Acute renal failure due to fenofibrate monotherapy

Fenofibrat monoterapisine bağlı akut böbrek yetersizliği

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Introduction

Rhabdomyolysis is a clinical and biochemical syndrome resulting from skeletal muscle injury and the release muscular cell constituents into extracellular fluid and the circulation (1). Rhabdomyolysis occurs due to drugs, toxins, ischemia and infections. Drug induced rhabdomyolysis mostly occurs with statins but rarely with fibrates. Fibrates are widely used for the treatment of hypertriglyceridemia and generally well tolerated (2, 3). Acute renal failure (ARF) secondary to rhabdomyolysis is an unusual but serious adverse effect with fibrate (especially fenofibrate) monotherapy, usually occurs when fibrates are combined with statins (4, 5).

We herein report a diabetic female patient who developed ARF secondary to rhabdomyolysis induced by fenofibrate monotherapy and also compared our patient's clinical and laboratory features with other cases reported in the literature (4, 6) (Table 1).

Case Report

A 61-year-old woman was admitted to our hospital with a 20-day history of generalized muscle tenderness. She had taken 250 mg fenofibrate daily for almost 1 month because of her hyperlipidemia. Her myalgia and elevated serum creatinine (Cr) (6.9 mg/dl N=0.5-1.6) and serum creatine phosphokinase (CPK) (11030 U/L N=16-190 U/L) concentrations had been noted, so she was referred to our hospital. Past medical history was insignificant other than diabetes mellitus and hypertension. She denied having any trauma, epilepsy, exercise or any other medication known to induce rhabdomyolysis. She has only used metformin, glimepiride and losartan potassium. Physical examination revealed no pathological findings expect for diffuse generalized muscle pain. There was no evidence of cardiac event and diabetic coma. Laboratory findings before fenofibrate therapy were normal (except triglyceride level). After she was admitted to our hospital her laboratory findings were: serum Cr level 5.91 mg/dl (N=0.5-1.6), CPK 8492 U/L (N=16-190 U/L) (Table 1). Before rhabdomyolysis treatment, 24-hour urine analysis showed 640 mg/dl proteinuria (proteinuria improved after treatment). Renal ultrasound and her biomicroscopic evaluation were normal. She was admitted with a diagnosis of ARF secondary to rhabdomyolysis induced by fenofibrate monothera-

Table 1. Comparison of characteristics of three cases with rhabdomyolysis associated ARF due to fenofibrate monotherapy

Clinical characteristics	Our case	Tahmaz et al. (6)	Wu et al. (4)
Age	61	42	52
Sex	Female	Female	Female
Medical History			
Diabetes mellitus	+	-	-
Hypertension	+	+	-
Hypothyroidism	-	-	-
Chronic renal failure	-	-	
Concomitant drugs potentially interacting with fenofibrate	Glimeperid, Metformin, Losartan potassium	Candesartan cilexetil +hydrochlorothiazide	-
Mean fenofibrate therapy duration time (week)	4	4	4
Main symptom	Weakness, myalgia	Generalized myalgia	Generalized myalgia
Laboratory			
Creatinine, mg/dl	5.91 (0.5-1.6)	5.5 (0.5-1.1)	Elevated
Blood urea nitrogen, mg/dl	88 (5-20)	90 (0-50)	43.89 (2.86-8.2)
Serum sodium, mEq/L	138 (135-150)	132 (136-145)	146 (136-145)
Serum potassium, mEq/L	5.26 (3.5-5.5)	4.02 (3.5-5.5)	3.88 (3.5-5.5)
Serum calcium, mg/dl	8.6 (8.5-10.5)	8.5 (8.6-10.2)	-
CPK, U/L	8492 (16-190)	21000 (26-140)	Elevated
AST, U/L	424 (7-39)	533 (0-35)	446 (3-40)
ALT, U/L	411 (2-40)	1400 (0-35)	428 (3-40)
LDH, U/L	2143 (240-480)	878 (0-480)	-
Serum TSH	0.74 (0.34-5.60 Uu/ml)	0.802 (0.27-4.2 Uu/ml)	1.46 (0.4-4.0 MU/L)
Serum fT4	0.93 (0.61-1.12 ng/dl)	0.93 (0.9-1.7 ng/dl)	10 (10.3-24.45 pmol/L)
Secondary acute renal failure	+	+	+
Outcome	Recovery with hydration	Recovery with hydration	Recovery with hemodialysis

ALT - alanine transaminase, AST - aspartate transaminase, CPK - creatine phosphokinase, fT4 - free thyroid hormones: thyroxine, LDH - lactate dehydrogenase, TSH - thyroid-stimulating hormone, +: present, -: absent

py. All medications were discontinued. She was treated by intravenous hydration and urine alkalinisation. Her CPK level returned to baseline within 7 days of hospitalization without any dialysis. She was discharged with complete recovery.

Discussion

Fibrates are generally well tolerated. Rhabdomyolysis associated with fibrates is rare and usually occurs when fibrates are combined with statins (2, 3). Wu et al. (4) reviewed 77 patients with rhabdomyolysis due to fibrate therapy. In this review only 24 cases were associated with fibrate monotherapy and 54 combined with statins or other drugs (colchicine, ibuprofen, warfarin e.g.). In our case she had no medications prescribed other than oral antidiabetics and antihypertensive agents.

Advanced age, diabetes mellitus, hypothyroidism, female sex, medications, renal insufficiency are associated with higher rates of adverse effects for antilipemic agents (7). Wu et al. (4) indicated that rhabdomyolysis associated with fibrates occurred in aged population with diabetes mellitus and/or hypertension. Our patient had diabetes mellitus and hypertension. Hypothyroidism is another risk factor for fenofibrate induced rhabdomyolysis (8). There was not hypothyroidism in two cases reported as well as our patient.

Fenofibrate is mainly excreted by kidney. Therapy with fenofibrate may induce renal dysfunction (9). Rhabdomyolysis also accounts for renal failure (10). In the literature, we found two case reports developed ARF secondary to fenofibrate monotherapy induced rhabdomyolysis (4, 6). In Wu et al.'s (4) review, 54 cases of rhabdomyolysis induced by fenofibrates were complicated with ARF (70%). Only sixteen of them were chronic renal failure before fibrate therapy and only 10 patients had normal renal function during rhabdomyolysis (4). In two cases as well as our patient, ARF developed during the rhabdomyolysis. Three of all recovered. Alternative causes of ARF other than rhabdomyolysis in these cases may be drug nephrotoxicity. However, after stopping the fenofibrate, rhabdomyolysis and ARF resolved promptly. This may imply that ARF was directly related with rhabdomyolysis rather than fenofibrate itself or another drug.

Conclusion

In spite of several cases of rhabdomyolysis associated with fibrates reported in the literature, few cases have been attributed to fenofibrate monotherapy. Physicians should be aware of potentially adverse effects including rhabdomyolysis and ARF after fenofibrate monotherapy even though the patient is diabetic or not. Muscle enzymes and creatinine levels should be monitored closely. Knowing the clinical and laboratory features of these kinds of patients would help us understand the risk factors leading to rhabdomyolysis.

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