Rhabdomyolysis and Acute Renal Failure Associated with Gemfibrozil Therapy

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Dear Sir,

Gemfibrozil is a fibric acid derivative introduced in 1982 as a lipid-lowering drug. Adverse effects such as myopathy [1], myosi-tis [2] and rhabdomyolysis [3, 4] have been reported when it is administered in conjunction with hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, and infrequent acute renal failure has also been published with this drug combination [5-7]. Preexisting mild renal impairment may increase the risk of rhabdomyolysis since the primary route of elimination of gemfibrozil is renal. We report a case of rhabdomyolysis and acute renal failure in a patient receiving gemfibrozil as the only lipid-lowering agent, and in absence of any other drug or clinical condition recognized as cause of rhabdomyolysis.

Material and Methods: The patient was a 70-year-old woman with a 12-year history of insulin-dependent diabetes mellitus, and in the last 7 years hypertension, currently in good control with enalapril 20 mg daily. The previous laboratory data to gemfibrozil treatment showed: plasma urea 25 mmol/l (71 mg/dl), plasma creatinine 159 mmol/l (1.8 mg/dl), hemoglobin 131 g/l, hematocrit 38.7%. The fasting lipid status showed: total plasma cholesterol 7.33 mmol/l (283 mg/dl), plasma triglyceride 3.45 mmol/l (305 mg/dl), plasma LDL-cholesterol 4.76 mmol/l (184 mg/dl), plasma HDL-cholesterol 0.95 mmol/l (37 mg/dl). Due to the inefficacy of dietary treatment to control hyperlipidemia during a 3-month period, gemfibrozil was administered at a dose of 600 mg twice a day. Four days later she complained of generalized muscle weakness and tenderness in lower extremities and lumbar region, with emission of dark urine. Diclofenac 75 mg daily was added, and 48 h later the patient became oliguric. At admission, the patient appeared unwell. The temperature was 36.5°C and the blood pressure was 170/85 mm Hg. Tenderness in the lower extremities and lumbar region were detected on physical examination.

Laboratory data showed: plasma urea 75.3 mmol/l (211 mg/dl), plasma creatinine 548 µmol/l (6.2 mg/dl), potassium 5.9 mmol/l, sodium 137 mmol/l, calcium 2.44 mmol/l (9.8 mg/dl), total proteins 7.1 g/dl, glucose 6.66 mmol/l (120 mg/dl), pH 7.27, carbon dioxide 18 mmol/l, creatine kinase (CK) 719 µmol/l (43,173 IU/l), CK-MB 2%, aspartate aminotransferase 15.2 µkat/l (912 U/l), aldolase 17 IU/L (ref. < 7.6), lactate dehydrogenase 47.2 µkat/l (2,836

U/l), hematocrit 36.2%. The white cell count was 6,100/mm³, with 79% neutrophils, 11% monocytes, 8% lymphocytes, 1% eosinophils, and 1% basophils. Plasma myoglobin 331 µg/l (ref. < 70), and urine myoglobin 2,064 µg/day (ref. < 50 µg/day). The urinalysis contained frequent granular casts, 3 white cells and 2 red cells per high-power field. No eosinophils were seen. Serum protein electrophoresis, coagulation tests and thyroid function were normal. Rheumatoid factor, circulating immune complexes, ANA, anti-DNA and ANCA were negative. X-ray films of the chest and abdomen were normal. A renal ultrasonographic and Doppler examination showed normal size and morphology without signs of renal artery stenosis. A deltoid muscle biopsy revealed nonspecific abnormalities with no inflammatory infiltrate, vasculitis or fibrinoid necrosis.

Administration of volume and infusion of bicarbonate were initiated, with a good diuretic response in the first 24 h, and progressive recovery of the renal function without requiring dialysis. Ten days later, the patient was asymptomatic, with normal CK values. Four months later the laboratory data showed: plasma urea 21 mmol/l (59 mg/dl), plasma creatinine 132.6 µmol/l (1.5 mg/dl), and creatinine clearance of 51 ml/min.

Discussion: In absence of other recognized causes, rhabdomyolysis was attributed to gemfibrozil treatment. We are not aware of a previously reported case where this drug, administered without HMG-CoA reductase inhibitors, has been linked to rhabdomyolysis and acute renal failure (Medline 1982-1995). Myopathy [1] and myositis [2] induced by gemfibrozil have been reported. When combined with lovastatin, rhabdomyolysis has been published at least in 17 patients [3-7], with acute renal failure in 5 of them. Corpier et al [8] have suggested a possible synergetic toxic effect between both drugs, since gemfibrozil appears to inhibit hepatic metabolism of lovastatin resulting in higher circulating levels of the active drug, predisposing to enzyme leakage and producing rhabdomyolysis.

The previous treatment with enalapril in this patient, and particularly the addition of the nonsteroidal anti-inflammatory drug diclofenac, could have contributed to the appearance of the acute renal failure. Although we did not perform renal biopsy, the urinalysis and the evolution of the patient did not suggest the diagnosis of interstitial nephritis due to diclofenac. In this sense, Marais and Larson [5] reported a patient who developed acute renal failure and rhabdomyolysis with gemfibrozil and lovastatin treatment while

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he was also receiving ibuprofen. This suggests that alterations in renal hemodynamics, particularly through inhibition of prostaglandin synthesis by diclofenac, could contribute, besides the rhabdomyolysis, to the pathogenesis of the acute renal failure in our patient. Preexisting mild renal impairment predisposes to a reduction in glomerular filtration rate when nonsteroidal anti-inflammatory drugs are given [9]. The decreased renal excretion of gemfibrozil in these circumstances increases its potential adverse effects [8]. In conclusion, gemfibrozil administered without HMG-CoA reductase inhibitors can produce rhabdomyolysis and acute renal failure, and should be used with great caution, particularly in patients with impaired renal function or concomitant use of nonsteroidal anti-inflammatory drugs.

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438

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