Case Report

Fenofibrate-induced rhabdomyolysis in a patient with stage 4 chronic renal failure due to diabetes mellitus

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Abstract

Rhabdomyolysis is defined as a pathological condition of skeletal muscle cell damage leading to the release of toxic intracellular components into the circulation. Several factors may lead to rhabdomyolysis. Fenofibrate is a fibric acid derivative agent that is used in the treatment of hyperlipidaemia. Although several case reports of rhabdomyolysis have been reported due to the combination of statin and fenofibrate, fenofibrate alone rarely causes rhabdomyolysis. When administering fenofibrate in chronic renal failure, dose should be adjusted. Here, we report a case with fenofibrate-induced rhabdomyolysis in a patient with chronic renal failure.

Keywords: Fenofibrate, Rhabdomyolysis, Chronic renal failure.

Introduction

Rhabdomyolysis is a clinical and biochemical syndrome characterized with muscle content's getting out of the cell as a result of skeletal muscle injury.[1] Its etiology includes severe physical exercise, trauma, infections, hereditary muscle enzyme deficiencies, drugs, alcohol, cocaine, convulsions, hypothyroidism and electrolyte imbalance.[2] Severity of rhabdomyolysis may vary from asymptomatic to severe conditions like serious electrolyte imbalance and acute renal failure.[3]

Fenofibrate is a derivative of fibric acid and indicated in the treatment of hypertriglyceridaemia and combined dyslipidaemia as monotherapy or in combination with statins. Side effects of fenofibrates are gastrointestinal and musculosceletal symptoms, cutaneous reactions, fatigue, headache, vertigo, sleep disorders and loss of libido. Rhabdomyolysis is a rare, but the most serious, even fatal side effect of fenofibrate.[2]

Although rhabdomyolysis cases due to usage of fenofibrate in combination with statins have been reported, rhabdomyolysis related to fenofibrate monotherapy is rare.[4] Presence of chronic renal failure and diabetes mellitus is among the precipitating factors for rhabdomyolysis.[5] When administering fenofibrate in chronic renal failure, dose should

be adjusted. Here, we report a case who had diabetes mellitus related stage 4 chronic renal failure (CRF) and developed rhabdomyolysis with fenofibrate monotherapy.

Case Report

A 56-year-old female patient was admitted with complaints of fatigue and diffuse myalgia. She had type 2 diabetes mellitus for 20 years, hypertension and heart failure for 10 years and chronic renal failure for 6 years. She had been using insulin, acetylsalycillic acid, furosemide and carvedilol. She stated that diffuse myalgia started one week after starting of fenofibrate (250 mg/day) 10 days ago. On her physical examination, arterial blood pressure was 140/80 mmHg, pulse 84 bpm, temperature 36.2°C, respiratory rate 16/min and she was oriented, cooperative and conscious. There were no significant physical examination findings except muscle tenderness and pretibial oedema. Her laboratory results on admission were as follows: glucose: 113 mg/dl, BUN: 78 mg/dl, creatinine: 6.5 mg/dl, sodium: 138 mmol/l, potassium: 4.7 mmol/l, calcium: 9.6 mg/d, AST: 276 U/L, ALT: 91 U/L, LDH: 1195 U/L, CK: 13000 U/L, total protein: 7 g/dl, albumin: 3.7 g/dl, cholesterol: 177 mg/dl, triglyceride: 265 mg/dl, LDL:165 mg/dl, HDL: 24 mg/dl, free T4 :0.88 m IU/ml, TSH: 4.7 m IU/ml, venous blood gas pH:, 33 HCO3:19, pCO2:37, glomerular filtration rate (GFR):17 ml/min, proteinuria: 3, 2 gr/day. Urinary analysis disclosed 3+ proteinuria and 3+ haematuria with dipstick, 14 red cells per high-power field . The patient whose creatinine level was 5.5 mg/dl 2 months before admission was hospitalized with prediagnosis of fenofibrate induced rhabdomyolysis. Fenofibrate was discontinued. IV hydration and bicarbonate infusion to alkalise urine were started. Creatinine which had risen to 8.4 mg/dl on day 4 of hospitalization reduced to 7.2 mg/dl on the day 6. Creatinine level of the patient on discharge was 7.2 mg/dl and 1.5 months later and muscle enzymes were completely normal.

Discussion

Rhabdomyolysis is a clinical and biochemical syndrome characterized by the CK, LDH, aldolase, AST and potassium out of the cell as the result of muscle cell injury . The typical clinical presentation includes muscle weakness, myalgias and dark-colored urine due to myoglobinuria, and the diagnosis is usually established by elevated serum skeletal muscle enzyme levels . Rhabdomyolysis is defined as a serum creatine kinase level of more than ten times the upper limit of normal.[1]

Severe physical exercises and trauma may lead to rhabdomyolysis.[2] Our patient did not have a history of severe physical exercises or trauma. Substance use as alcohol and cocaine can also lead to rhabdomyolysis.[6] Our case did not have the history of using these substances. Hypothyroidism is another cause of rhabdomyolysis.[7] In our case, thyroid function tests were normal. In addition, several case reports on rhabdomyolysis due to the combined treatment of fibrates and other drugs including colchicine, ibuprofen, indomethacin, warfarin, abacavir and mizoribine have been reported in literature.[1] Our patient was not on a statin therapy or any other similar medication.

The most important fatal side effect of fenofibrate is rhabdomyolysis. 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 . It was also hypothesized that fibrates only exacerbate latent preexisting mitochondrial myopathies or accelerate the normal physiologic changes in skeletal muscle associated with aging.[1]

Presence of accompanying renal or hepatic diseases, diabetes mellitus, age more than 65 years, female gender, high doses of drug use (using fenofibrate in larger doses than 250 mg/day) are the major risk factors for fenofibrate induced rhabdomyolysis.[5] Our patient was a 56-year-old female. She had diabetes mellitus and chronic renal failure and she had been administered high doses of (250 mg/day) fenofibrate without taking renal functions into consideration.

Myoglobin formed as the result of muscle injury is filtrated and causes direct renal injury by being reabsorbed from renal tubuli. Myoglobin causes renal injury by renal tubular obstruction.[6] Cases who developed acute renal failure due to fenofibrate induced rhabdomyolysis have been reported.[8,9] CRF is known to be a risk factor for development of fenofibrate related rhabdomyolysis. However only 3 cases heve been reported in literature.[10] Two of them are dialysis patients and the third one is stage 3 CRF patient and all three had hypothyroidism. Simvastatin was also being used in one of them. Our patient was euthyroid and had developed acute renal failure superimposed on stage 4 CRF. While basal creatinine value was 5.5 mg/dl, it was elevated to 8.4 mg/dl and stayed constant at a level of 7.2 mg/dl.

Fenofibrate is mainly excreted from kidneys. It is recommended to be administered by making a renal dose adjustment because its blood level elevates in renal failure (Fenofibrate should be given in a dose of 200 mg/day; if GFR>90 ml/min, if GFR: 60-90 ml/min, 134 mg/day; if GFR: 15-59 ml/min, 67 mg/day; if GFR<15 ml/min, fenofibrate is not recommended) (4). GFR value of our patient was 17 ml/min and she should have been given 67 mg/day of fenofibrate according to renal dose adjustment, she was using it in a dose of 250 mg daily which may have increased the risk of rhabdomyolysis. Although CRF is a risk

factor, it has been used in high doses without making a renal dose adjustment in other cases in literature also.[10]

Conclusion

In conclusion, risk factors precipitating rhabdomyolysis and accompanying diseases should meticulously be reviewed as fenofibrate induced rhabdomyolysis may lead to severe life-threatening conditions. That fenofibrate related side effects may be reduced by making a dose adjustment according to GFR especially in presence of renal failure which should be taken into consideration. Additionally, patients should be informed about side effects of the drug and should be followed up closely in the course of treatment.

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