
Fibrate Induced Myopathy in Renal Replacement Therapy Patients

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Introduction

Rhabdomyolysis is a clinical syndrome characterized by necrosis of striate muscles and acute increases of serum creatinine kinase more than five times the normal value, (CK-MB fraction less than 5%).

At the cellular level, the initial insult causes a series of reactions to the cell internal environment, accumulation of sarcoplasmic calcium, toxic damage to intracellular organelles and eventual necrosis of muscular fibrils. Rhabdomyolysis is usually the result of traumatic muscular injuries (1). However, 25% of cases occur in a setting of non-traumatic events and are attributed to various clinical conditions (inflammatory myopathies, heat stroke, seizures, neuroleptic malignant syndrome, viral infections and disorders of endocrine glands) and/or drug overdosage and intoxication (amphetamines, phencyclidine, alcohol, antilipidemic therapy et al) (2).

Although the first description of rhabdomyolysis following therapy with clofibrate dates back to 1968, toxic induced rhabdomyolysis has emerged with increasing frequency especially after the introduction of modern lipid-lowering drugs (statins) (3). Apparently all fibrates can induce myopathy that seems to be attributed to inhibition of cellular sterol synthesis and is independent of the duration of therapy. The risk is amplified when fibrates are combined with statins, however even in this case true rhabdomyolysis rarely (<0, 1%) occurs (4, 5).

The incidence of myopathy and eventual rhabdomyolysis during a fibrate regimen seems to be multifactorial. Genetic predisposition certainly plays a role, as evidenced by the high occurrence of myopathy in patients with inherited metabolic disorders (phosphorilase, phosphofructokinase, carnitine deficiency), even after small doses of fibrates (6). More importantly renal failure, acute viral infections, hypothyroidism, major trauma and drug interactions especially concomitant use of statins, cyclosporine, macrolide antibiotics and azole antifungals linearly increase the risk (7, 8).

The onset of the clinical syndrome is insidious and heralded by an unexplained proximal myalgia, weakness and tenderness. With time, symptoms extend to involve the upper and lower limbs (myositis). Beyond this point continuous drug administration, results in frank rhabdomyolysis, release of creatinine-phosphokinase (CPK) and myoglobin in the circulation, myoglobinuria and eventually acute toxic tubular necrosis (9).

Case report

Two case reports are presented in this study. The first concerns a patient with diabetic end-stage renal disease (ESRD) undergoing haemodialysis (HD). The second, a patient with ESRD due to Alport's syndrome, on peritoneal dialysis (PD). Both complained of muscle pain, weakness and tenderness especially of the extremities, at the time of their admittance in the Nephrology Department.

Both patients had a history of coronary heart disease and hyperlipidaemia and no history of alcohol abuse. They have been treated for the past three months with gemfibrozil but in a dosage not adjusted for their residual renal function levels. Both of them described weakness, myalgia and stiffness around the hips and neck initially, that became generalized, however more pronounced in the proximal muscles a few days later and before their admittance in our hospital. They denied dyspnoea or dysphagia nor did they have any numbness, syncope, cardiac symptoms, or recent history of trauma. On physical examination the patients temperature, blood pressure and pulse rate were normal. Examination of the abdomen, chest and thyroid gland were unremarkable. Functions of the cerebellum and cranial nerves appeared to be intact. Neither neurological symptoms nor signs of infection or trauma were observed. Laboratory tests showed leucocytosis with neutrophilia, high erythrocyte sedimentation rate and increased levels of the hepatic enzymes (AST, ALT, γ -GT), CPK (3915 IU/l and 786IU/l for HD and PD patient respectively) with normal CK-MB fraction. Lactic dehydrogenase (LDH) was increased (1629 IU/l and 1087 IU/l respectively) as well as myoglobin (1550 ng/dl and 920 ng/dl respectively). On the basis of the clinical picture, the laboratory findings and the drug history, the diagnosis of toxic-induced myopathy was considered. In order to establish the diagnosis an electromyographic study was performed in both cases. Diagrams of small, short-duration, polyphasic motor unit action potentials, without fasciculation or fibrillation potentials were observed (myopathic pattern of injury). Thus fibrates were discontinued and the patients received non-steroidal anti-inflammatory drugs. Four days later, the levels of CPK and LDH gradually declined to normal. Approximately after a week of hospitalization the patients were asymptomatic and able of physical exercise.

Discussion

Patients with ESRD, often (estimated 30-70% of the population) exhibit a disturbance of their lipid profile, which increases morbidity and mortality mainly due to accelerated cardiovascular disease. The disorder is complex and varies substantially within groups of patients according to the type of renal replacement therapy chosen (haemodialysis, continuous ambulatory peritoneal dialysis or transplantation). The phenotype of the observed hyperlipidaemia is similar to that of type IV (according to the old Friedrikson classification) or hyperprobetaipoproteinaemia. The accumulation of triglycerides-rich particles observed in uraemic patients may in principle reflect either increased production or diminished removal of lipoproteins from the circulation, or combination of both. In addition, patients in PD are at greater risk of developing hypercholesterolaemia, mainly due to lipoprotein overproduction resulting from the absorption of dialysate glucose and the loss of lipoproteins into the peritoneal effluent (10).

In patients with ESRD electrophoresis of circulating lipoproteins certificate that triglycerides are delivered to the periphery from the intestine as chylomicrons and from the liver as VLDL. Chylomicrons contain the intestinal apolipoprotein (apo) B-48, whereas VLDL contain the liver-specific apo-100. Recently another apolipoprotein the so-called lipoprotein (a) has become important for patients with renal disease because high concentrations appear to be especially atherogenic. In uremia the distribution of lipid and apoproteins in lipoprotein density classes is distorted.

Studies with fibrates showed that these drugs improve the lipidemic profile of ESRD patients. These drugs undergo hepatic metabolism via the cytochrome P450 enzyme (3A4 isoenzyme) system. Drug metabolites are excreted in the urine through filtration and tubular secretion. Moreover approximately 95% of the drug is bound to plasma proteins. In chronic renal failure the pharmacokinetics of fibrates are disturbed in part due to the loss of renal excretion and in part to the high protein binding, so that a smaller fraction of the drug is eliminated from the circulation (11). The net result is accumulation of the drug and toxic plasma levels. Indeed the risk of myopathy in these cases is increased in a fraction of more than 0,1-0,5% in monotherapy with fibrates and more than 0,5-2,5% in combination therapy with other antilipidemics. Thus dose adjustment in ESRD is considered to be mandatory.

Patients with ESRD suffer from disorders of lipid metabolism. Therapy should be instituted so that accelerated cardiovascular disease is prevented. However the decision for the prescription of antilipidemic regimens must be based on the presence, type and degree of hyperlipidaemia, estimation of residual renal function, type of renal replacement therapy and concomitant drug therapy, if undesirable effects like myopathy or rhabdomyolysis are to be avoided.

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