CASE REPORT

MYOPATHY DUE TO CONCOMINANT USE OF STATIN AND GEMFIBROSIL IN A PATIENT WITH CHRONIC RENAL FAILURE :CASE REPORT

İpek Midi, Özgur Bilgin, Pınar Kahraman Koytak, Tülin Tanrıdağ
Department of Neurology, School of Medicine, Marmara University, Istanbul, Turkey

ABSTRACT
Lipid lowering agents including fibric acid derivatives (fibrates) and HMG-CoA reductase inhibitors (statins) can result in the development of a primarily proximal lower extremity myopathy, occasionally associated with myoglobinuria. These adverse effects increase when the patients are treated concomitantly with statins and fenofibrates or statins and gemfibrozils.

We present a case of chronic renal failure accompanied by acute muscle pain and weakness following the daily administration of 600 mg of gemfibrozil for a month in addition to simvastatin treatment. The clinical state of the patient improved dramatically after cessation of both fibrate and statin therapy. In general, patients with a normal renal function seem to tolerate these drugs well, but they must be used with caution in patients with renal or hepatic failure.

Keywords: Statin, emfibrozil, Chronic renal failure, Myopathy, Rhabdomyolysis, Creatine kinase

INTRODUCTION
Lipid lowering agents are one of the most widely prescribed families of drugs world-wide 1. This widespread usage of these drugs remarks the physicians for the adverse events especially liver, muscle and kidney tissues. The patients generally complain of nausea, constipation, dyspepsia 2. Adverse reactions affecting the skeletal muscle are myalgia, muscle cramps, elevation of creatine kinase (CK). Myositis and rhabdomyolysis are the most severe reactions of these drugs 2. Combined use of different subgroups of antilipidemic agents can increase the risk of adverse side events. Advanced age, diabetes, females, concomitant medications, renal insufficiency, excess in alcohol intake, exercises, trauma and surgery are all associated with higher rates of adverse effects. Rapid remission of symptoms can be achieved after discontinuation of therapy 2.

CASE REPORT
A 73-year-old female patient was admitted to our hospital in March 2005 complaining of weakness in the extremities, more pronounced in her lower limbs, and difficulty in walking for the past 6 days.
The patient complained about fatigue, joint pain and difficulty in climbing stairs for the last year. However, she pointed out that these complaints had increased within the last month.

She had a history of diabetes mellitus and hypertension; which led to chronic renal failure (CRF), for 16 years. She was having peritoneal dialysis for the last 6 months. She also had restless leg syndrome, glaucoma, duodenal ulcer and colonic diverticule.

Her sister had hypertension, her uncle died of bladder cancer and her aunt died of hepatic cancer. She had no history of tobacco or alcohol usage. Meanwhile she was under aspirin 1x300 mg, Metoprolol 2x50 mg, Pantoprazol 1x1, Furosemid 2x2, Simvastatin 1x40 mg, Insulin (mixtard morning: 34units, evening : 24 units) treatment. She had used simvastatin alone for six years and simvastatin and gemfibrozil together for the last month.

On the neurological examination, her bilateral upper extremities had 4/5 muscle strength according to the MRC scale proximally, while her distal hand muscles had normal strength. In her lower limbs the muscle strength was 3/5 of normal strength proximally and 5/5 distally. She had difficulty in foot stepping because of her proximal weakness.

Laboratory findings were as follows; glucose:108 mg/dl (70-110), BUN:87 mg/dl (6-23), creatinine:6.16 mg/dl (0.5-1.1), Na:140.7 mEq/L (138-147), K:5.03 mEq/L (3.5-5.3), Ca:9.3 mg/dL (8.4-10.5), Ionized Ca: 1.21 mmol/L (1.16-1.32), Mg: 2.8 mg/dL (1.2-2.6), AST:128 U/L (10-37), ALT:59 U/L (10-40), LDH:1463 U/L (220-450), ESR:92 mm/h (0-20), Hgb:11.1 g/dL (12.0-17.0), Hct:31.5 % (36.0-50.0), WBC: 11100 u/L (4.0-10.0 X 10 ^3), Platelets:210000 u/L (150.0-440.0 X 10 ^3), Total cholesterol:173 mg/dl (80-200), triglycerid :139 mg/dl (30-200), HDL:43 mg/dl (35-70), LDL: 102 mg/dl (0-140), AntiHbs(+) mIU/mL (<10), AntiHAVlG(+) S/CO (>1), TSH:2.56 uIU/mL (0.27-8.9), T3:62.81 ng/dL (40-181),T4:3.32 ug/dL (5.00-10.7).

Normal levels of Ca²⁺, Mg²⁺ and K⁺ displayed that the situation was not related to electrolyte imbalance. Viral infections may also cause myopathy in CRF. For this reason we planned to look for Coxackie IgM, IgG antibodies. The results were; Coxackie Ig G < 20 U/ml (<80), Coxackie Ig M: 16 U/ml [-(<30).

Her first CK was 3653 and CK-MB was 18.34. Due to these values, the patient was asked to stop using Simvastatin and Gemfibrozil. In the following days her CK level continued to rise and peaked at 6241 U/L on day 5 of the drug break, before it gradually decreased (see table I). Myoglobinuria (895 ng/ml, N: 0-200) was detected in the urine analyses. The last analyses for CK and CK-MB before EMG were 1280 and 18.34 respectively. The EMG was compatible with polyneuropathy and myopathy. Since the patient had CRF and diabetes it was thought that she had an underlying neuropathy. Our patient’s clinical course and laboratory data suggest that the combination of simvastatin with gemfibrozil was the most probable cause of her myopathy. Knowing that furosemid could also augment drug interaction, this drug was discontinued for a period after consulting nephrologists for a short time. She was referred to the physical therapy and rehabilitation section for gait and balance exercises. During the follow up, her gait and muscle strength improved dramatically in a week. However the decrease in CK level was not as rapid as the clinical improvement. In her last neurological examination, the muscle strength was normal in all extremities proximally and distally and her gait was also normal.

<table>
<thead>
<tr>
<th>Table I: CK, AST and ALT values of the patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>16th.03.2005</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td><strong>CK(U/L)</strong></td>
</tr>
<tr>
<td><strong>AST(U/L)</strong></td>
</tr>
<tr>
<td><strong>ALT(U/L)</strong></td>
</tr>
</tbody>
</table>
DISCUSSION

Statins are first-line drugs for the prevention and treatment of hypercholesterolemia. Although statins are generally well tolerated, adverse side effects resulting from prolonged use have been reported, particularly nausea, dyspepsia, flatulence and intestinal constipation. Recently, both muscular and peripheral nervous system disturbances have been cited. The muscle disorder shows a broad clinical spectrum, from asymptomatic elevated serum creatine kinase levels to life-threatening myopathies. These effects usually start after a few days of medication or after prolonged use. Myalgia, muscle cramps, rhabdomyolysis, aching, proximal weakness and elevation of creatine kinase (CK) have been reported as adverse reactions affecting the skeletal muscle for using lipid lowering drugs. The incidence of muscular aches is between 2% to 7%. Myalgia is a common complaint and significant problem for patients taking statins and rate of myalgia ranges from 1% to 5%. Although myopathy induced lipid lowering agents is a rare adverse effect, the incidence rate is between 0.1% to 0.5% in monotherapy while increasing to 0.5%-2.5% in combination therapy.

There is an increasing trend among physicians to use 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) in combination with other antilipidemic agents, particularly for patients who have mixed dyslipidemia. These combinations can be with fibrate or gemfibrozil derivatives. Their interaction greatly increases the risk of muscle damage, particularly in patients with a possible underlying predisposition to myopathy (e.g., chronic renal failure patients, dehydrated patients, elderly patients). High dose statins, concurrent use of hepatic cytochrome P450 inhibitors, acute viral infections, major trauma, surgery, hypothyroidism, renal and hepatic disease, diuretics usage, diabetes mellitus, excessive alcohol intake are other factors related to a high risk of muscle damage.

The adverse effects of antilipidemic drugs may first come to attention with an elevated CK level. A rise in CK level during therapy with statins is well documented, ranging between 0.1% and 10%, usually not exceeding 10 times over the upper normal limit, but Calvalho A, et al., reported that CK levels ranged from 2 to 100 times above normal in 8 of their patients. On the other hand, some patients can have normal CK levels although they complain of myalgia and proximal weakness. Statins have been shown to cause myotoxicity and rhabdomyolysis. In most cases rhabdomyolysis occurs following the use of these drugs for at least one week. A case of rhabdomyolysis after just a single dose of simvastatin is reported by S Jamil et al. We report a case with clinical manifestations such as myalgia, proximal muscular weakness, myoglobinuria and elevated CK levels resulting from the prolonged use of statins combined with a new addition of fibrates. The predisposition factor for our patient is related to this as she is a diabetic, suffers from renal insufficiency and also uses high dosage diuretics.

Rhabdomyolysis is a rare, serious side effect and it can cause acute renal failure, dialysis and death. It is especially important for patients with chronic renal failure such as our patient. In the literature there are some reports which emphasize the earlier requirement for hemodialysis treatment after the prolonged use of antilipidemic agents in patients with chronic renal insufficiency in the oliguric phase who used to survive without dialysis.

The mechanism of antilipidemic agents-induced myopathy remains unclear. Endocrine, metabolic and genetic factors might play a role in the pathophysiology. The best approach to managing statin-related myopathy is to prevention. This includes using the lowest dose and avoiding, when possible, concomitant therapy with drugs known to increase the risk of myopathy. Patients should be instructed unexpected muscle pain or discoloration of urine. Management of frank rhabdomyolysis requires stopping the drug. There is no need to discontinue statin therapy in asymptomatic patients whose CK levels are elevated but not more than 10 times. Patients complaining of myalgias without elevated CK levels can continue the medication until their symptoms are tolerable. There are reports of restarting a lower dose of the offending statin or switching to a different statin.

Our patient’s clinical state became asymptomatic after withdrawal of the drug, although the CK level remained elevated and we continue to monitor CK levels in the following months.
Statins and other lipid lowering drugs are in favor and are generally well tolerated but their myotoxic properties should keep physicians on alert especially in high risk patients such as those suffering from CRF and in the case of concurrent use of multiple drugs.

REFERENCES