MEDICAL EDUCATION SYSTEMS

Rhabdomyolysis

Medical Education Systems, Inc

TOLL FREE 1-877-295-4719
FAX (619) 295-0252
EMAIL: Info@mededsys.com
www.mededsys.com
P.O Box 81831 San Diego, CA 92138-3939

Incidence of Hospitalized Rhabdomyolysis in Patients Treated With Lipid-Lowering Drugs

Learning Objectives

- Define rhabdomyolysis and identify its signs and symptoms
- Identify the impact that lipid-lowering agents have on rhabdomyolysis
- Identify the risks and benefits of prescribing Lipid-lowering agents
- Identify the recognized treatment protocols for rhabdomyolysis

ABSTRACT

Context Lipid-lowering agents are widely prescribed in the United States. Reliable estimates of rhabdomyolysis risk with various lipid-lowering agents are not available.

Objective To estimate the incidence of rhabdomyolysis in patients treated with different statins and fibrates, alone and in combination, in the ambulatory setting.

Design, Setting, and Patients Drug-specific inception cohorts of statin and fibrate users were established using claims data from 11 managed care health plans across the United States. Patients with at least 180 days of prior health plan enrollment were entered into the cohorts between January 1, 1998, and June 30, 2001. Person-time was classified as monotherapy or combined statin-fibrate therapy.

Main Outcome Measure Incidence rates of rhabdomyolysis per 10 000 person-years of treatment, number needed to treat, and relative risk of rhabdomyolysis.

Results In 252 460 patients treated with lipid-lowering agents, 24 cases of hospitalized rhabdomyolysis occurred during treatment. Average incidence per 10 000 person-years for monotherapy with atorvastatin, pravastatin, or simvastatin was 0.44 (95% confidence interval [CI], 0.20-0.84); for cerivastatin, 5.34 (95% CI, 1.46-13.68); and for fibrate, 2.82 (95% CI, 0.58-8.24). By comparison, the incidence during unexposed person-time was 0 (95% CI, 0-0.48; $P = .056$). The incidence increased to 5.98 (95% CI, 0.72-216.0) for combined therapy of atorvastatin, pravastatin, or simvastatin with a fibrate, and to 1035 (95% CI, 389-2117) for combined cerivastatin-fibrate use. Per year of therapy, the number needed to treat to observe 1 case of rhabdomyolysis was 22 727 for statin monotherapy, 484 for older patients with diabetes mellitus who were treated with both a statin and fibrate, and ranged from 9.7 to 12.7 for patients who were treated with cerivastatin plus fibrate.

David J. Graham, MD, MPH; Judy A. Staffa, PhD; Deborah Shatin, PhD; Susan E. Andrade, ScD; Stephanie D. Schech, MPH; Lois La Grenade, MD, MPH; Jerry H. Gurwitz, MD; K. Arnold Chan, MD, ScD; Michael J. Goodman, PhD; Richard Platt, MD, MSc

Conclusions Rhabdomyolysis risk was similar and low for monotherapy with atorvastatin, pravastatin, and simvastatin; combined statin-fibrate use increased risk, especially in older patients with diabetes mellitus. Cerivastatin combined with fibrate conferred a risk of approximately 1 in 10 treated patients per year.

INTRODUCTION

Disorders of muscle, ranging in severity from asymptomatic creatine kinase elevation to rhabdomyolysis, are among the most discussed adverse effects associated with use of lipid-lowering agents, especially 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins).[1-5] Fibric acid derivatives (fibrates) have also been associated with primary muscle injury, especially when used in combination with a statin.[6-11]

The epidemiology of statin-associated and fibrate-associated myopathy is poorly described, with most attention focused on rhabdomyolysis. Based on review of case reports, older age, female sex, low body mass index, hypothyroidism, diabetes mellitus, and impaired renal or hepatic function have been cited as potential risk factors for rhabdomyolysis,[10-11] but these have not been confirmed by clinical trials or observational studies. Myopathy, defined as a serum creatine kinase level of more than 10 times the upper limit of normal, has been estimated to occur in 0.1% to 0.5% of patients treated with statins during randomized controlled trials.[10] However, the incidence of rhabdomyolysis has not been reliably estimated.

The product labeling for some statins presents incidence estimates for myopathy and rhabdomyolysis combined, although in labeling for other statins the occurrence of rhabdomyolysis is described as rare.[12-13] One epidemiologic study estimated the incidence of myopathy associated with lipid-lowering drugs at 2.3 per 10 000 person-years of treatment and suggested that fibrate use as monotherapy conferred a 5.5-fold increased risk compared with statin use.[14] Another study reported 1 case of rhabdomyolysis among 2935 patients treated concurrently with a statin and fibrate.[15] Two separate analyses, based on case reports submitted to the US Food and Drug Administration, found that reporting of rhabdomyolysis was greater for simvastatin and cerivastatin than for other statins,[16] and that reporting of fatal rhabdomyolysis was 17- to 79-fold greater for cerivastatin than for other statins.[17]

Following the withdrawal of cerivastatin from the US market in August 2001 because of high reporting of rhabdomyolysis in association with its use,[18] we conducted this study to estimate the incidence of rhabdomyolysis in patients treated with statins and fibrates, alone and in combination, in the ambulatory setting.

METHODS

Inception cohorts of statin and fibrate users were established retrospectively from patients enrolled in 11 geographically dispersed US health plans, which included independent practice associations, staff, and group-model health maintenance organizations.[19-20] Each of these health plans provides pharmacy benefits to its enrollees and has automated claims files covering prescription drugs, outpatient medical encounters, hospitalizations, and medical procedures. Using prescription claims, a separate inception cohort was created for each statin (atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, simvastatin) and fibrate (fenofibrate, gemfibrozil) marketed in the United States from January 1, 1998, through June 30, 2001. A patient was entered into an inception cohort if on the date of first prescription with an administered lipid-

lowering drug during the study period, there had been no prescription for the same drug in the preceding 180 days. With drug switching, a patient could contribute exposure to more than 1 cohort.

Person-time on drug was estimated for each patient based on the days supply field from his/her prescription claims. To account for imperfect compliance, gaps of less than 30 days between the expected and actual fill-date of successive prescriptions were counted as exposed days as was the 30-day period following the end of a patient's final prescription within a given cohort. Person-time within each drug cohort was classified as either monotherapy or combined statin-fibrate therapy, to permit separate risk estimates to be obtained for each type of exposure.

To identify potential cases of rhabdomyolysis, medical records were sought and abstracted for selected hospitalizations of inception cohort members occurring during the study period. Hospitalization claims were used to flag the following discharge diagnoses possibly indicative of severe muscle injury: a primary or any secondary discharge diagnosis (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] code) of myoglobinuria (791.3); a primary discharge diagnosis of other disorders of muscle, ligament, and fascia (728.89, includes rhabdomyolysis), myositis (729.1), myopathy (359.4, 359.8, 359.9), polymyositis (710.4), muscle weakness (728.9), musculoskeletal symptoms of the limbs (729.8X), or adverse effect from antihyperlipidemic agents (E942.2); any secondary discharge diagnosis for a muscle-related disorder (any of the previous diagnoses) plus a laboratory claim for serum creatine kinase measurement within 7 days before admission or after discharge; a primary discharge diagnosis of acute renal failure (584 and subcodes) plus any muscle-related secondary diagnosis; or any discharge diagnosis of acute renal failure plus a serum creatine kinase test within 7 days before admission or after discharge.

Information abstracted from each medical record included age, sex, symptom onset, hospital course, outcome, laboratory test results (urine myoglobin, and serum creatine kinase, potassium, alanine aminotransferase, aspartate aminotransferase, creatinine), and drug exposure history (if any). Past history of diabetes mellitus, liver disease, and renal failure was identified from automated claims data.

Medical record abstracts were reviewed by 3 authors (D.J.G., J.A.S., and L.L.G.) who were blinded to statin or fibrate exposure status. A patient was classified as having rhabdomyolysis if medical record review showed that severe muscle injury was present at the time of hospital admission and, in addition, the patient's physician had made a diagnosis of rhabdomyolysis or the patient's creatine kinase level was more than 10 times the upper limit of normal. Severe rhabdomyolysis was defined as the subset of these patients with serum creatine kinase exceeding 10 000 IU/L or with serum creatine kinase of more than 50 times the upper limit of normal.

Relative risk (RR) estimates of rhabdomyolysis adjusted for age, sex, and diabetes mellitus were calculated using Poisson regression. Incidence rates of rhabdomyolysis per 10 000 person-years of treatment with 95% confidence intervals (CIs) and number needed to treat to observe a case of rhabdomyolysis were calculated.[21] All analyses were performed using Stata version 7 (StataCorp, College Station, Tex). This study was approved by institutional review boards for the participating health plans.

RESULTS

A total of 252 460 patients contributed 225 640 person-years of monotherapy for a statin or fibrate and 7300 person-years of combined therapy (Table 1). The proportion of patients with diabetes mellitus was greater among fibrate users, consistent with the use of these agents to treat hypertriglyceridemia.[22] Because usage of fluvastatin and lovastatin was very low, these drugs were excluded from subsequent analyses.

Each of the statins included in this study were in use at the start of the study, with cerivastatin appearing during the first quarter of 1998 (Figure). Cerivastatin use increased slowly but did not achieve high-volume use within the health plans studied. Atorvastatin use increased steadily with a corresponding decline in pravastatin use through 2003.

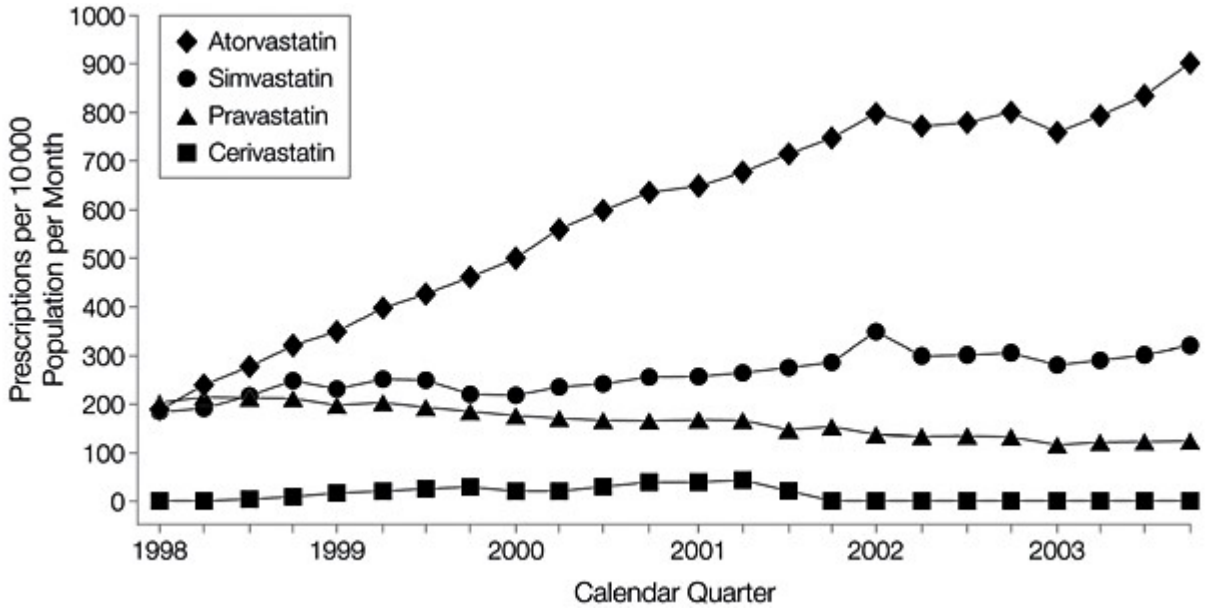

Figure. Monthly Rate of Prescription Dispensings for Atorvastatin, Cerivastatin, Pravastatin, and Simvastatin per 10 000 Population by Calendar Quarter Within 11 Managed Care Health Plans

Of 194 potential cases, hospital medical records were obtained for 174 patients (90%). In 139 records, the serum creatine kinase level was less than 10 times the upper limit of normal and there was no diagnosis of rhabdomyolysis in the chart. Acute myocardial infarction was

responsible for creatine kinase elevations in 3 patients and 1 patient, admitted for elective surgery, developed rhabdomyolysis postoperatively. The remaining 31 patients met the case definition for incident rhabdomyolysis. Seven of these patients were excluded from analysis because their rhabdomyolysis event occurred during a period when, according to automated claims data, they were not exposed to a lipid-lowering drug and therefore were not contributing exposed time to an inception cohort. In each of these instances, however, the hospital record explicitly noted that the patient had been taking a statin at the time of the event (atorvastatin-1, cerivastatin-1, fluvastatin-1, pravastatin-3, simvastatin-1). Among these patients, 2 died, of whom 1 patient also underwent hemodialysis.

Within the inception cohorts, there were 16 cases of rhabdomyolysis with monotherapy (13 with a statin and 3 with gemfibrozil) and 8 cases with combined statin-fibrate therapy. The mean (SD) age of patients with rhabdomyolysis was 64.6 (2.7) years (Table 2). Twenty-three patients (94.4%) had symptoms of muscle pain or weakness preceding hospitalization, with a mean symptom duration of 6.9 days (range, 1-30 days) before admission. Eighteen patients (75%) had severe rhabdomyolysis. With monotherapy, cases occurred after a mean length of therapy of 348 days for atorvastatin or simvastatin (range, 21-1050 days), 56 days for cerivastatin (range, 21-106 days), and 77 days for gemfibrozil (range, 21-179 days). The mean time to onset after initiation of combined statin-fibrate therapy was 32 days (range, 18-78 days). Mean hospital length of stay was 5.7 days (range, 1-11 days), during which all patients were treated with hydration and 10 patients (41.6%) with diuretics. Two patients (8.3%) required hemodialysis, 1 of whom died. Five patients were taking thyroid hormone therapy and 1 had concurrent exposure to erythromycin. No patients were taking an azole antifungal agent or cyclosporine.

Table 2. Characteristics of Patients Hospitalized With Rhabdomyolysis While Taking Statins and Fibrates Alone or in Combination

	Patients With Rhabdomyolysis (N=24)
Age, mean (SD) [range], y	64.6 (2.7) [41-84]
Women, No. (%)	13 (54.2)
Duration of therapy, mean (SD) [range], d	160 (286) [18-1050]
Hospital stay, mean (SD) [range], d	5.7 (0.6) [1-11]
Muscle pain or weakness symptoms, No. (%)	23 (94.4)
Symptom duration before admission, mean (SD) [range], d	6.9 (1.9) [1-30]
Creatinine, mean (SD) [range], mg/dL	2.1 (2.1) [0.6-8.3]
Creatine kinase, mean (SD) [range], IU/L	49721 (15395) [2382-307846]
Creatine kinase ratio, mean (SD) [range]*	274 (89) [15-1780]

SI conversion: To convert creatinine to mol/L, multiply by 88.4.
*Creatine kinase ratio = [(creatine kinase)/(upper limit of normal)].

Table 2. Characteristics of Patients Hospitalized With Rhabdomyolysis While Taking Statins and Fibrates Alone or in Combination

The incidence rates of rhabdomyolysis with monotherapy of atorvastatin, pravastatin, and simvastatin were statistically indistinguishable, with a summary point estimate of 0.44 per 10 000 person-years of use (95% CI, 0.20-0.84) (Table 3). A sensitivity analysis including the 7 cases that occurred during time outside the inception cohorts yielded a summary estimate of 0.68 (95% CI, 0.38-1.15) and the individual incidence rates remained indistinguishable. The incidence rates for cerivastatin and gemfibrozil as monotherapy were similar and both were more than those for the 3 other statins analyzed ($P = .002$ for cerivastatin and $P = .02$ for gemfibrozil). Although there were no cases with fenofibrate monotherapy, the 95% CI for its incidence rate completely bounded that for gemfibrozil monotherapy, which suggested comparability. The summary incidence rate per 10 000 person-years for the 2 fibrates (fenofibrate and gemfibrozil) combined was 2.82 (95% CI, 0.58-8.24). In comparison, there were no unexposed cases during 76 681 person-years of unexposed person-time within the inception cohorts, resulting in an incidence of 0 (95% CI, 0-0.48; $P = .056$). The number needed to treat for 1 year with monotherapy to observe 1 case of hospitalized rhabdomyolysis was 22 727 patients receiving atorvastatin, pravastatin, or simvastatin; 1873 patients receiving cerivastatin; and 3546 patients receiving a fibrate.

Table 3. Rhabdomyolysis per 10000 Person-Years of Therapy With Lipid-Lowering Drugs Used as Monotherapy or as Combination Therapy With Another Drug

Drug	Monotherapy, Incidence Rates (95% CI)	Combination Therapy	
		Combination	Incidence Rates (95% CI)
Atorvastatin	0.54 (0.22-1.12)	Atorvastatin + fenofibrate	22.45 (0.57-125)
Cerivastatin	5.34 (1.46-13.68)	Cerivastatin + gemfibrozil	1035 (389-2117)
Pravastatin	0 (0-1.11)	No cases	0 (0-67.71)
Simvastatin	0.49 (0.06-1.76)	Simvastatin + gemfibrozil	18.73 (0.47-104)
Fenofibrate	0 (0-14.58)	Fenofibrate + atorvastatin	16.86 (0.43-93.60)
Gemfibrozil	3.70 (0.76-10.82)	Gemfibrozil + cerivastatin	789 (166-2138)

Abbreviation: CI, confidence interval.

Table 3. Rhabdomyolysis per 10000 Person-Years of Therapy With Lipid-Lowering Drugs Used as Monotherapy or as Combination Therapy With Another Drug

The incidence rates for rhabdomyolysis for monotherapy with atorvastatin, pravastatin, or simvastatin remained statistically indistinguishable over time. For therapy intervals of less than 6 months, 6 to 12 months, 13 to 24 months, and more than 24 months, the incidence of rhabdomyolysis per 10 000 person-years was 0.7 (95% CI, 0.3-1.6), 0.2 (95% CI, 0.01-1.2), 0.2 (95% CI, 0.01-1.1), and 0.6 (95% CI, 0.1-2.1), respectively. A similar pattern was observed with cerivastatin and fibrate monotherapy.

Incidence rates of rhabdomyolysis with combined statin-fibrate therapy were higher than those observed with monotherapy (Table 3). Based on the statin-fibrate combinations for which there were cases, the magnitude of the effect appeared to be similar regardless of the statin and fibrate involved, with the exception of cerivastatin. For the other statins, the composite incidence with

combined use was 5.98 (95% CI, 0.72-216) per 10 000 patient-years, although inspection of individual cohorts suggested that the point-estimate was probably between 16.9 and 22.5 per 10 000 person-years. For combined cerivastatin-fibrate therapy, 2 separate estimates of the incidence rate of rhabdomyolysis, 1 obtained from the cerivastatin inception cohort and 1 from the gemfibrozil inception cohort, were similar, with point estimates ranging from 789 to 1035 per 10 000 person-years. The number needed to treat for 1 year with combined therapy involving atorvastatin, pravastatin, or simvastatin and fibrate was 1672 patients. With combined cerivastatin and gemfibrozil, the number needed to treat ranged from 9.7 to 12.7 patients.

All patients with rhabdomyolysis were taking statins at daily dosages within the dose-range recommended in product labeling (Table 4). For atorvastatin and simvastatin, 3 (27%) of 11 cases occurred at the 40-mg dose, half the recommended maximum dose. The remaining 8 cases (73%) occurred at even lower daily doses. For cerivastatin, 3 (30%) of 10 cases occurred at the maximum recommended dose of 0.8 mg, with the remaining 7 cases (70%) occurring at lower daily doses.

Hospitalized rhabdomyolysis with statin monotherapy was increased for patients aged 65 years or older (RR, 5.4; 95% CI, 1.3-21.6) and the point estimate of the RR was increased for patients with diabetes mellitus (2.9; 95% CI, 0.7-11.8). There was no increase in RR among women (0.9; 95% CI, 0.2-3.2). The RRs of rhabdomyolysis with fibrate or cerivastatin use, as monotherapy or combination therapy, were estimated using statin monotherapy (atorvastatin, pravastatin, and simvastatin) as the reference.

With monotherapy, fibrate use was associated with a 5.5-fold increase (95% CI, 1.5-20.4) and cerivastatin with a 10.0-fold increase (95% CI, 3.1-32.7) in risk compared with statin use. Combined statin-fibrate use conferred a 12-fold increase in risk vs statin monotherapy (RR, 12.20; 95% CI, 2.59-57.44). The risk of hospitalized rhabdomyolysis for a patient aged 65 years or older with diabetes mellitus, treated with both a statin and fibrate was increased 48-fold (95% CI, 5.2-446.0), translating to a number needed to treat of 484 patients. The risk from combined cerivastatin-fibrate use was increased 1411-fold (95% CI, 496-4013).

COMMENT

Using population-based inception cohorts of patients treated with various statins and fibrates, the incidence rate of rhabdomyolysis was found to be similar for monotherapy with atorvastatin, pravastatin, and simvastatin, currently the 3 most widely prescribed statins in the United States.[17] Compared with statin monotherapy, fibrate use was associated with a 5.5-fold increase in risk and the combined use of a statin and fibrate increased risk by an additional 2-fold vs fibrate alone. The risk of rhabdomyolysis with cerivastatin monotherapy was 10-fold greater than with other statins, and in combination with a fibrate, was increased more than 1400-fold. With an estimated incidence of approximately 1000 per 10 000 person-years of use, rhabdomyolysis might have occurred in approximately 1 of every 10 patients treated with cerivastatin and fibrate

for a year. The risk of rhabdomyolysis did not appear to diminish with longer-term use of statins or fibrates as monotherapy. Also, the occurrence of rhabdomyolysis in the absence of statin or fibrate therapy appears to be extremely rare.

In the only published population-based study to our knowledge of myopathy risk with lipid-lowering drugs, monotherapy with fibrates was associated with a 5.5-fold increased risk vs statin monotherapy, and fenofibrate carried the highest individual RR.[14] Our study was considerably larger, involving more than 10 times as many exposed patients, and focused on severe disease requiring hospitalization rather than including nonhospitalized events. In addition, the previous study included patients if their creatine kinase level was even minimally elevated above the upper limit of normal; whereas, in our study, creatine kinase levels for patients ranged from 15 to 1780 times the upper limit of normal.

Statin-associated rhabdomyolysis risk has been described as dose-dependent and concentration-dependent,[4-5] and much work has been performed to identify pharmacokinetic differences between statins in an effort to understand the mechanisms of their myotoxicity. All statins except pravastatin are metabolized within the liver by the cytochrome P450 system, with atorvastatin, cerivastatin, lovastatin, and simvastatin handled by the cytochrome P450 isoenzyme 3A4 (CYP 3A4).[1, 23] Competitive inhibition of CYP 3A4 by drugs, such as ketoconazole, erythromycin, or cyclosporine, has been shown to block oxidation of these statins and increase their serum concentration, which in turn has been cited as an explanation for increased rhabdomyolysis risk.[5, 23-24] Only 1 case-patient of 24 in our study was concurrently treated with 1 of these potent CYP 3A4 inhibitors. Pharmacokinetic complexity is further increased with the concurrent use of fibrates and statins.[25-30]

The above factors alone may not explain the RRs observed in our study. The magnitude of increase in statin serum concentration observed with combination use of gemfibrozil and a variety of statins only ranged from 2- to 5.5-fold.[25-30] In contrast, we found that the risk of rhabdomyolysis with combined statin-fibrate use was increased 12-fold vs with statin use alone. With cerivastatin, combination use conferred more than a 1400-fold increase in risk. The occurrence of rhabdomyolysis, as a pharmacodynamic response to combined use, appears to be disproportionate to any expected effect on statin serum concentration. This suggests that the mechanism underlying the occurrence of rhabdomyolysis could be nonlinear and possibly independent of pharmacokinetic interactions.

To our knowledge, this is the first comprehensive study of rhabdomyolysis incidence associated with statin and fibrate therapy. The use of inception cohorts permitted the identification and classification of incident person-time, both as monotherapy and combination therapy, and accounted for drug switching, which is common among statin users. We used a strict case definition that was validated by medical record review. In addition, the strategy for identifying cases was broad and inclusive, reducing the likelihood that cases were missed. These factors should contribute to reliable estimates of incidence rates and RRs for rhabdomyolysis.

There were also limitations in our study. The primary analysis was based on 24 case-patients, which could be viewed as too small for reliability. Although this may be a relatively low number of case-patients, it represents a large number for rhabdomyolysis. To compensate for the relative

rarity of the outcome, we assembled large exposure cohorts and applied a rigorous case-finding strategy. For several drugs, the incidence rate estimates had wide 95% CIs, reflecting the small number of events. Nonetheless, there was sufficient precision in the estimates to establish the similarity in rhabdomyolysis risk for atorvastatin, pravastatin, and simvastatin. Additionally, there was adequate statistical power to demonstrate the impact of combined statin-fibrate use, especially in higher risk patients such as those aged 65 years or older with diabetes mellitus. Seven cases of rhabdomyolysis were identified during what were thought to be periods of nonexposure to statins. Medical records indicated that all patients were taking a statin at the time of symptom onset, demonstrating that computerized prescription claims did not identify all statin use within the study population. Because of the high expense of prescription statin drugs, a common assumption made by researchers using health claims data has been that patients would not purchase prescription medications out-of-pocket if they could be paid for by insurance.[19-20] Possible explanations for this potential exposure misclassification include use of free product samples, dual–health insurance coverage by case-patients and their spouses, or use of products prescribed for others. A sensitivity analysis showed that inclusion of these cases in the primary analysis did not significantly alter the estimates of rhabdomyolysis risk and would not have altered the qualitative conclusions of our study.

We also encountered one instance in which the exposure status of a case-patient based on prescription claims was classified as fibrate monotherapy, but based on the hospital medical record, may have involved combination therapy with cerivastatin. Per study protocol, this patient was classified as fibrate monotherapy for analysis purposes because exposure classification of all study patients was based on the computerized prescription claims. Also, there was no way to identify similar episodes of unrecognized statin use among the several hundred thousand non–case patients for whom medical records were not reviewed. Additional research is needed to better define the nature and magnitude of rhabdomyolysis risk with fibrate monotherapy and to determine if risks with gemfibrozil and fenofibrate are similar or different.

With the potential for a substantial increase in the number of patients treated with statins over the next several years,[31] our study provides reassurance that the risk of rhabdomyolysis is relatively low with 3 frequently prescribed statins. For patients treated with both statins and fibrates combined, such as persons with diabetes mellitus with elevated cholesterol and triglyceride levels, the higher risk conferred by combination therapy may warrant that physicians instruct their patients to stop therapy and be evaluated if symptoms suggestive of rhabdomyolysis develop.

Definition of Rhabdomyolysis

Rhabdomyolysis: A condition in which skeletal muscle cells break down, releasing myoglobin (the oxygen-carrying pigment in muscle) together with enzymes and electrolytes from inside the muscle cells. The risks with rhabdomyolysis include muscle breakdown and kidney failure since myoglobin is toxic to the kidneys.

Rhabdomyolysis can occur from extensive muscle damage as, for example, from a crushing injury or an electrical shock. Drugs or toxins, particularly some of the cholesterol lowering medications such as cerivastatin (Baycol), may cause this disorder. Underlying diseases such as

systemic lupus erythematosus can also lead to rhabdomyolysis. It is a common complication of major burns.

The key signs and symptoms of rhabdomyolysis include dark, red, or cola colored urine and muscle tenderness, stiffness, aching (myalgia) or weakness. Laboratory confirmation can come from the demonstration of myoglobin in the blood or urine.

Ideal treatment involves early and aggressive hydration with very large amounts of IV fluids to flush the myoglobin out of the kidneys. Diuretics may help. So may bicarbonate which makes the urine alkaline to prevent the breakdown of myoglobin into more toxic compounds.

From the Greek roots rhabdo-, striped (striated) + -myo-, muscle + -lysis, breakdown = the breakdown of striated muscle (skeletal muscle).

Rhabdomyolysis is the breakdown of muscle fibers that results in the release of muscle fiber content into the circulation. It results from the toxicity of destroyed muscle cells, causing kidney damage or failure. Predisposing factors include trauma, ischemia, polymyositis, and drug overdose. Toxins and environmental, infectious, and metabolic factors may induce it. Rhabdomyolysis accounts for 8% to 15% of cases of acute renal failure; about 5% of cases result in death.

Causes and incidence

Rhabdomyolysis follows direct injury to the skeletal muscle fibers, specifically the sarcolemma, which then release myoglobin into the bloodstream. Myoglobin is an oxygen-binding protein pigment found in skeletal muscle. When this muscle is damaged, myoglobin is released into the bloodstream. It's then filtered by the kidneys.

Myoglobin may occlude the structures of the kidney causing damage, such as acute tubular necrosis or kidney failure. Myoglobin can also cause kidney failure because it breaks down into potentially toxic compounds. Necrotic skeletal muscle may cause massive fluid shifts from the bloodstream into the muscle, reducing the relative fluid volume of the body and leading to shock and reduced blood flow to the kidneys.

The disorder may be caused by any condition that results in damage to skeletal muscle. Rhabdomyolysis may result from blunt trauma; extensive burn injury; viral, bacterial, or fungal infection (such as legionnaire's disease or, especially, influenza type A or B); prolonged immobilization; near electrocution or near drowning; metabolic or genetic factors; drug therapy;

or toxins. Heavy exercise in children may result in rhabdomyolysis. Other causes include shaken baby syndrome, exposure to extreme cold, heatstroke, and snakebite.

In the United States, rhabdomyolysis affects about 8% to 15% of people with acute renal failure and has a slightly higher incidence in men than in women. The overall mortality rate is 5%. It can occur in infants, toddlers, and adolescents who inherited enzyme deficiencies of carbohydrate and lipid metabolism or those with inherited myopathies, such as Duchenne's muscular dystrophy, and malignant hyperthermia.

Signs and symptoms

Signs and symptoms of rhabdomyolysis include myalgias or muscle pain (especially in the thighs, calves, or lower back), weakness, tenderness, malaise, fever, dark urine, nausea, and vomiting. The patient may also experience weight gain, seizures, joint pain, and fatigue. Symptoms may be subtle initially. Rhabdomyolysis can result in acute renal failure.

Diagnosis

A serum or urine myoglobin test is positive. *Creatine kinase* results 100 times above normal or higher suggest rhabdomyolysis. A urinalysis may reveal casts and may be positive for hemoglobin without evidence of red blood cells on microscopic examination. Serum potassium may be very high (potassium is released from cells into the bloodstream when cell breakdown occurs).

Treatment

Early, aggressive hydration may prevent complications from rhabdomyolysis by rapidly eliminating the myoglobin from the kidneys. I.V. hydration and diuretics promote diuresis. Diuretic medications, such as mannitol or furosemide, may aid in flushing the pigment out of the kidneys. If urine output is sufficient, bicarbonate may be given to maintain an alkaline urine state, thereby helping to prevent the dissociation of myoglobin into toxic compounds. Hyperkalemia should be treated if present. Kidney failure should be treated as appropriate. Dialysis may be necessary and, in severe cases, kidney transplantation.

Special considerations

❑ Monitor the patient's intake and output, vital signs, electrolyte levels, daily weight, and laboratory results.

❑ Watch for signs of renal failure (such as decreasing urine output and increasing urine specific gravity), fluid overload (such as dyspnea and tachycardia), pulmonary edema, and electrolyte imbalances (such as serum potassium).

❑ Provide reassurance and emotional support for the patient and his family.

❑ To help prevent rhabdomyolysis from occurring, ensure adequate hydration, monitor the patient for adverse reactions to any of his prescribed drugs, and monitor blood transfusion administration carefully.

Glossary for Rhabdomyolysis

Aldolase A deficiency: A rare condition where a deficiency of the enzyme called aldolase A causes muscle problems and anemia.

Bacterial toxic-shock syndrome: A very rare, potentially fatal infection caused by toxins produced by bacteria, especially bacteria such as Staphylococcus aureus or Streptococcus pyogenes. The condition is often associated with tampon use but can originate from other sources.

Carnitine palmitoyl transferase 1 deficiency: A very rare inherited deficiency of a particular enzyme (Carnitine palmitoyl transferase I) prevents fatty acids being transported to the part of the cell that converts it to energy.

Carnitine palmitoyl transferase 2 deficiency: A very rare inherited deficiency of a particular enzyme (Carnitine palmitoyl transferase) which prevents fatty acids being transported to the part of the cell that converts it to energy. There are two main subtypes of the disorder with each involving a slightly different form of the enzyme. Type I can be readily managed through diet. Type II has three subtypes: the myopathic form affects mainly the muscles; the hepatocardiomuscular form affects the liver and heart muscle; and the lethal neonatal form affects muscles and organs and usually results in death during the first year of life.

Carnitine transporter deficiency: An inherited deficiency of carnitine caused by the impaired ability of the carnitine transporter protein to carry the carnitine to where it is needed. Instead the carnitine is excreted through the urine. Fasting or illness can trigger a severe attack.

Dark urine: A dark discolouration of the urine.

Dermatomyositis: A muscle disease characterized by chronic muscle inflammation resulting in progressive muscle weakness and a characteristic rash.

Exercise: The use of the human muscles to improve ones health

Fatigue: Excessive tiredness or weakness.

Fentanyl toxicity: The toxic reaction of the body to the substance, possibly via allergic reaction or overdose.

Fever: Elevation of the body temperature above the normal 37 degrees celsius

Heatstroke: Heat exhaustion and collapse from heat exposure

Hemorrhagic shock and encephalopathy syndrome: A very rare severe condition characterized by sudden severe shock, brain disease and liver and kidney dysfunction which occurs in infants. The cause is unknown.

Hereditary carnitine deficiency syndrome: An inherited deficiency of carnitine resulting primarily in muscle weakness. The carnitine deficiency may be due to excessive loss of insufficient production.

Hereditary carnitine deficiency syndrome, systemic: An inherited deficiency of carnitine in tissues other than the muscles resulting primarily in muscle weakness.

Hyperkalaemia: Increased concentration of potassium in the blood.

Hyperphosphataemia: An increased level of phosphate in the circulation above that which is considered normal

Hypocalcaemia: Decreased concentration of calcium in the blood.

Hypokalaemia: Decreased concentration of potassium in the blood

Hypophosphatemia: Low blood phosphate levels. Causes include malnourishment, chronic alcoholism excessive carbohydrate consumption, malabsorption, phosphaturia, liver failure, respiratory alkalosis and certain genetic disorders.

Idiopathic myopathy: A rare condition involving inflammation of the skeletal muscles which become weak and wasted.

Morphine toxicity: The toxic reaction of the body to the substance, possibly via allergic reaction or overdose.

Muscle weakness: A condition which is characterized by an inability of the muscles to function at their full strenght

Myalgia: Muscle aches and pains

Nausea: The queasy feeling of nausea and often also vomiting.

Neuroleptic Malignant Syndrome: A severe, potentially fatal reaction to antipsychotic drugs.

Opioid toxicity: The toxic reaction of the body to the substance, possibly via allergic reaction or overdose.

Phosphoglycerate Kinase Deficiency: A condition which is characterized by a deficiency in the enzyme phosphoglycerate kinase

Proteinuria: Protein in the urine

Serotoninergic syndrome: A disorder involves high levels of serotonin which can result from use of medications such as selective serotonin reuptake inhibitors.

Staphylococcal toxic shock syndrome: A very rare, potentially fatal infection caused by the bacterial toxins produced by Staphylococcus aureus or Streptococcus pyogenes. The condition is often associated with tampon use but can originate from other sources.

Systemic monochloroacetate poisoning: Monochloracetate acid is a dangerous chemical which can cause systemic poisoning even if only skin exposure occurs. Exposure to the chemical can be life-threatening with serious symptoms starting within hours of the exposure.

Toluene sniffing syndrome: Symptoms caused by sniffing vapor containing a chemical called toluene.

Tramadol toxicity: The toxic reaction of the body to the substance, possibly via allergic reaction or overdose.

Very-Long-Chain Acyl-CoA Dehydrogenase Deficiency: A condition which is characterized by a very long chain acyl coa dehydrogenase deficiency

Vomiting: Vomiting or retching symptoms.

REFERENCES

1. Ucar M, Mjörndal T, Dahlqvist R. HMG-CoA reductase inhibitors and myotoxicity. *Drug Saf.* 2000;22:441-457. FULL TEXT | ISI | PUBMED

2. Phillips PS, Haas RH, Bannykh S, et al. Statin-associated myopathy with normal creatine kinase levels. *Ann Intern Med.* 2002;137:581-585. **FREE** FULL TEXT

3. Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. *JAMA.* 2003;289:1681-1690. **FREE** FULL TEXT

4. Ballantyne CM, Corsini A, Davidson MH, et al. Risk of myopathy with statin therapy in high-risk patients. *Arch Intern Med.* 2003;163:553-564. **FREE** FULL TEXT

5. Rosenson RS. Current overview of statin-induced myopathy. *Am J Med.* 2004;116:408-416. FULL TEXT | ISI | PUBMED

6. Clouâtre Y, Leblanc M, Ouimet D, Pichette V. Fenofibrate-induced rhabdomyolysis in two dialysis patients with hypothyroidism [letter]. *Nephrol Dial Transplant.* 1999;14:1047-1048. **FREE** FULL TEXT

7. Barker BJ, Goodenough RR, Falko JM. Fenofibrate monotherapy induced rhabdomyolysis [letter]. *Diabetes Care.* 2003;26:2482-2483. **FREE** FULL TEXT

8. Gorriz JL, Sancho A, Lopez-Martin JM, et al. Rhabdomyolysis and acute renal failure associated with gemfibrozil monotherapy. *Nephron.* 1996;74:437-438. ISI | PUBMED

9. Layne RD, Sehbai AS, Stark LJ. Rhabdomyolysis and renal failure associated with gemfibrozil monotherapy. *Ann Pharmacother.* 2003;38:232-234. **FREE** FULL TEXT

10. Shek A, Ferrill MJ. Statin-fibrate combination therapy. *Ann Pharmacother.* 2001;35:908-917. ABSTRACT

11. Omar MA, Wilson JP, Cox TS. Rhabdomyolysis and HMG-CoA reductase inhibitors. *Ann Pharmacother.* 2001;35:1096-1107. ABSTRACT

12. Zocor. *Physicians' Desk Reference.* 58th ed. Montvale, NJ: Thompson PDR; 2004: 2113-2118.

13. Lipitor. *Physicians' Desk Reference.* 58th ed. Montvale, NJ: Thompson PDR; 2004: 2543-2546.

14. Gaist D, Garcia-Rodriguez LA, Huerta C, Hallas J, Sindrup SH. Lipid-lowering drugs and risk of myopathy. *Epidemiology.* 2001;12:565-569. FULL TEXT | ISI | PUBMED

15. Black C, Jick H. Etiology and frequency of rhabdomyolysis. *Pharmacotherapy.* 2002;22:1524-1526. FULL TEXT | ISI | PUBMED

16. Omar MA, Wilson JP. FDA adverse event reports on statin-associated rhabdomyolysis. *Ann Pharmacother.* 2002;36:288-295. ABSTRACT

17. Staffa JA, Chang J, Green L. Cerivastatin and reports of fatal rhabdomyolysis [letter]. *N Engl J Med.* 2002;346:539-540. **FREE** FULL TEXT

18. Furberg CD, Pitt B. Withdrawal of cerivastatin from the world market. *Curr Control Trials Cardiovasc Med.* 2001;2:205-207.

19. Shatin D, Drinkard C, Stergachis A United Health Group. In: Strom BL, ed. *Pharmacoepidemiology.* 3rd ed. New York, NY: John Wiley & Sons; 2000:295-306.

20. Chan KA, Platt R. Harvard Pilgrim Health Care/Harvard Vanguard Medical Associates. In: Strom BL, ed. *Pharmacoepidemiology.* 3rd ed. New York, NY: John Wiley & Sons; 2000:285-294.

21. McAlister FA, Straus SE, Guyatt GH, Haynes RB, Evidence-Based Medicine Working Group. Users' guides to the medical literature, XX: integrating research evidence with the care of the individual patient. *JAMA.* 2000;283:2829-2836. **FREE** FULL TEXT

22. Cottrell DA, Marshall BJ, Falko JM. Therapeutic approaches to dyslipidemia in diabetes mellitus and metabolic syndrome. *Curr Opin Cardiol.* 2003;18:301-308. FULL TEXT | ISI | PUBMED

23. Baker SK, Tarnopolsky MA. Statin myopathies: pathophysiological and clinical perspectives. *Clin Invest Med.* 2001;24:258-272. ISI | PUBMED

24. Evans M, Rees A. Effects of HMG-CoA reductase inhibitors on skeletal muscle: are all statins the same? *Drug Saf.* 2002;25:649-663. FULL TEXT | ISI | PUBMED

25. Backman JT, Kyrklund C, Kivistö KT, et al. Plasma concentrations of active simvastatin acid are increased by gemfibrozil. *Clin Pharmacol Ther.* 2000;68:122-129. FULL TEXT | ISI | PUBMED

26. Kyrklund C, Backman JT, Kivistö KT, Neuvonen M, Latila J, Neuvonen PJ. Plasma concentrations of active lovastatin are markedly increased by gemfibrozil but not by bezafirate. *Clin Pharmacol Ther.* 2001;69:340-345. FULL TEXT | ISI | PUBMED

27. Backman JT, Kyrklund C, Neuvonen M, et al. Gemfibrozil greatly increases plasma concentrations of cerivastatin. *Clin Pharmacol Ther.* 2002;72:685-691. FULL TEXT | ISI | PUBMED

28. Prueksaritanont T, Subramanian R, Fang X, et al. Glucuronidation of statins in animals and humans. *Drug Metab Dispos.* 2002;30:505-512. **FREE** FULL TEXT

29. Prueksaritanont T, Zhao JJ, Ma B, et al. Mechanistic studies on metabolic interactions between gemfibrozil and statins. *J Pharmacol Exp Ther.* 2002;301:1042-1051. **FREE** FULL TEXT

30. Prueksaritanont T, Tang C, Qiu Y, et al. Effects of fibrates on metabolism of statins in human hepatocytes. *Drug Metab Dispos.* 2002;30:1280-1287. **FREE** FULL TEXT

31. Kolata G. Health officials urge sharply lower cholesterol levels. *New York Times.* July 13, 2004:A1.

Rhabdomyolysis Examination

Select the ***best*** answer to each of the following items. Mark your responses on the Answer Form.

1. Rhabdomyolysis risk was similar and low for monotherapy with _____. Cerivastatin combined with fibrate conferred a risk of approximately 1 in 10 treated patients per year.

a. Atorvastatin
b. Pravastatin
c. Simvastatin
d. All of the above

2. The epidemiology of statin-associated and fibrate-associated myopathy is poorly described, with most attention focused on rhabdomyolysis.

a. True
b. False

3. The product labeling for some statins presents incidence estimates for myopathy and rhabdomyolysis combined, although in labeling for other statins the occurrence of rhabdomyolysis is described as rare.

a. True
b. False

4. Rhabdomyolysis is a condition in which skeletal muscle cells break down, releasing _____ together with and from inside the muscle cells. The risks with rhabdomyolysis include muscle breakdown and kidney failure since myoglobin is toxic to the kidneys.

a. Myoglobin (the oxygen-carrying pigment in muscle)
b. Enzymes
c. Electrolytes
d. All of the above

5. The key signs and symptoms of rhabdomyolysis include _____. Laboratory confirmation can come from the demonstration of myoglobin in the blood or urine.

a. Dark, red, or cola colored urine
b. Muscle tenderness
c. Aching (myalgia) or weakness
d. All of the above

6. Ideal treatment of rhabdomyolysis involves early and aggressive hydration with very large amounts of IV fluids to flush the myoglobin out of the kidneys. Diuretics may help. So may bicarbonate which makes the urine alkaline to prevent the breakdown of myoglobin into more toxic compounds.

a. True
b. False

7. Rhabdomyolysis is the breakdown of muscle fibers that results in the release of muscle fiber content into the circulation. It results from the toxicity of destroyed muscle cells, causing kidney damage or failure. Predisposing factors include _____.

a. Trauma
b. Ischemia
c. Polymyositis
d. All of the above

8. Early, aggressive hydration may prevent complications from rhabdomyolysis by rapidly eliminating the myoglobin from the kidneys. I.V. hydration and diuretics promote diuresis. Diuretic medications, such as mannitol or furosemide, may aid in flushing the pigment out of the kidneys.

a. True
b. False

9. Rhabdomyolysis accounts for _____ of cases of acute renal failure; about 5% of cases result in death.

a. 4% to 10%
b. 8% to 15%
c. 16% to 27%
d. 20% to 30%

10. A serum or urine myoglobin test is positive. *Creatine kinase* results 100 times above normal or higher suggest rhabdomyolysis. A urinalysis may reveal casts and may be positive for hemoglobin without evidence of red blood cells on microscopic examination. Serum potassium may be very high (potassium is released from cells into the bloodstream when cell breakdown occurs).

a. True
b. False

11. To help prevent rhabdomyolysis from occurring_____.

a. ensure adequate hydration
b. monitor the patient for adverse reactions to any of his prescribed drugs
c. monitor blood transfusion administration carefully
d. All of the above

12. In working with a patient with rhabdomyolysis, it is important to monitor the patient's intake and output, vital signs, electrolyte levels, daily weight, and laboratory results.

a. True
b. False

13. In working with a patient with rhabdomyolysis, it is important to watch for signs of renal failure (such as decreasing urine output and increasing urine specific gravity), fluid overload (such as dyspnea and tachycardia), pulmonary edema, and electrolyte imbalances (such as serum potassium).

a. True
b. False

14. In treating rhabdomyolysis, diuretic medications, such as mannitol or furosemide, may aid in flushing the pigment out of the kidneys. If urine output is sufficient, bicarbonate may be given to maintain an alkaline urine state, thereby helping to prevent the dissociation of myoglobin into toxic compounds. Hyperkalemia should be treated if present. Kidney failure should be treated as appropriate. Dialysis may be necessary and, in severe cases, kidney transplantation.

a. True
b. False

15. Heavy exercise in children may result in rhabdomyolysis. Other causes include _____.

a. shaken baby syndrome
b. exposure to extreme cold
c. heatstroke
d. All of the above

MEDEDSYS
PO BOX 83939, San Diego, CA, 92138-3939
TOLL FREE 1-877-295-4719
FAX: 619-295-5267
info@mededsys.com
www.mededsys.com

How to Complete Your Test and Print Your Certificate Online

If you chose to receive your order by postal mail, you have been mailed the printed course material(s) and the printed test(s). To take a test, simply complete the mailed test and send it back. Upon successful completion of a test, a certificate will be mailed or faxed to you. If you don't wish to mail the test back, customers who chose to have the course material(s) mailed may also follow the steps below to complete a test and print a certificate online.

INSTRUCTIONS

1. Go to www.mededsys.com
2. Login and go to "My Account".
3. On the page that opens, select an option from the "My Courses" menu.
4. Select the test you wish to complete.
5. After completion of test, print your certificate online by clicking on the "Continue" button. Alternatively, you may return to the "My Courses" section and select the option to print a certificate.