Clinical Case Report

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Fenofibrate monotherapy-induced rhabdomyolysis in a patient with hypothyroidism

A rare case report and literature review

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Abstract

Rationale: Fenofibrate is a fibric acid derivative indicated for use in hypertriglyceridemia and mixed dyslipidemia treatment among adults. Rhabdomyolysis is a syndrome characterized by muscle necrosis and the release of intracellular muscle contents into the systemic circulation, which is the most serious and fatal side effect of fenofibrate. The objective of this paper is to discuss fatal side effect of fenofibrate and keep safe medication.

Patient concerns: A patient with hypothyroidism who presented with rhabdomyolysis during fenofibrate monotherapy for hypertriglyceridemia was reported.

Diagnoses: Fenofibrate Monotherapy Induced Rhabdomyolysis.

Interventions: Fenofibrate was stopped. Adequate fluid resuscitation, mannitol diuresis, myocardium protection, hepatoprotection and urine alkalinization with sodium bicarbonate were performed.

Outcomes: Blood tests were normal and the patient was good and discharged 2 weeks later.

Lessons: 13 cases associated with fenofibrate monotherapy-induced rhabdomyolysis were reviewed, which had been published in the English literature. The severity of fenofibrate muscle toxicity may be the result of the combination of two rhabdomyolysis enhancers, such as hypothyroidism and female gender. To avoid it, strict clinical and laboratory monitoring should be maintained, particularly hypothyroidism. Patients should be informed of possible potentially irreversible effects after taking fibrates.

Abbreviations: ARF = acute renal failure, BUN = Blood urea nitrogen, CABG = coronary artery by-pass graft, CAD = coronary artery disease, CK = creatine kinase, Cr = creatinine, CRF = chronic renal failure, DL = dyslipidemia, DM = diabetes mellitus, HT = hypertension, HTD = Hypothyroidism, NA = not available, TG = triglyceride.

Keywords: fenofibrate, hypertriglyceridemia, hypothyroidism, induced, monotherapy, rhabdomyolysis

1. Introduction

Rhabdomyolysis is a clinical, and biochemical syndrome characterized by skeletal muscle injury, muscle necrosis, and the release of muscle cell constituents into systemic circulation. While fenofibrate monotherapy-induced rhabdomyolysis is rare, it is a serious, even fatal side effect of fenofibrate[1] that is often associated with acute renal failure (ARF) and myoglobinuria. Comorbidities, such as renal, or liver disease, hypothyroidism (HTD), diabetes mellitus (DM), female gender, high dose, and advanced age (older than 65 years old) are major risk factors for fenofibrate-induced rhabdomyolysis.[2] We report the case of a patient with HTD who experienced rhabdomyolysis while on fenofibrate monotherapy for hypertriglyceridemia.

2. Case report

A 36-year-old sterile woman was admitted twice to the hospital. Seventeen years prior to her second admission, she had undergone an initial craniotomy, and the pathological diagnosis showed pituitary adenoma. Her post-operative course was benign. Two months prior to her second admission, she complained of chills, hypohidrosis, pachulosis, fatigue, and anorexia. Fifteen days prior to her second admission, she had an endocrine test showing a marked decrease in basal hormone levels (i.e., cortisol, thyroid, and gonadal hormones). Her liver function, and renal function tests were within normal limits, and there was no history of coronary heart disease. Pituitary hypofunction was diagnosed, and she was admitted to our hospital. The patient took prednisone, and levothyroxine, and had started to use 200 mg micronized fenofibrate a day for hypertriglyceridemia (triglyceride [TG] level of 10.72 mmol/L). After taking fenofibrate for 15 days, the patient complained of diffuse myalgia, and muscle weakness, which had not been alleviated for 2 days. She was readmitted to the hospital. Except for muscle weakness, her physical examination was normal.

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Ethical Statement: This study involving human beings comply with the ethics committee regulations and informed consent was obtained from the patient.

The authors declare that they have no conflict of interest.

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Table 1

A summary of reported 13 cases of rhabodomyolysis associated with fenofibrate monotherapy.

Reference	Year	Age	Sex	Medical history	Fenofibrate	Cr, mg/dL	CK, IU/L	Outcome
Clouatre et al[11]	1999	57	F	CRF, DL, HT, HTD	200 mg, for 4 wk	12.4	8850	Recovery
Barker et al[12]	2003	56	F	HT, DM-II, DL, CRF	200 mg, for 10 d	2	5632	Recovery
Ghosh et al[13]	2004	58	M	CAD, DL	200 mg, for 5 wk		1129	Improved
Tahmaz et al[6]	2007	42	F	HT, DL	250 mg, for 4 wk	5.5	21000	Recovery
Yildiz et al[14]	2008	74	M	CABG, HT, DL	267 mg, for 2 wk	5.3	26680	Improved
Cetinkaya et al[15]	2008	60	F	DM-II, HT, DL	200 mg, for NA	4.2	11867	Recovery
Wu et al[16]	2009	52	F	DL	200 mg, for 1 mo			Recovery
Alessandra et al[17]	2009	54	M	DL, CRF, HTD, DM-I	200 mg, for 3 mo	4.9	52749	Improved
Danis et al[2]	2010	45	F	DM-II, HT, DL	200 mg, for 3 wk	2.2	5698	Recovery
Soyoral et al[18]	2012	56	F	DM-II,HT, DL, CRF	250 mg, for 10 d	6.5	13000	Recovery
Erdur et al[18]	2012	26	M	HT, CRF	200 mg, for 1 wk	1.79	28261	Recovery
Kiskac et al[19]	2013	51	F	HT, DL	250 mg, for 2 y	1.49	9627	Recovery
Marques et al[20]	2014	14	F	HT, CRF, HTD	100 mg, for 9 m	8.42	8332	Improved

CABG = coronary artery by-pass graft, CAD = coronary artery disease, CK = serum creatine kinase, Cr = creatinine, CRF = chronic renal failure, DL = dyslipidemia, DM = diabetes mellitus, HT = hypertension, HTD = Hypothyroidism.

Laboratory testing at admission revealed the following: a marked increase in creatinine kinase (CK) of 9890 U/L (approximately 51 times the upper limit of normal), TG of 0.67mmol/L, serum creatinine (Cr) of 140 μmol/L, blood urea nitrogen (BUN) of 11.70 mmol/L, and blood myoglobin of greater than 500 ng/mL. A diagnosis of fenofibrate monotherapy-induced rhabdomyolysis and rhabdomyolysis-induced ARF was made. Because of the seriousness of her side effects, and the fact that her TG level was within normal range, fenofibrate was discontinued. Adequate fluid resuscitation, mannitol diuresis, myocardium protection, hepatoprotection, and urine alkalinization with sodium bicarbonate were performed. At the end of 5 days, the patient's CK and Cr concentrations had declined to 2350 U/L and 106 μmol/L, respectively. After suspending fenofibrate, the blood test irregularities gradually improved. Two weeks after her second admission, the patient's laboratory values were normal, the patient was well, and she was discharged. After discharge, the patient did not resume hypolipidemic drugs. Rather, her blood lipids were controlled through diet and exercise. Under this regimen, her TGs remained within normal range.

Table 2

A summary of reported 13 cases of rhabodomyolysis associated with fenofibrate monotherapy.

Varialble	Cases of rhabdomyolysis
Sex, n (%)	
male	4
female	9
Mean age, years (range)	50 (14~74)
Medical history, n (%)	
Hypertension	10
Diabetes mellitus	5
Chronic renal failure	6
Coronary artery disease	2
Hypothroidism	3
Not reported	0
Mean fenofibrate monotherapy duration (range), week	14.8 (10d~2y)
Dose, n (%)	
200mg	8
>200mg	4
<200mg	1
Mean serum creatine kinase (range), U/L	16069 (1129~52749)
Not reported, n	1
Mean serum creatinine Cr (range), mg/dL	5 (1.49~12.4)
Not reported, n	2
Outcome, n (%)	
Recovery	9
Improved	4
Death	0
Not reported	0

3. Discussion

Fenofibrate is a fibric acid derivative indicated for use as mono- or combination therapy in adults with hypertriglyceridemia and mixed dyslipidemia (DL).[3] Micronized fenofibrate is better absorbed than standard preparations, which allows for lower daily dosage and once daily administration.[4] In general, fenofibrate is well tolerated and side effects are fairly uncommon (e.g., gastrointestinal, and musculoskeletal symptoms, cutaneous reactions, fatigue, headache, vertigo, sleep disorders, and loss of libido).[5] However, fenofibrate monotherapy-induced rhabdomyolysis can occur.

We report a new case of fenofibrate monotherapy-induced rhabdomyolysis. The patient was diagnosed with rhabdomyolysis based on myalgia, muscle weakness, prominent elevation of CK, lactate dehydrogenase, aspartate aminotransferase, and Cr serum levels.[6] Those values represent a broad clinical spectrum, from asymptomatic elevation of muscle enzymes to potentially, life-threatening clinical situations such as electrolyte disturbances, and ARF, the most common complication of rhabdomyolysis (10–40% of patients).[7] Because fenofibrate led to such serious side effects, and the patient's TG level was normal, then she discontinued fenofibrate, and other hypolipidemic drugs, after which her TG levels remained satisfactory. Thus, one limitation of this case study lies in that it does not investigate the treatment of hyperlipidemia in patients with fenofibrate-induced rhabdomyolysis.

For a more in-depth analysis, we searched for relevant studies in the English literature in the PubMed, and Embase electronic databases from inception to August 1, 2016. The following terms were used: *fenofibrate*, *fibrates*, *hypertriglyceridemia*, and *rhabdomyolysis*. In addition, the reference lists of all accepted papers were manually searched to ensure that no studies were ignored. Thirteen cases of fenofibrate monotherapy–associated rhabdomyolysis were found (Tables 1 and 2). Nevertheless, the

cause of rhabdomyolysis could not be precisely defined. The majority of cases were associated with additional risk factors for muscle injury,[6] while one patient with HTD presented with rhabdomyolysis while on fenofibrate monotherapy for hypertriglyceridemia. Monotherapy-induced, and hypothyroid-associated rhabdomyolysis were rarely described, with only 3 cases having been published in English literature. Consequently, the precise pathophysiology of rhabdomyolysis in HTD remains unclear.[8]

HTD is associated with impairment of mitochondrial oxidative metabolism and many other metabolic pathways. These metabolic abnormalities may sensitize muscle cells to other factors related to muscle injury and increase the risk of rhabdomyolysis. Thyroid hormones that regulate genes encoding structural, and regulatory proteins are lower in the skeletal muscles of hypothyroid patients compared to that of euthyroid patients.[9,10] Previously reported cases of HTD were due to thyroid diseases. Our patient's case is the first reported for thyroid hypofunction after craniotomy for pituitary adenoma. In her case, the severity of fenofibrate-induced muscle toxicity may have been the result of the combination of 2 confounding risk factors for rhabdomyolysis: HTD and the female gender. To avoid rhabdomyolysis, strict clinical, and laboratory monitoring should be employed, especially, for those with HTD. In addition, patients should be informed of the possible, potentially, irreversible effects of taking fibrates.

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