Bezafibrate induced rhabdomyolysis

Eduardo Kanterewicz, Raimon Sanmarti, Jaume Riba, Isabel Trias, Josefina Autonell, Joan Brugués

Abstract
The case is presented of a 70 year old woman with mild hypercholesterolaemia and hypertension who was readmitted to hospital six months after a previous admission for angina pectoris. The patient was treated with verapamil, nifedipine, and aspirin, and had been receiving bezafibrate (400 mg every 12 hours) for the previous 40 days. Twenty four hours after admission she developed podagra, which was treated with indomethacin (100 mg daily). Eight days after admission myocardial infarction was suspected, and the next day she presented with symptoms of rhabdomyolysis, which was confirmed by laboratory tests. Bezafibrate was withdrawn and the patient became asymptomatic after seven days. It is recommended that doctors should be aware of the possibility of patients, especially those with impaired renal function, developing rhabdomyolysis while being treated with bezafibrate.

Bezafibrate, a fibrac acid derivative related to clofibrate, is widely prescribed in Europe for type II and IV hyperlipoproteinaemia. A few cases of myopathy, diagnosed as rhabdomyolysis or myositis have been reported as side effects of its use. This paper describes the clinical and pathological findings in a 70 year old woman with acute rhabdomyolysis after treatment with bezafibrate and a review of the literature is presented.

Case report
A 70 year old woman presented in 1980 with mild hypercholesterolaemia and hypertension. At presentation six months earlier for angina pectoris, her serum chemistry results were: creatinine 168·0 μmol/l, cholesterol 7·9 mmol/l, triglycerides 5·7 mmol/l, and uric acid 0·46 mmol/l. Creatine kinase value was 29 IU/l (normal value up to 170). The patient was readmitted with typical angina. There were no abnormalities on examination, and serum creatine kinase and serum aspartate aminotransferase (AST) levels were within the normal range; the creatinine value was 176·8 μmol/l. Her angina disappeared completely on treatment with intravenous nitrates. The patient received verapamil 120 mg every 12 hours, nifedipine 20 mg daily, and aspirin 200 mg daily. She had also been receiving bezafibrate (400 mg every 12 hours) for the previous 40 days.

Twenty four hours after readmission she developed podagra and indomethacin (100 mg daily) was given with good response. Eight days after admission the patient suddenly developed diffuse thoracic and upper limb pain, and although there were no electrocardiographic changes a myocardial infarction was suspected. Creatine kinase levels were high (6480 IU/l; MB fraction 1·9%, normal value up to 10%) and AST was 300 IU/l (normal value up to 40). She was transferred to the intensive care unit.

The next day the patient presented with profound weakness and muscular cramps and her limb muscles were painful on examination. Urine was reddish and reactive strip analysis showed positive haemoglobin with no cells on the sediment. Rhabdomyolysis was suspected, bezafibrate was discontinued and vigorous hydration with urine alkalisation was started. The diagnosis was confirmed with myoglobin blood values of 14·274 ng/ml (normal value up to 90 ng/ml) and myoglobinuria of 21·316 μg/24 hours (normal value up to 50 μg/24 hours). Creatinine levels reached 238·7 μmol/l.

A right gastrocnemius muscle biopsy sample was taken and showed groups of muscle fibres with degenerative changes (hyalinisation and fragmentation) and several necrotic fibres were surrounded by a large number of macrophages (fig); inflammatory infiltrates were not found.

Seven days after bezafibrate withdrawal the patient was asymptomatic and a week later creatine kinase values returned to normal, and creatinine levels stabilised at about 176·8 μmol/l. At six months follow up the patient remained well without muscular symptoms. Further investigations, including thyroid function tests, antinuclear antibodies, rheumatoid factor, and antibodies to Jo-1 were normal or negative, and creatine kinase levels remained within the normal range.

Discussion
Compared with other tissues, striated musculature is usually thought to be tolerant to drug induced injuries. Rhabdomyolysis, defined as acute or subacute damage or necrosis of striated musculature with leakage of myoglobin, creatine kinase and other substances into the plasma is a potentially fatal, although rare event. Several drugs have been implicated as causative agents in this syndrome. Since the first description in 1968 of clofibrate acute muscular syndrome, this lipid lowering drug has been associated with rhabdomyolysis. In the review by Rush et al in 1986, 78 cases of clofibrate myopathy were quoted and data available from half of these showed that toxicity developed after three to 370 days of treatment; 43 of 64 patients had
muscle enzymes are known to occur with bezafibrate and other fibric acid compounds.

Almost all patients had some degree of decreased renal function before the introduction of bezafibrate. With discontinuation of the drug recovery usually occurred, although a transient but considerable renal injury sometimes requiring haemodialysis was observed. Histopathological features of bezafibrate myopathy are described in only one patient and these confirm the presence of necrotic material along with phagocytosis without evidence of active inflammation, as in our patient. In a patient with rhabdomyolysis induced by lovastatin, a lipid lowering drug which is not related to the fibric acid derivatives, the histology was described as 'consistent with polymyositis'. These workers suggest that the cellular infiltrate was due to mononuclear elements being present to remove tissue debris. We feel that these histological findings are not sufficient to diagnose polymyositis in the absence of inflammatory infiltrates. We also maintain that the lack of adequate definition in patients with drug induced rhabdomyolysis may lead to conflicting situations with respect to treatment and prognosis.

It is interesting to note that lovastatin induced rhabdomyolysis has been described in association with other drugs such as gemfibrozil, cyclosporin, and erythromycin. Our patient developed acute rhabdomyolysis just after the introduction of indomethacin; this drug has not been involved in drug induced rhabdomyolysis, but it is known that indomethacin can lead to an impairment of renal function in older patients and in this way it may predispose patients to bezafibrate toxicity.

The actual mechanism of this toxic effect by bezafibrate is far from clear; the drug is rapidly absorbed after a dose by mouth, is highly protein bound, and is largely excreted unchanged in urine; therefore a dose reduction is recommended in patients with impaired renal function. Our patient was receiving a larger dose than normally advised (400 mg daily or less in case of renal failure), but from other reports it seems that even with adjusted doses, the concentrations of bezafibrate in blood were high enough to be toxic. Several cases of clofibrate induced rhabdomyolysis have, however, been described in patients with previously normal renal function and hence a direct toxic effect of these drugs, not related to accumulation, might be another aetiological possibility. Muscular toxicity has been suggested to be related to the

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<th>Myoglobin (ng/ml)</th>
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Abbreviations: M = male; F = female; NA = not available; ND = not done.
chlorine molecule present in all fibrin acid derivatives, with the exception of gemfibrozil, but this has not been studied in detail. Different studies have shown that hypolipaemic drugs interfere with several pathways of muscle cell energy metabolism, and muscular lipoprotein lipase activity. 

Bezafibrate is a well tolerated hypolipaemic drug that is being used increasingly in older patients with other chronic diseases. Doctors should be aware that, although rare, muscular toxicity, either as asymptomatic serum creatine kinase elevation, or, more seriously, as full range rhabdomyolysis, may occur in patients receiving bezafibrate treatment, mainly in those with impairment of the renal function or receiving other drugs at the same time.

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