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REVIEW ARTICLE

# Rhabdomyolysis associated with fibrate therapy: review of 76 published cases and a new case report

**Jianyong Wu · Yan Song · Heng Li · Jianghua Chen**

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**Abstract**
*Purpose* Fibrates are used to manage mixed dyslipidemia. However, these drugs have the potential risk of inducing rhabdomyolysis. This paper gives an overview of the literature on rhabdomyolysis associated with fibrate therapy.
*Methods* We reported a case of rhabdomyolysis induced by fenofibrate and reviewed the published rhabdomyolysis cases associated with fibrate therapy.
*Results* Seventy-six published rhabdomyolysis cases associated with fibrates were evaluated, and a nondiabetic, nonhypertensive patient who presented with rhabdomyolysis caused by fenofibrate was reported. The onset time of the reaction varied between 36 h and 6 months. Gemfibrozil was the most frequent agent associated with rhabdomyolysis, followed by bezafibrate, fenofibrate, ciprofibrate, and clofibrate. Twenty-three cases were associated with fibrate monotherapy and 54 with fibrate therapy combined with statins or other drugs potentially interacting with fibrates. Sixteen cases had chronic renal failure before fibrate therapy, and 6 had hypothyroidism. Fifty-four complicated acute renal failure. After discontinuation of the fibrates and hydration, most patients recovered.
*Conclusions* Chronic renal failure may be a risk factor for rhabdomyolysis associated with fibrates. Although rhabdomyolysis usually occurred when fibrates were combined with statins, a well-known class of agents that potentially induce rhabdomyolysis, precautions against serious adverse effects should also be taken with fibrate monotherapy.

**Keywords** Drug adverse reaction · Rhabdomyolysis · Fibrates · Drug interaction

## Introduction

Fibric acid derivatives, or fibrates, are widely used and are effective drugs in the treatment of mixed dyslipidemia. The fibrates bind to the peroxisome proliferator-activated receptor-α, thus changing the transcription of target genes that control lipid metabolism, which subsequently causes decreased triglyceride and increased high-density lipoprotein cholesterol [1]. Commonly prescribed fibrates are generally well tolerated. The more frequent side effects include upper gastrointestinal system discomfort, nausea, headache, anxiety, and skin rash [2, 3]. Rhabdomyolysis is an unusual but serious adverse event in fibrate treatment [2, 3]. Rhabdomyolysis can injure the skeletal muscle or myocardium and lead to renal failure, infections, disseminated intravascular coagulation, and death [4].

Here, we present a case of rhabdomyolysis induced by fenofibrate monotherapy. As far as we know, this is the second report following that of Tahmaze et al. [5]. The patient only had hypertriglyceridemia without any other significant medical history. In order to develop a good understanding of the risk factors, clinical manifestations, management, and outcomes of the side effects, we further reviewed 76 reported cases of rhabdomyolysis associated with fibrate therapy retrieved from the PubMed database.

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J. Wu · Y. Song · H. Li · J. Chen (✉)
Kidney Disease Center, First Affiliated Hospital,
College of Medicine, Zhejiang University,
79 Qingchun Road,
Hanghzou 310003 Zhejiang, People's Republic of China
e-mail: chenjianghua@zju.edu.cn

## Methods

A new case of rhabdomyolysis induced by fenofibrate monotherapy was reported. The English-language literature in the PubMed database was searched from inception to 1 February 2009 using the terms "fenofibrate," "gemfibrozil," "bezafibrate," "ciprofibrate," "clofibrate," "fibrates," and "rhabdomyolysis." Articles were primarily evaluated if they reported on rhabdomyolysis associated with fibrates and a serum creatine kinase level of more than ten times the upper limit of normal [4]. We excluded cases if they fulfilled at least one of the following criteria: no individual patient reported, insufficient clinical or laboratory data, or serum creatine kinase level less than ten times the upper limit of normal. We assigned three outcome categories for each reported case: "recovery" was defined as disappearance of the rhabdomyolysis symptoms and serum creatine kinase and creatinine levels had returned to the normal range or the levels before onset; "improved" was defined as asymptomatic but with laboratory findings, and serum creatine kinase and creatinine, in particular, still in the abnormal range at the end of follow-up; the last outcome was "death."

## Results

### Case report

A 52-year-old woman, who was a farmer, was admitted to the Kidney Disease Center of our hospital with a 10-day history of generalized muscle tenderness. The tenderness was progressive, and she was unable to walk on admission. She complained of oliguria for more than 1 week and had brown and turbid urine for about 6 days. She had taken 200 mg fenofibrate daily for almost 1 month because of her dyslipidemia. Her myalgia and elevated serum creatinine and creatine kinase concentrations had been noted, so she was referred to our hospital (Table 1).

Past medical history was insignificant other than dyslipidemia. She denied smoking, drinking alcohol, or taking any medications besides the fenofibrate. Physical examination revealed no pathological findings except for tenderness of muscles on the buttocks and the proximal limbs. Laboratory findings before and after the lipid-lowering therapy are listed in Table 1. Testing for antinuclear antibody, anti-double-stranded DNA (anti-dsDNA) antibody, anti-smooth-muscle antibody, human immunodeficiency virus antibody, and rheumatoid factor were negative. Complement C3 and C4 levels were unremarkable. Electrocardiogram and abdominal ultrasonography were normal. On the basis of these data, there was no evidence of myocardial infarction or stroke. It was suggested that this was a case of rhabdomyolysis induced by fenofibrate monotherapy with secondary renal failure.

When the patient arrived in our hospital, the fenofibrate was discontinued. She was treated by intravenous hydration and urine alkalinization with sodium bicarbonate. Despite this treatment, the patient developed hyperkalemia, elevated serum creatinine and creatine kinase concentrations, and metabolic alkalosis. Hemodialysis was started and per-

**Table 1** Laboratory findings of our case

| | Before fenofibrate therapy | Time after admission (days) | | | | | | | 1month after discharge | Reference range |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 0 | 2 | 3 | 6 | 11 | 15 | 18 | | |
| Glomerular filtration rate (MDRD) | ND | 4.54 | ND | 6.74 | 5.66 | 5.42 | 9.85 | 11.81 | 60.38 | 80–120 ml/min |
| Serum glucose | 5.78 | 5.84 | ND | 5.55 | ND | 5.02 | 4.95 | 4.67 | 5.65 | 3.92–6.16 mmol/L |
| Serum uric acid | ND | 759 | 751 | 340 | 413 | 511 | 395 | 272 | 418 | 44–133 μmol/L |
| Serum aspartate aminotransferase | 36 | 446 | ND | 172 | ND | 24 | ND | 20 | 17 | 3–40 U/L |
| Serum alanine aminotransferase | 66 | 428 | ND | 274 | ND | 66 | ND | 33 | 12 | 3–50 U/L |
| Serum albumin | 48.2 | 28 | ND | 29 | ND | 29 | ND | 29 | 47.1 | 35–55 g/L |
| Blood urea nitrogen | ND | 43.89 | 47.13 | 22.82 | 15.86 | 12.57 | 11.41 | 9.32 | 6.33 | 2.86–8.2 mmol/L |
| Serum sodium | ND | 146 | 146 | 136 | 138 | 146 | 146 | 144 | 144 | 135–145 mmol/L |
| Serum potassium | ND | 3.88 | 4.01 | 3.37 | 3.18 | 3.38 | 3.86 | 3.9 | 3.85 | 3.5–5.5 mmol/L |
| Blood hemoglobin | 117 | 101 | ND | 98 | ND | 102 | ND | 81 | 97 | 110–150 g/L |
| Serum thyroid-stimulating hormone | ND | 1.460 | ND | ND | ND | ND | ND | ND | 3.390 | 0.4–4.0 μU/L |
| Serum free thyroxine | ND | 10.0 | ND | ND | ND | ND | ND | ND | 14.0 | 10.3–24.45 pmol/L |
| Serum total thyroxine | ND | 47.2 | ND | ND | ND | ND | ND | ND | 81.6 | 58.0–161.0 pmol/L |

*ND* not detected

formed nine times during the following 2-week period. Abnormalities of the blood tests improved gradually (Table 1), and the patient was discharged after 2 weeks. Follow-up 1 month after discharge showed that she was well and blood tests were normal except for anemia (Table 1).

## Analysis of reported cases

Fifty-four reports with 76 cases meeting the criteria were included in the review [5–58]. Supplementary Table 1 lists, in addition to our case, all patients' characteristics in cases of rhabdomyolysis associated with fibrate therapy. The patients were aged from 16 to 82 years [60±13 standard deviation years]. Thirty-six were male (29–82 years) and 41 were female (16–79 years), 16 had chronic renal failure before fibrate therapy, 24 had hypertension, 21 had diabetes mellitus, and 18 had coronary artery disease (Table 2).

Time of reaction onset varied between 36 h and 6 months. Onset was ≤3 weeks in 52% of cases and ≤3 months in 95% (Table 2). Gemfibrozil was the agent most frequently associated with rhabdomyolysis (40 cases). Only four cases were associated with gemfibrozil monotherapy, and there were 35 cases of combination therapy with a statin. Drugs potentially interacting with fibrates other than statins included colchicine [27], ibuprofen [47], mizoribine [12], abacavir [16], indomethacin [54], and warfarin [34]. Seventeen cases were associated with bezafibrate therapy (ten with monotherapy, three with combination therapy with a statin, and four with combination with other agents). Thirteen cases were associated with fenofibrate therapy (seven with monotherapy and six with fenofibrate–statin combination therapy). Six cases were associated with ciprofibrate therapy (two with monotherapy and four with combination therapy).

The clinical manifestations of rhabdomyolysis associated with fibrates were nonspecific. The cases presented as myalgias, weakness, fatigue, and darkened urine. Fifty-four cases of rhabdomyolysis were complicated with acute renal failure. Sixteen were chronic renal failure patients before fibrate therapy (Table 2). Only in ten patients was renal function still normal during rhabdomyolysis. Cardiac involvement occurred in two patients [15, 21]. The peak serum creatine kinase levels ranged from 719 to 289,000 U/L (mean was 43,882±60,990 U/L). Thyroid function was tested in 14 patients, and six had hypothyroidism (43%) [8, 13, 14, 43]. Detection of blood/urine myoglobin was reported in 21 patients, with 19 positive. Fibrates were withdrawn in all cases. In addition, most patients were treated by hydration, urine alkalinization, and/or intravenous diuretics. Of the reported cases, rhabdomyolysis outcome was reported for 72 cases: 62 recovered, five improved, and five died (Table 2).

**Table 2** Summary of reported cases of rhabdomyolysis associated with fibrates

| Variable | Cases of rhabdomyolysis |
|---|---|
| Sex, *n* (%) | |
| male | 36 (47%) |
| female | 41 (53%) |
| Mean age, years (range) | 60 (16–82) |
| Mean fibrate therapy duration (range), week | 5 (36 h–26) |
| Concomitant drugs potentially interacting with fibrates, *n* (%) | |
| Cerivastatin | 13 (17%) |
| Simvastatin | 9 (12%) |
| Atorvastatin | 2 (3%) |
| Fluvastatin | 1 (1%) |
| Lovastatin | 16 (21%) |
| Pravastatin | 2 (3%) |
| Rosuvastatin | 2 (3%) |
| Colchicine | 1 (1%) |
| Ibuprofen | 2 (3%) |
| Mizoribine | 1 (1%) |
| Abacavir | 1 (1%) |
| Warfarin | 1 (1%) |
| Indomethacin | 1 (1%) |
| No suspected drugs | 17 (23%) |
| Not reported | 7 (9%) |
| Medical history, *n* (%) | |
| Hypertension | 24 (31%) |
| Diabetes mellitus | 21 (27%) |
| Chronic renal failure | 16 (21%) |
| Coronary artery disease | 18 (23%) |
| Hypothyroidism | 6 (6/14, 43%) |
| Not reported | 13 (17%) |
| Mean serum creatine kinase (range), U/L | 43,882 (719–289,000) |
| Mean serum creatinine (range), μmol/L | 500 (71–2,086) |
| Not reported, n | 21 |
| Detection of blood/urine myoglobin *n* | |
| Positive | 19 |
| Negative | 2 |
| Not reported | 56 |
| Secondary acute renal failure, *n* (%) | 54 (70%) |
| Outcome, *n* (%) | |
| Recovery | 62 (82%) |
| Improved | 5 (6%) |
| Death | 5 (6%) |
| Not reported | 5 (6%) |

## Discussion

There is a broad spectrum of drug-induced toxicity. The term "myopathy" can be used to describe acute skeletal

muscle symptoms in the absence of raised creatine kinase activity, whereas the term "myositis" is generally used when creatine kinase activity is elevated; "rhabdomyolysis" is generally reserved for cases where creatine kinase activity is increased (commonly creatine kinase >1,000 U/L is the cutoff) and there is other evidence of injury (e.g., myoglobinuria) [59].

Consistent with previous reports [60–62], our review also indicated that the cases of rhabdomyolysis associated with fibrates occurred in the aged population with diabetes mellitus and/or hypertension. However, it is uncertain whether these underlying diseases are risk factors for the rhabdomyolysis associated with fibrates, because the risk factors for hypertension, coronary artery disease, and diabetes mellitus are also risk factors for dyslipidemia [63]. Thus, the very subjects who are candidates for fibrate therapy are at higher risk for developing hypertension, coronary artery disease, and diabetes mellitus than the general population. Furthermore, antidiabetic and antihypertensive medications might directly or indirectly influence the risk of rhabdomyolysis, but it is impossible to deduce the relationship between these medications and rhabdomyolysis from our review data.

In hypothyroidism, mitochondrial activity in muscle cells and some metabolic activities including fatty-acid catabolism are inhibited [8]. Our review found that hypothyroidism was detected in six patients. It is regrettable that thyroid function was only tested in 14 cases. Therefore, it is difficult to conclude that hypothyroidism predisposes to rhabdomyolysis in patients using fibrates.

All approved fibrates were associated with rhabdomyolysis either in monotherapy or in combination with statins or other agents. Gemfibrozil had the highest rates of reported rhabdomyolysis, followed by bezafibrate, fenofibrate, ciprofibrate, and clofibrate. The most usually combined statin was cerivastatin, which was withdrawn from the market in 2001 as a result of death from rhabdomyolysis [60, 64]. Statins and fibric-acid derivatives have complementary effects on mixed dyslipidemia in patients with or at risk for cardiovascular disease [62]. However, such combination therapy increases the risk of life-threatening rhabdomyolysis [60, 65]. In all presented cases, almost 58% of fibrate-associated rhabdomyolysis documented concomitant statin use. Although lipophilic statins are hydrolyzed by the cytochrome P450 enzymes to increase water solubility for renal excretion, statins are also metabolized by glucuronidation. Gemfibrozil uses the same family of glucuronidation enzymes as the statins, thereby inhibiting statin acid glucuronidation [2, 62]. This could partially explain the observed higher risk for myotoxicity when the two drugs were used together. Therefore, use of this combination therapy only after assessing risk versus benefits is recommended.

Theoretically, combination use of any agents potentially interacting with fibrates can increase myopathy toxicity. There are also some reports of rhabdomyolysis associated with combination use of an agent potentially interacting with fibrates. The agents reported are colchicine [27], ibuprofen [47], mizoribine [12], abacavir [16], indomethacin [54], and warfarin [34]. So these drugs should be carefully used along with fibrates.

Rhabdomyolysis associated with fibrates appeared after medication for ≤3 weeks in 52% of the cases and for ≤3 months in 95%. Therefore, the muscle-related examinations, muscle tenderness, and serum creatine kinase should be carried out before and after fibrates are used, especially in those taking a fibrate−statin combination.

Symptoms of rhabdomyolysis associated with fibrates are not specific. The clinical signs, such as progressive proximal myalgia, stiffness, weakness, and dark urine usually develop abruptly and may present within a few days of starting the treatment, particularly in patients with renal failure. Patients usually could not raise their arms or legs. Muscle symptoms were typically more widespread and intense with exercise or excessive drinking. Therefore, the appropriate investigations were necessary for patients who had muscle abnormalities.

Laboratory findings can give hints to diagnose rhabdomyolysis. When rhabdomyolysis was present, a significantly increased serum creatine kinase was usually accompanied by dramatically raised concentrations of serum creatinine, alanine aminotransferase, and aspartate aminotransferase. Myoglobin was positive in most cases in urine and/or blood samples. Creatine kinase is more reliable than myoglobin in assessing the presence and intensity of muscle damage [4]. Therefore, rhabdomyolysis is defined as a serum creatine kinase level of more than ten times the upper limit of normal [4]. Hemoglobin was decreased in a case report [53] and our patient. The mechanism of anemia, however, is not yet known.

The mechanism of rhabdomyolysis associated with fibrate therapy remains unclear. It is suggested that fibrates cause a cell-specific injury to human embryonal rhabdomyosarcoma cells in vitro via activation of the nuclear receptor peroxisome proliferator-activated receptor-α, through which the lipid-lowering action of fibrates is mediated [66]. It was also hypothesized that fibrates only exacerbate latent preexisting mitochondrial myopathies or accelerate the normal physiologic changes in skeletal muscle associated with aging [2].

If a patient taking a fibrate develops intolerable muscle symptoms and/or a marked creatine kinase elevation, the drug should be discontinued. Generally, rapid remission of symptoms is achieved after the discontinuation of therapy. Acute renal failure secondary to the rhabdomyolysis occurred in most patients. The basis of treatment involves

early, aggressive hydration with intravenous crystalloids to maintain a high urine output in order to prevent renal complications, as well as alternate application of bicarbonate infusion to alkalinize the urine. Hemodialysis should be considered in patients with significant renal impairment or severe acid-base and metabolic disturbances despite conservative measures. Most patients suffering from acute renal failure secondary to rhabdomyolysis returned to health or to his/her status before fibrate therapy. Rhabdomyolysis associated with fibrate therapy in some patients with deteriorated original disease or serious complications was fatal.

One must be cautious when interpreting data from case reports. Published case reports incompletely assess or describe important details and sometimes emphasize atypical features and outcomes. Many patients with drug-induced adverse events are never reported in the literature, and we may have missed some case reports by limiting our search to the English language in the PubMed database.

## Conclusion

Rhabdomyolysis is a serious adverse event associated with the use of fibrates alone or in combination with drugs influencing the metabolism of fibrates (especially statins). Patients must be closely monitored and be informed of the potential adverse events and symptoms of muscle toxicity, even with fibrate monotherapy. Awareness of the predictors for fibrate-associated rhabdomyolysis will improve the benefits to risks for treating dyslipidemia with fibrates.

**Conflicts of interest** None.

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