Rhabdomyolysis Induced by Fenoverine: A Case Report and Literature Review

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Abstract- Fenoverine is a derivative of phenothiazine. It is commonly used in the treatment of gastrointestinal and gynecological spasmodic disorders. Myalgia is a common side effect, but rhabdomyolysis has only been scarcely reported before. A 77-year-old patient without previous history of liver diseases received fenoverine therapy for four days due to abdominal pain. Acute onset of myalgia, proximal muscle weakness and high creatinine phosphokinase (CK) occurred. The foregoing symptoms and signs and abnormal biochemistry improved gradually after discontinuation of fenoverine use. The pathophysiology of fenoverine-induced rhabdomyolysis is unclear. Some predisposing factors, especially liver cirrhosis, had been reported. However, our patient had none of the well-known precipitating factors. Physicians should be aware of the possibility of rhabdomyolysis in patients receiving fenoverine, whether they are healthy or have musculoskeletal or liver dysfunction.

Key Words: Liver cirrhosis, Fenoverine, Rhabdomyolysis, Myopathy

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INTRODUCTION

Fenoverine is a spasmolytic drug commonly used in the treatment of gastrointestinal spasmodic disorders[1] in Taiwan. This myotropic compound is a non anticholinergic phenothiazine derivative that may also inhibit calcium channel currents[2,3]. Fenoverine has been repeatedly implicated in the occurrence of rhabdomyolysis, a potentially fatal adverse effect, in France. Thes drug has been therefore unavailable in France since December 1995[4,5]. In Taiwan, fenoverine was popularly used and probable fenoverine-induced rhabdomyolysis has also been reported[6,7]. However, previously reported cases in Taiwan all had a history of severe hepatic dysfunction. Here we describe one patient who had normal hepatic function and developed rhabdomyolysis after fenoverine medication. He recovered completely after discontinuation of fenoverine.

CASE REPORT

A 77-year-old patient had suffered from abdominal pain for one week. Gastric ulcer was diagnosed after a duodenoscopy examination. Sonogram of the abdomen showed only mild fatty liver. Ranitidine 150 mg PO bid, Silymarin (Sirin) 70 mg PO tid, and fenoverine 100 mg

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Table 1. *Blood chemistry data*

Date	AST(U/L)	ALT(U/L)	LDH(U/L)	CK(U/L)	Total bilirubin(mg/dl)
5 months before admission	No data	50	No data	No data	No data
On admission	1003	294	1602	59772	1.1
2 days after admission	1206	470	2124	31227	No data
4 days after admission	482	380	2142	5922	No data
6 days after admission	162	265	1745	1921	No data
8 days after admission	124	214	1456	809	No data
12 days after admission	43	114	875	156	No data
21 days after admission	20	31	No data	83	No data

Normal range AST (8-38 U/L), ALT (4-44 U/L), LDH (120-240 U/L), CK (10-160 U/L), total bilirubin (0.1-1.2 mg/dl).

PO tid were prescribed. Four days later, the patient suffered from generalized soreness and weakness of four limbs and the neck with proximal accentuation. He was admitted to our hospital four days after the onset of muscle pain. The patient had no history of exposure to industrial or chemical products, and he could jog for about 1000 meters daily before this event.

Neurological examination showed tenderness in the extremities, especially at proximal muscles. There was mild proximal weakness (Medical Research Concil, or MRC grade 4) in both upper and lower limbs. Deep tendon reflexes showed general areflexia and Babinski sign was bilaterally negative. There was no sensory loss. Serum CK was 59772 U/L (normal < 80) (Table 1). The alanine aminotransferase/aspartate aminotransferase (ALT/AST) were 294/1003 U/L (normal < 44/38) at admission, but were lowered to 31/20 U/L 21 days later. Electromyography (EMG) and nerve conduction velocity study showed normal results two days after admission. The normal EMG findings could imply that sampling did not cover the focal or patchy abnormality (necrosis) of the affected muscles Fenoverine was discontinued immediately after admission. He then received sodium bicarbonate for urine alkalization and hydration for 10 days with gradual improvement in muscle weakness and soreness. He was discharged 12 days later with only mild residual muscle soreness.

DISCUSSION

Toxins and drugs play a role in up to 80% of adult cases of rhabdomyolysis[8,9]. The pathophysiology of fenoverine-induced rhabdomyolysis remains unclear. Ischemia of muscle caused by fenoverine is one of the probable mechanisms[4]. The precipitating factors of fenoverine-induced rhabdomyolysis include patients with concurrent treatment of cholesterol-lowering agents, severe hepatic dysfunction, and skeletomuscular defect such as hunched back and hiatal hernia[4,5,10]. Jouglard et al. reported seven patients who suffered from rhabdomyolysis after fenoverine. Some showed abnormalities in histological examinations of the muscle, including mitochondrial abnormalities and increased lipid storage. Some also showed susceptibility to malignant hyperthermia by contracture tests, or had disorders of oxidative metabolism shown by 31-phosphorus nuclear magnetic resonance spectroscopy[5]. Before taking fenoverine, they all had normal daily life activities. In one of these seven patients, his two sons also presented the same oxidative metabolic dysfunction in the muscle. These cases suggest the existence of genetic predisposition factors and fenoverine may unmask these factors[5]. So far, five cases of probable fenoverine-induced rhabdomyolysis were reported in Taiwan[6,7], all having liver cirrhosis (Table 2). There were also two similar cases with severe hepatic dysfunction reported in France (Chariot et al in 1995). These seven cases and our case were listed in Table 2. Our case had only mild fatty liver shown by sonogram. He was in good health with normal liver function, except for benign prostate hyperplasia under regular medical treatment for 10 months. He received ranitidine and fenoverine concurrently. Though hepatotoxicity induced by ranitidine had been reported before[11], our patient continued ranitidine after the onset of rhabdomyolysis. The

Table 2. *Reported patients of fenoverine-induced rhabdomyolysis*

Sex	Age†	fenoverine	Onset	baseline liver enzymes	liver enzymes after rhabdomyolysis	Concomitant drugs	underlying disease
Cases in France							
M[4]	61	300 mg daily	3rd day	No data	No data	No data	Alcoholic liver cirrhosis, moderate hepatic failure
F[4]	86	600 mg daily	4th day	No data	No data	Ciprofibrate	hypercholesterolemia
Cases in Taiwan							
F[7]	58	100 mg bid	4th day	No data	AST 620 ALT 194	Bumetanide, spironolactone, ursodesoxycholic acid	Liver cirrhosis, portal hypertension
F[7]	77	100 mg bid	14th day	No data	AST 1031 ALT 332	Enalapril, bumetanide, glibenclamide, felodipine, spironolactone, metformin	Diabetes, hypertension, liver cirrhosis, hepatic tumor
M[6]	83	100 mg tid	3rd day	ALT 42	AST 1007 ALT 415	Chlorpheniramine, Nicametate	Hepatitis C, liver cirrhosis, Child A
F[6]	70	100 mg tid	2nd day	AST 44 ALT 39	No data	Proheparum, spironolactone, nizatidine, vitamin B complex, furosemide, acetaminophen, metoclopramide	Hepatitis B, liver cirrhosis, Child C
M[6]	80	100 mg tid	3rd day	No data	AST 186 ALT 879	Proheparum, spironolactone, atenolol, lederscon, sputant	Alcoholic liver cirrhosis, hypertension
M‡	77	100 mg tid	4th day	ALT 50	AST 1003 ALT 294	Tamsulosin, flavoxzte, Spasmo-Evuernil, silymarine, ranitidine	Benign prostate hyperplasia

F: female; M: male; AST: aspartate aminotransferase; ALT: alanine aminotransferase; † in years; ‡ Our patient

ALT/AST level returned to normal after discontinuation of fenoverine. Tests for viral hepatitis B and C were negative, and the bilirubin level was normal. All the clinical data suggested that the elevation of liver enzymes probably resulted from rhabdomyolysis rather than hepatitis.

According to the assessment scheme of the causal relation of suspected adverse drug reactions, our case may be classified as a "probable" reaction[12,13]. A physician should be careful in prescribing fenoverine, especially when a patient has had previous skeletomuscular defects, impaired liver function, and concurrent treatment of drugs with risks of rhabdomyolysis. Monitoring of creatine kinase level is recommended during the treatment of fenoverine especially when myalgia occurs.

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