin,[86-88] perhaps because they are not metabolized as extensively by the CYP3A4 system,[31] and also because they are newer agents and thus relatively less experience exists with their use. As of October 2000, there were no published reports of rhabdomyolysis with atorvastatin or cerivastatin monotherapy, but a few reports do exist of combination therapy of these statins with gemfibrozil[84,86,87]

and cyclosporine.[85,88] The product literature[89,90] for these agents carry a class warning regarding the possibility of rhabdomyolysis. In addition, the combined use of cerivastatin with gemfibrozil is contraindicated.[89] Fluvastatin undergoes metabolism mainly via the CYP2C9 system,[33] and thus has a different spectrum of interactions than do the statins metabolized via the CYP3A4 system. No reports of myopathy or rhabdomyolysis have appeared in the literature in patients receiving fluvastatin alone or concurrently with other agents.[37,91,92] Cerivastatin is metabolized via a dual metabolic pathway: the CYP3A4 and the CYP2C8 isoenzymes. It has been suggested[86] that because of this dual pathway, cerivastatin does not interact significantly with warfarin, cimetidine, erythromycin, or digoxin. Pravastatin is a weak inducer of CYP3A4, and thus has minimum potential for pharmacokinetic drug interactions.[93] The major drug classes and the specific drugs within these classes that have been reported to precipitate rhabdomyolysis as a result of interactions with the statins are listed in Table 2.

The interaction of the statins with fibrates such as gemfibrozil and fenofibrate is particularly important, since hyperlipidemic patients are often treated with multiple lipid-lowering agents. In addition to various reports of skeletal muscle toxicity manifested as myopathy with or without rhabdomyolysis with either fibric acid derivatives or statins alone, there have been several reports[15,38,94] of this condition as a result of combination therapy, suggesting that these effects may be additive. One report[95] indicates a frequency of myopathy of about 1% in patients taking statins and fibrates concurrently. In an earlier report,[96] 5% of patients (4 of 80) developed myopathy when lovastatin was combined with gemfibrozil, compared with 0.2% of patients who were not undergoing either gemfibrozil or immunosuppressant therapy. The mechanism of the interaction between statins and fibrates is not completely understood. Some suggest[11,33] that the interaction might be pharmacodynamic rather than pharmacokinetic in nature. Others believe,[38] however, that fibrates, such as gemfibrozil, may impair liver function, resulting in diminished extraction of the statin from the portal circulation, and thus creating high concentrations of the statin with subsequent myopathy and rhabdomyolysis. Diminished renal function in patients with myopathy may potentiate the likelihood of developing rhabdomyolysis, since fibric acid derivatives are excreted mainly via the kidneys.[97] Some reports[15,39,98] of rhabdomyolysis have also appeared for the combination of lovastatin with niacin, possibly due to impairment in hepatocyte function by niacin, which leads to higher drug concentrations of the statin.

Another important drug interaction that predisposes patients to myopathy and rhabdomyolysis is that between the statins and cyclosporine. The incidence of myopathy with this combination of drugs has been reported to be about 30%.[96] Immunosuppression with cyclosporine in patients who have received renal and cardiac transplants is important. However, these patients are frequently undergoing concomitant statin therapy to impede the progression of graft atherosclerosis.[40] It is believed that cyclosporine reduces the clearance of statins, thereby causing an increase

Table 2. Drugs Associated with Rhabdomyolysis Due to Interaction with Statins

Drug Class	Specific Drugs
Antibiotics	
macrolides	erythromycin clarithromycin azithromycin
other	fusidic acid
Anticoagulants	warfarin dicoumarol
Antidepressants	nefazodone
Azole antifungals	ketoconazole itraconazole
Bile acid resins	cholestyramine
Calcium-channel blockers	mibefradil
Cardiac glycosides	digoxin
Fibrates	gemfibrozil
Immunosuppressants	cyclosporine
Skeletal muscle relaxants	chlorzoxazone
Vitamins	niacin

Table 1. Comparison of the Pharmacokinetic Properties of Statins[29,33,34]

Characteristic	Lovastatin	Pravastatin	Simvastatin	Atorvastatin	Fluvastatin	Cerivastatin
Maximal dose (mg/d)	80	40	80	80	40	0.8
Oral dose absorbed (%)	30	34	60–85	30	98	98
Effect of food on drug absorption	increased	decreased	none	none	negligible	none
Optimal administration time	with meals (am & pm)	bedtime	evening	evening	bedtime	evening
Plasma half-life (h)	1.1–2.9	1.3–2.8	1.9–3	15–30	0.5–3.1	1.7–3.1
Renal elimination of absorbed drug (%)	10	20–48	13	2	5–6	30–33
Hepatic extraction of absorbed drug (%)	62–70	46–66	78–87	70	68	not available
Lipophilicity	lipophilic	hydrophilic	lipophilic	lipophilic	hydrophilic	lipophilic
Mechanism of hepatic metabolism	CYP3A4	sulfation	CYP3A4	CYP3A4	CYP2C9	CYP3A4, CYP2C8

in serum concentrations of the statins or their metabolites. In addition, cyclosporine may reduce the first-pass effect of the statins and consequently increase their bioavailability. Therefore, careful titration of the statins in these patients is critical, with an emphasis on maintaining the lowest possible effective dose.[64] If rhabdomyolysis has occurred and cyclosporine is subsequently withheld, the time to restart the drug to continue with immunosuppression depends on its serum concentrations and the rate of recovery of kidney function.[99] The concurrent use of agents such as fibrates, macrolide antibiotics, or azole antifungals should also be strongly avoided in these patients, since these drugs further increase the likelihood of muscle injury.

Erythromycin,[40,41,56-58] clarithromycin,[60,61,81] and azithromycin[60] are macrolide antibiotics that have also been reported to precipitate rhabdomyolysis in patients who are undergoing concurrent statin therapy. This class of antibiotics is commonly prescribed to treat patients with respiratory tract and dermatologic infections, especially in patients who are allergic to penicillins and cephalosporins. Clinicians should be careful when administering these drugs together, since the potential exists for drug interaction–induced muscle injury. In 1988, Corpier et al.[41] reported the first case of rhabdomyolysis as a result of interaction of a statin with erythromycin. Since then, eight additional case reports of rhabdomyolysis involving the combined use of macrolide antibiotics with statin therapy appear in the literature (4 involving erythromycin, 3 reports with clarithromycin, 1 with azithromycin). Both erythromycin and clarithromycin can increase the concentration of the statins by inhibiting the cytochrome P450 enzyme system, explaining their role in development of rhabdomyolysis. Azithromycin is not metabolized via this pathway, and its role in precipitating rhabdomyolysis in patients concurrently receiving statin therapy is yet to be elucidated.

Cases of rhabdomyolysis have also been reported in patients undergoing statin therapy who are also receiving the azole derivative antifungals ketoconazole[80] and itraconazole.[54,65,78] The azole antifungals inhibit the CYP3A4 isoenzyme system, leading to increased plasma concentrations of the statins when coadministered.[33] With the increase in direct-to-consumer advertisements for treatment of conditions such as nail fungus, combined therapy of the azole antifungals with the statins may be seen more frequently in clinical practice. To prevent the possibility of this drug interaction, clinicians should consider suspending statin therapy for the duration of treatment or using an alternative antifungal agent.[65] If the interaction of the statins with the azole derivative antifungals is a class effect, then care should also be taken when administering the statins with other azole derivatives such as fluconazole, miconazole, and clotrimazole.

There are various precautionary measures that clinicians must take to reduce the adverse sequelae associated with statin-induced rhabdomyolysis. Counseling patients appropriately on the signs and symptoms of rhabdomyolysis will help with early intervention. Ascertaining the patient's complete medication history, including drugs prescribed by other physicians who may be caring for the patient, is also important in preventing drug interactions with the statins that may lead to rhabdomyolysis. In addition, it is imperative for clinicians to diligently conduct liver function tests at the commencement of statin therapy, at six and 12 weeks, and then semiannually thereafter, or after a dosage increase. A decrease in statin dosage or stopping therapy altogether may become necessary in patients with persistent elevations in liver transaminases greater than three times the normal range.[100]

Prescribers considering combination therapy must be able to justify the need for the presence of the interacting medications, and be especially alert during the initial months of combined therapy or during upward dosage titration of any of the interacting drugs. In addition, in patients who have experienced prior statin-induced myopathy, reintroduction of the same or a different statin may be an appropriate option; however, in such cases, the lowest therapeutic dosage of the statin should be used initially and any potentially interacting drugs should be avoided. Except in patients who are at high risk for developing rhabdomyolysis, periodic measurement of CK is not advised because concentrations rise rapidly after the sudden development of rhabdomyolysis.

Clinicians should also be alert for certain risk factors that may increase the likelihood of patients undergoing statin therapy developing rhabdomyolysis. These include advanced age; chronic renal insufficiency; severe infections; metabolic, endocrine, or electrolyte disorders; debilitated status; surgery; uncontrolled seizures; or treatment with large doses of statins.[87,101] Care should also be taken in patients with hepatic function impairment. Renal clearance may become more important in drug elimination in these patients, and if they also have some degree of preexisting renal insufficiency, this may further compound the problem of toxic drug concentrations.[42]

A literature search for case reports of statin-induced rhabdomyolysis was conducted using MEDLINE (January 1985–October 2000). Table 3 lists the frequency of occurrence of rhabdomyolysis with monotherapy and combination therapy for each of the six statins, and selected information extracted from the case reports is presented in Table 4.[16,38-88,98,102-109] In all the cases, the statin and/or the suspect-

Table 3. Frequency of Case Reports in the Literature Associated with Statin Monotherapy and Combination Therapy

Statin	Monotherapy	Combination Therapy	Total
Atorvastatin	0	2	2
Cerivastatin	0	3	3
Fluvastatin	0	0	0
Lovastatin	5	30	35
Pravastatin	5	5	10
Simvastatin	5	19	24

Table 4. Case Reports of Rhabdomyolysis Caused by Statin Monotherapy or Combination Therapy

Reference	Age (y)/ Gender	Statin	Statin Dose (mg/d)	Duration[a]	Concomitant Medications[b]	Time to Event[c]	Peak CK Reported (U/L)	Time to Peak CK (d)[d]	Serum Creatinine (mg/dL)[e]	Treatment[f]	Time to Resolve	Outcomes
Pierce et al. (1990)[38]	79/W	lova	40	19 d	gemfibrozil	19 d	148 000	5	1.4 (base) 2.9 (eval)	N/R	7 wk	R
	49/M	lova	80	N/R	gemfibrozil	N/R	45 000	N/R	3.9 (eval)	N/R	N/R	N/R
	72/W	lova	40	1 mo	gemfibrozil	1 mo	25 200	N/R	1.5 (base) 2.2 (eval)	hydration	5 d	R
Reavan and Witztum (1988)[98]	43/M	lova	40	3 y	nicotinic acid	10 mo	233 000	N/R	NR	hydration	2 wk	R
Norman et al. (1988)[39]	53/M	lova	80	10 mo	cyclosporine nicotinic acid	5 mo	178 000	1	0.8 (base) 6.1 (eval)	hemodialysis	4 wk	R
East et al. (1988)[40]	39/M	lova	40	6 wk	cyclosporine gemfibrozil	N/R	29 920	N/R	2.0 (eval)	hydration	3–5 d	R
	47/W	lova	40	9 mo	cyclosporine gemfibrozil	N/R	14 140	N/R	2.0 (eval)	hydration	3–5 d	R
	36/M	lova	80	9 mo	cyclosporine	N/R	8920	N/R	9.7 (eval)	hydration	3–5 d	R
	46/M	lova	80	16 mo	cyclosporine erythromycin	N/R	23 832	N/R	2.8 (eval)	hydration	3–5 d	R
Corpier et al. (1988)[41]	46/M	lova	80	15 mo	cyclosporine erythromycin	2 wk	28 832	0	1.7 (base) 2.8 (eval)	saline diuresis	N/R	R
	36/M	lova	80	9 mo	cyclosporine	9 mo	8920	6	2.0 (base) 5.9 (eval)	hydration, mannitol diuresis, bicarbonate	2 wk	R
Manoukian et al. (1990)[42]	59/W	lova	40	2 wk	none	N/A	176 500	12	0.3 (eval)	hemodialysis	14 d	R,D
Wallace and Mueller (1992)[43]	60/M	lova	40	14 mo	none	N/A	2840	3	1.7 (base) 7.5 (eval)	hemodialysis	12 d	R
Fernandez-Zatarain et al. (1994)[44]	65/W	lova	20	2 wk	none	N/A	>100 000	N/R	4.2 (eval)	hydration, mannitol, furosemide, bicarbonate, hemodialysis	3 mo	R
Beisenbach et al. (1996)[45]	67/M	lova	20	5 y	none	N/A	9470	0	9.0 (base) 9.8 (eval)	hemodialysis	10 d	PR
Chu et al. (1997)[46]	55/W	lova	40	26 d	none	N/A	8996	N/R	1.9 (eval)	hemodialysis	21 d	R
Abdul-Ghaffar and el-Sonbaty (1995)[47]	55/W	lova	80	9 mo	gemfibrozil	8 wk	1906	N/R	1.0 (eval)	N/R	10 d	R
Marais and Larson (1990)[48]	63/M	lova	40	8 mo	gemfibrozil	2 wk	2100	0	2.0 (base) 3.0 (eval)	hemodialysis	3 mo	PR
Goldman et al. (1989)[49]	68/W	lova	40	1 mo	gemfibrozil	N/R	43 600	N/R	2.4 (eval)	corticosteroids	29 d	R

CK = creatine kinase; lova = lovastatin; N/A = not applicable; N/R = not reported; PR = partial recovery; R = recovery; R,D = recovery followed shortly by death due to unrelated cause.

[a]Duration of statin therapy prior to onset of rhabdomyolysis.

[b]Other concomitant or immediately discontinued medications that may have interacted with the statin to cause rhabdomyolysis.

[c]Time between addition of last concomitant medication or an increase in dose of statin and onset of rhabdomyolysis. Duration and Time to Event are the same if statin therapy was most recent addition or was started together with concomitant medication.

[d]Time for CK to peak since hospitalization; 0 means that the highest CK concentration was found on admission.

[e]Serum creatinine concentration on baseline (base) or first evaluation (eval) of symptoms of rhabdomyolysis.

[f]Treatment other than withholding of suspect medications.

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Table 4. Case Reports of Rhabdomyolysis Caused by Statin Monotherapy or Combination Therapy (continued)

Reference	Age (y)/ Gender	Statin	Statin Dose (mg/d)	Duration[a]	Concomitant Medications[b]	Time to Event[c]	Peak CK Reported (U/L)	Time to Peak CK (d)[d]	Serum Creatinine (mg/dL)[e]	Treatment[f]	Time to Resolve	Outcomes
Kogan and Orenstein (1990)[50]	79/W	lova	20	21 d	gemfibrozil	21 d	148 000	5	N/R	supportive	16 d	R
De Alava et al. (1994)[51]	48/M	lova	40	3 d	cyclosporine gemfibrozil	3 d	14 100	0	6.2 (eval)	hemodialysis	4 wk	R
Knoll et al. (1993)[52]	64/M	lova	60	N/R	niacin gemfibrozil	4 wk	357 900	N/R	5.6 (eval)	hydration, hemodialysis	4 wk	R
Hill and Bilbao (1999)[53]	54/M	lova	20	12 mo	niacin	N/R	121 000	N/R	N/R	corticosteroids	N/R	R
Lees and Lees (1995)[54]	63/W	lova	80	10 y	niacin itraconazole	2 wk	47 100	4	N/R	coenzyme Q	18 d	R
Chrysanthopolous and Kounis (1992)[55]	31/M	lova	40	1 mo	cholestyramine	1 mo	N/R	N/R	N/R	hydration	2 wk	R
	42/M	lova	40	2 wk	cholestyramine	2 wk	N/R	N/R	1.0 (base) 4.5 (eval)	hemodialysis	2 mo	R
Spach et al. (1991)[56]	68/W	lova	40	7 mo	erythromycin	15 d	26 400	1	3.5 (base) 4.2 (eval)	alkaline fluid, diuretic therapy, dialysis refused	N/A	D
Ayanian et al. (1988)[57]	65/M	lova	60	3 mo	erythromycin	13 d	76 000	2	N/R	hydration, furosemide	6 wk	R
Wong et al. (1998)[58]	73/M	lova	20	7 y	erythromycin	15 d	4235	0	1.8 (base) 6.1 (eval)	furosemide	10 d	R
Alejandro and Petersen (1994)[59]	57/M	lova	80	3 y	cyclosporine	3 wk	41 754	0	1.5 (base) 11.3 (eval)	hydration, hemodialysis	3 wk	R
Grunden and Fisher (1997)[60]	76/W	lova	40	5 y	clarithromycin	12 d	4952	2	2.3 (eval)	hydration, saline diuresis, bicarbonate	20 d	R
	51/M	lova	40	5 y	cholestyramine azithromycin	6 d	1273	0	2.0 (base)	hydration, saline diuresis, bicarbonate	3 d	R
Landesman et al. (1999)[61]	57/M	lova	40	N/R	gemfibrozil clarithromycin	3 wk	80 920	0	1.7 (base) 4.5 (eval)	hydration, mannitol, bicarbonate, hemodialysis	10 d	R
Dallaire and Chamberland (1994)[62] (French)[g]	72/M	lova	40	9 mo	danazol	15 d	20 816	3	1.7 (base) 4.5 (eval)	hydration, saline diuresis, mannitol, bicarbonate	14 d	R
Hermida et al. (1997)[63] (Spanish)[g]	62/N/R	lova	40	N/R	cyclosporine	N/R	5620	0	N/R	N/R	1 mo	N/R
Berland et al. (1991)[16]	67/W	simva	10	3 mo	gemfibrozil	3 mo	20 000	0	6.7 (eval)	hemodialysis	1 mo	R
Weise and Possidente (2000)[64]	55/W	simva	20	7 mo	cyclosporine	7 mo	10 157	0	N/R	N/R	N/A	D

CK = creatine kinase; D = death; lova = lovastatin; N/A = not applicable; N/R = not reported; R = recovery; simva = simvastatin.
[a]Duration of statin therapy prior to onset of rhabdomyolysis.
[b]Other concomitant or immediately discontinued medications that may have interacted with the statin to cause rhabdomyolysis.
[c]Time between addition of last concomitant medication or an increase in dose of statin and onset of rhabdomyolysis. Duration and Time to Event are same if statin therapy was most recent addition or was started together with concomitant medication.
[d]Time for CK to peak since hospitalization; 0 means that the highest CK concentration was found on admission.
[e]Serum creatinine concentration on baseline (base) or first evaluation (eval) of symptoms of rhabdomyolysis.
[f]Treatment other than withholding of suspect medications.
[g]Information from foreign-language journals was extracted primarily from the abstract, tables, or retrievable information from the text; blank entries indicate irretrievable information.

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Table 4. Case Reports of Rhabdomyolysis Caused by Statin Monotherapy or Combination Therapy (continued)

Reference	Age (y)/ Gender	Statin	Statin Dose (mg/d)	Duration[a]	Concomitant Medications[b]	Time to Event[c]	Peak CK Reported (U/L)	Time to Peak CK (d)[d]	Serum Creatinine (mg/dL)[e]	Treatment[f]	Time to Resolve	Outcomes
Horn (1996)[65]	74/M	simva	40	N/R	itraconazole	3 wk	22 800 000	0	N/R	hydration, activity restriction	N/R	N/R
Deslypere and Vermeulen (1991)[66]	53/M	simva	40	22 mo	none	N/A	1899	0	N/R	N/R	14 d	R
Bertrand et al. (1992)[67] (French)[g]	68/W	simva	20	2 mo	none	N/A	3100	0	N/R	N/R	1 mo	R
Chariot et al. (1993)[68]	63/W	simva	20	8 mo	none	N/A	20 000	0	N/R	N/R	21 d	PR
Alvarez et al. (1999)[69]	62/M	simva	10	7 y	none	N/A	14 746	4	3.9 (eval)	hemodialysis, furosemide, dopamine, mannitol	45 d	R
Tal et al. (1997)[70]	52/W	simva	40	11 wk	gemfibrozil	21 d	13 580	0	1.0 (base) 1.7 (eval)	hydration, prednisone	7 d	R
Van Puijenbroek et al. (1996)[71]	62/M	simva	20	N/R	gemfibrozil	N/R	34 782	0	5.8 (eval)	supportive	N/R	R
	50/W	simva	80	2.5 y	gemfibrozil	3 mo	8280	0	N/R	supportive	N/R	R
Blaison et al. (1992)[72] (French)[g]	60/M	simva	20	5 mo	cyclosporine	5 mo	7310	0	1.6 (eval)	N/R	N/R	R
Mogyorosi et al. (1999)[73]	82/M	simva	20	18 mo	warfarin	7 d	>785	1	1.5 (base) 3.4 (eval)	hydration, saline diuresis, urine alkalization	5 d	R
Bizarro et al. (1992)[74]	68/W	simva	10	3 mo	digoxin dicoumarol	3 mo	25 600	N/R	2.5 (eval)	N/R	30 d	R
Dromer et al. (1992)[75] (French)[g]	78/W	simva	10	10 mo	fusidic acid	N/R	100 000	0	N/R	N/R	15 d	R
Jacobson et al. (1997)[76]	44/M	simva	40	19 wk	nefazodone	1 mo	6081	0	0.9 (eval)	hydration with alkalinized fluids	3 wk	R
Bielecki et al. (1999)[77] (German)[g]	73/W	simva	30	N/R	chlorzoxazone		23 990	3	2.0 (eval)	hydration, forced diuresis		R
Segaert et al. (1996)[78]	70/M	simva	40	3 y	cyclosporine itraconazole	2 wk	14 000	0	1.8 (base) 2.2 (eval)	N/R	1 mo	R
Schmassmann-Suhijar et al. (1998)[79]	83/W	simva	20	1 y	mibefradil	4 wk	50 125	0	N/R	hemodialysis, physiotherapy	1 mo	PR
Gilad and Lampl (1999)[80]	73/M	simva	20	7 mo	ketoconazole	3 wk	43 900	0	N/R	N/R	3 wk	R
	54/W	simva	20	1 y	ketoconazole	4 wk	31 200	0	N/R	N/R	1 wk	R
Meier et al. (1995)[81]	58	simva	20	4 y	cyclosporine clarithromycin	2 wk	19 712	0	2.7 (eval)	hydration	1 wk	R
(German)[g]	58	simva	40	N/R	cyclosporine		7400	0	2.5 (eval)	hydration	1 wk	R

CK = creatine kinase; N/A = not applicable; N/R = not reported; PR = partial recovery; R = recovery; simva = simvastatin.
[a]Duration of statin therapy prior to onset of rhabdomyolysis.
[b]Other concomitant or immediately discontinued medications that may have interacted with the statin to cause rhabdomyolysis.
[c]Time between addition of last concomitant medication or an increase in dose of statin and onset of rhabdomyolysis. Duration and Time to Event are same if statin therapy was most recent addition or was started together with concomitant medication.
[d]Time for CK to peak since hospitalization; 0 means that the highest CK concentration was found on admission.
[e]Serum creatinine concentration on baseline (base) or first evaluation (eval) of symptoms of rhabdomyolysis.
[f]Treatment other than withholding of suspect medications.
[g]Information from foreign-language journals was extracted primarily from the abstract, tables, or retrievable information from the text; blank entries indicate irretrievable information.

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ed interacting drug were withdrawn. Common treatments included hydration, diuresis, alkalization of urine, and hemodialysis. Coenzyme Q and corticosteroids were seldom used. The most common complication was acute renal failure, and most patients recovered completely from it. In most cases, the statin was gradually reintroduced shortly after recovery, without any consequences. Except in organ transplant patients, in whom it was important to continue

Table 4. Case Reports of Rhabdomyolysis Caused by Statin Monotherapy or Combination Therapy (continued)

Reference	Age (y)/ Gender	Statin	Statin Dose (mg/d)	Duration[a]	Concomitant Medications[b]	Time to Event[c]	Peak CK Reported (U/L)	Time to Peak CK (d)[d]	Serum Creatinine (mg/dL)[e]	Treatment[f]	Time to Resolve	Outcomes
Wombolt et al. (1999)[82]	47/M	simva	40	2 y	cyclosporine mibefradil	1 mo	255 862	3	2.7 (base) 4.8 (eval)	hemodialysis	6 wk	R
Franc et al. (1997)[83]	51	simva	20	N/R	none	N/R	2200	0	N/R	N/R		R
	51	prava	10	N/R	none		4300	30	N/R	N/R		R
(French)[g]	37	prava	20	N/R	fenofibrate				N/R	N/R		R
Perault et al. (1993)[102] (French)[g]	72/W	prava	10	N/R	none		14 300	5	N/R	N/R		
Rosenberg et al. (1995)[103]	56/M	prava	20	N/R	none	N/A	3090	0	1.1 (base) 8.8 (eval)	saline diuresis, furosemide, mannitol, bicarbonate	N/R	R
Takei and Chiba (1999)[104]	72/W	prava	20	2 y	none	N/A	4400	0	N/R	N/R	3 wk	R
Hino et al. (1996)[105]	63/W	prava	10	N/R	none	N/A	8280	0	1.0 (eval)	hydration	1 wk	R
Colombo et al. (1996)[106] (Italian)[g]	65/W	prava	10		bezafibrate		16 100		3.4 (eval)	hydration		R
Decoulx et al. (1993)[107] (French)[g]	61/W	prava	N/R	3 wk	clofibrate	3 wk	682	0	N/R	N/R	10 d	R
Alderman (1999)[108]	74/M	prava	20	N/R	nefazodone	3 d	877	3	N/R	N/R	17 d	R
Raimondeau et al. (1992)[109] (French)[g]	55/M	prava	10	2 d	fenofibrate	2 d	3666	2	N/R	N/R	few days	R
Pogson et al. (1999)[86]	74/W	ceriva	0.3	3 wk	gemfibrozil	3 wk	16 094	1	0.9 (base) 1.2 (eval)	hydration, diuretics	N/R	R
Bermingham et al. (2000)[87]	64/W	ceriva	0.3	3 wk	gemfibrozil	3 wk	>16 000	0	0.6 (base) 0.6 (eval)	hydration, urine alkalization	11 d	R
Rodriguez et al. (2000)[88]	52/W	ceriva	0.1	3 wk	cyclosporine	3 wk	12 615	0	0.1 (eval)	saline diuresis, bicarbonate	10 d	R
Duell et al. (1998)[84]	43/W	atorva	20	3 wk	gemfibrozil	3 wk	4633	0	N/R	hydration	14 d	R
Maltz et al. (1999)[85]	40/W	atorva	10	2 mo	cyclosporine	2 mo	1846	2	2.2 (eval)	saline hydration, bicarbonate	4 d	R

atorva = atorvastatin; ceriva = cerivastatin; CK = creatine kinase; N/A = not applicable; N/R = not reported; prava = pravastatin; R = recovery; simva = simvastatin.
[a]Duration of statin therapy prior to onset of rhabdomyolysis.
[b]Other concomitant or immediately discontinued medications that may have interacted with the statin to cause rhabdomyolysis.
[c]Time between addition of last concomitant medication or an increase in dose of statin and onset of rhabdomyolysis. Duration and Time to Event are same if statin therapy was most recent addition or was started together with concomitant medication.
[d]Time for CK to peak since hospitalization; 0 means that the highest CK concentration was found on admission.
[e]Serum creatinine concentration on baseline (base) or first evaluation (eval) of symptoms of rhabdomyolysis.
[f]Treatment other than withholding of suspect medications.
[g]Information from foreign-language journals was extracted primarily from the abstract, tables, or retrievable information from the text; blank entries indicate irretrievable information.

immunosuppression as well as statin therapy, the interacting drugs were not reintroduced.

Summary

The HMG-CoA reductase inhibitors play an essential role in the management of dyslipidemic patients. Rhabdomyolysis is a rare but important adverse event associated with this class of drugs that deserves attention. The syndrome is caused by injury to skeletal muscle cells and the consequent release of cellular contents such as CK, creatinine, potassium, and myoglobin into systemic circulation. This can eventually lead to complications such as cardiac arrest or arrhythmias, acute renal failure, or compartment syndrome. The diagnosis is made primarily by measurement of serum CK concentrations and the presence of myoglobin in the urine. Treatment is focused on correcting hypotension, hypovolemia, and dehydration, and preventing the complications associated with acute renal failure. Administration of large volumes of fluid along with a diuretic is an important part of therapy. The statin drugs by themselves are capable of inducing rhabdomyolysis. However, the occurrence increases greatly when statins are administered with other agents that are toxic to skeletal muscle cells or that inhibit the metabolism of statins and thus increase their plasma concentration. Clinicians should counsel patients appropriately regarding symptoms of muscle injury, monitor liver function periodically, and exercise caution when prescribing statins to high-risk patients or when prescribing other medications that interact with the statins. To date, reports of statin-induced rhabdomyolysis, either as monotherapy or in combination with other agents, appear in the literature for all the statins except fluvastatin. It is important that clinicians be aware of the potential of statin-induced rhabdomyolysis, since early intervention may avoid potentially life-threatening complications of acute renal failure and cardiac arrest.

Mohamed A Omar MSc, PharmD Student, College of Pharmacy, University of Texas at Austin, Austin, TX

James P Wilson PhD, Associate Professor, College of Pharmacy, University of Texas at Austin

Tamara S Cox PharmD, at time of writing, PharmD Student, College of Pharmacy, University of Texas at Austin

Reprints: Mohamed A Omar MSc, Pharmacy Practice and Administration, College of Pharmacy, Rm. 2.212, University of Texas at Austin, Austin, TX 78712-1157, FAX 512/471-8762, E-mail maomar@mail.utexas.edu

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EXTRACTO

OBJETIVO: Repasar la rabdomiólisis y discutir el papel de los inhibidores de la reductasa HMG-CoA (estatinas) y sus interacciones con otros agentes en precipitar esta condición. Además, se presentan informes de casos de rabdomiólisis inducida por estatinas.

FUENTES DE INFORMACIÓN: Se obtuvo literatura clínica relevante utilizando MEDLINE (enero 1985– octubre 2000). Los siguientes términos fueron utilizados para la búsqueda: rabdomiólisis, eventos adversos, interacciones de fármacos, estatinas e inhibidores de la reductasa HMG-CoA.

DISCUSIÓN: La rabdomiólisis ocure cuando daño muscular extenso resulta en la liberación del contenido celular a la circulación sistémica. Las complicaciones principales incluyen: fallo renal agudo, anormalidades cardíacas, y el síndrome de compartimiento. El tratamiento de rabdomiólisis es de soporte, con la finalidad primaría de prevenir complicaciones renales y cardíacas. La monoterapia o terapia en combinación con estatinas podría resultar en miopatía que rara vez progresa a rabdomiólisis. El mecanismo de la interacción de fármacos con las estatinas envuelve su propiedad de solubilidad en lípidos o en agua. Esta característica determina el grado de metabolismo entero-hepático o renal de las estatinas. Todas las estatinas con excepción de provastatina experimentan metabolismo por el sistema enzimático del citocromo P450. Otros agentes farmacológicos que también son metabolizados por esta vía, potencialmente podrían interaccionar con las estatinas y ocasionar rabdomiólisis. El riesgo de rabdomiólisis inducido por estatinas aumenta significativamente cuando las estatinas son utilizadas concurrentemente con fármacos tales como los "fibrates," ciclosporina, antibióticos macrólidos, y los antimicóticos de tipo azol.

CONCLUSIONES: La rabdomiólisis es un evento adverso raro, pero clínicamente importante, de la monoterapia o terapia en combinación con estatinas. Un entendimiento completo de esta condición podría ayudar a prevenir o minimizar resultados de salud adversos en pacientes que están recibiendo tratamiento con estatinas.

Brenda R Morand

RÉSUMÉ

OBJECTIF: Réviser les connaissances sur la rhabdomyolyse et discuter de l'implication des inhibiteurs de l'HMG-CoA réductase (statines) et de leurs interactions avec d'autres agents dans la survenue de cette condition. Des rapports de cas de rhabdomyolyse associée aux statines sont aussi présentés.

REVUE DE LITTÉRATURE: Une recherche MEDLINE (janvier 1985–octobre 2000) a permis d'accéder à de la documentation clinique pertinente. Les mots clé suivants ont été utilisés: rhabdomyolysis, adverse events, drug interactions, statins, et HMG-CoA reductase inhibitors.

DISCUSSION: La rhabdomyolyse se produit quand un dommage important aux muscles conduit à la libération du contenu des cellules musculaires dans la circulation systémique. Les complications majeures incluent l'insuffisance rénale aiguë, des anormalités cardiaques, et le syndrome du compartiment. L'objectif principal du traitement de support de la rhabdomyolyse est de prévenir les complications rénales et cardiaques. Une thérapie avec une statine seule ou en association peut causer une myopathie, laquelle progresse rarement vers la rhabdomyolyse. Le mécanisme des interactions médicamenteuses avec les statines tient compte de leur propriété de solubilité dans l'eau ou dans les lipides. Cette caractéristique détermine le degré de métabolisme rénal, hépatique, ou intestinal des statines. Toutes les statines à l'exception de la pravastatine subissent un métabolisme impliquant le système enzymatique du cytochrome P450. D'autres agents pharmacologiques également métabolisés par cette voie peuvent interagir avec les statines et causer une rhabdomyolyse. Le risque qu'une statine cause une rhabdomyolyse est augmenté de façon significative quand elle est utilisée concomitamment avec des médicaments tels les fibrates, la cyclosporine, les antibiotiques de la classe des macrolides, et les antifongiques de la classe des azoles.

CONCLUSIONS: La rhabdomyolyse est un effet indésirable rare mais cliniquement important des statines utilisées seules ou en association. Une compréhension approfondie de cette condition peut aider à prévenir ou minimiser les effets néfastes de ce problème sur la santé des patients recevant une thérapie à base de statines.

Marie Larouche