

Rhabdomyolysis and Acute Renal Failure Following a Switchover of Therapy between Two Fibric Acid Derivatives

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ABSTRACT

Drug induced myopathy has been reported with the use of fibric acid derivatives, hydroxymethylglutaryl coenzyme A (HMG - CoA) reductase inhibitors and nicotinic acid. Over the last three decades, hypolipemiant like fibric acid derivatives and statins have been increasingly recognised as causes of rhabdomyolysis and acute renal failure especially during combination therapy and in the presence of underlying renal impairment.

We report two cases of bezafibrate-induced rhabdomyolysis in patients with underlying coronary artery disease and pre-existing renal impairment. Both patients developed rhabdomyolysis leading to acute renal failure soon after their hyperlipidaemia treatment was changed from gemfibrozil to bezafibrate. There were no intercurrent illnesses or co-administration of other lipid lowering drugs in both patients. Even though both drugs belong to the same fibric acid derivatives group, these patients developed the complication only after a switchover of therapy.

Keywords : rhabdomyolysis, acute renal failure, lipid-lowering drugs.

Singapore Med J 2001 Vol 42(8):368-372

INTRODUCTION

Rhabdomyolysis and deposition of myoglobin in the kidney is a major cause of acute renal failure, accounting for 7% of all cases of acute renal failure⁽¹⁾. Adverse effects such as myopathy, myositis and rhabdomyolysis leading to acute renal failure have been reported with the use of fibric acid derivatives such as clofibrate^(2,3), fenofibrate⁽⁴⁾, bezafibrate^(5,6) and gemfibrozil⁽⁷⁻⁹⁾. Pre-existing renal impairment may increase the risk of rhabdomyolysis since the primary route of excretion of fibric acid derivatives and their metabolites is via the renal route^(10,11). We report two patients with underlying renal impairment who were previously treated with gemfibrozil but only developed

rhabdomyolysis and acute renal failure soon after a changeover of treatment to bezafibrate (also a fibric acid derivative).

METHODS

This is a retrospective case report describing two male patients who were admitted to Hospital Universiti Sains Malaysia between March to May 1998 and diagnosed to have rhabdomyolysis. Both were elderly patients with underlying coronary artery disease, renal impairment and hyperlipidaemia. They developed rhabdomyolysis several days following a change of hyperlipidaemic treatment from gemfibrozil to bezafibrate. Both patients developed acute renal failure requiring dialysis support. The biochemical changes and course of clinical events in both patients are described.

Case 1

A 64-year-old Malay man was admitted with a day history of generalised muscle weakness and tenderness. He had underlying coronary artery disease, hypertension, previous stroke, renal impairment (baseline serum creatinine of 254 $\mu\text{mol/l}$) and hyperlipidaemia. His medications were atenolol 100 mg daily, isosorbide dinitrate 10 mg three times daily, frusemide 20 mg daily, aspirin 150 mg daily, nifedipine 10 mg three times daily and gemfibrozil 600 mg twice daily. There was no history of ingestion of traditional medication. The fasting lipid profile showed : total cholesterol, 7.16 mmol/l and plasma triglyceride, 2.02 mmol/l. The patient has been taking gemfibrozil 600 mg twice daily for one year. Three days prior to admission, he was prescribed bezafibrate 200 mg three times daily when gemfibrozil supply became unavailable. On the day of admission, he complained of lethargy, generalised muscle weakness and tenderness with decreased urine output and dark coloured urine. There was no history of trauma, seizure, fever or recent illness. The patient appeared unwell, afebrile with a blood pressure of 180/100 mm Hg on admission. Generalised muscle tenderness was detected.

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Plasma urea and creatinine rose from 18.8 mmol/l and 477 micromol/l at the time of admission to a maximum of 48.6 mmol/l and 999 micromol/l respectively by the third day of admission. Serum potassium was 4.5 mmol/l, sodium 140 mmol/l, calcium 2.12 mmol/l and phosphate 3.15 mmol/l. Serum glucose was 8.2 mmol/l. Creatine kinase was 2331 IU/l and later peaked to a value of more than 10,000 IU/l. Total protein was 79 g/l, aspartate aminotransferase 1496 U/l, alanine aminotransferase 363 U/l, alkaline phosphatase 75 U/l, lactate dehydrogenase 4576 U/l. Haemoglobin was 13.4 g/dl and white cell count 11,000/mm³. Urine myoglobin was positive. Total cholesterol was 3.41 mmol/l and triglycerides 4.26 mmol/l. The coagulation test prothrombin time (PT/INR) was 1.16 and partial thromboplastin time (PTT) 46.2 sec. with a control of 28.0 sec. Thyroid function was normal. Rheumatoid factor and antinuclear antibody (ANA) were negative. Chest radiograph was normal. ECG tracing showed sinus rhythm with leftward axis and changes of previous inferior myocardial infarction and left ventricular hypertrophy. Transthoracic ECHO of the heart revealed left ventricular hypertrophy with satisfactory systolic function and mild pericardial effusion. The patient was oliguric.

A diagnosis of acute renal failure secondary to drug-induced rhabdomyolysis was made. The patient developed fluid overload, hyperkalaemia and metabolic acidosis and was supported with hemodialysis on the fourth day of admission. He had bleeding manifestations from the catheter site and passed melaenic stool needing blood transfusion. He developed an acute coronary event on the seventh day of admission following his third haemodialysis. He subsequently became hypotensive, developed complete heart block and succumbed despite active resuscitation and transvenous cardiac pacing.

Case 2

A 64-year-old Malay man was admitted with a day history of generalised muscle weakness and tenderness. He had underlying hypertension, diabetes mellitus, ischaemic heart disease, hyperlipidaemia and renal insufficiency (baseline serum creatinine 140 ummol/l). His medications were atenolol 50 mg daily, enalapril 20 mg twice daily, aspirin 150 mg daily, chlorothiazide 500 mg daily and gemfibrozil 600 mg twice daily. There was no history of taking traditional medication. Fasting lipid profile showed: total cholesterol, 7.16 mmol/l; plasma triglyceride, 4.11 mmol/l. The patient was taking gemfibrozil at a dose of 600 mg twice daily for almost one year. Several days prior to admission he was put on a trial

of bezafibrate 400 mg twice daily as his lipid profile had not shown much improvement. Four days later, he complained of generalised muscle weakness and tenderness associated with lethargy but he was not oliguric. There was no history of trauma, seizure, fever or recent illness. The patient appeared unwell, afebrile with a blood pressure of 140/80 mm Hg on admission. Generalised muscle tenderness was detected.

Plasma urea and creatinine rose from 24.4 mmol/l and 544 micromol/l at the time of admission to a maximum of 33 mmol/l and 850 micromol/l respectively by the third day of admission. Serum potassium was 3.6 mmol/l, sodium 131 mmol/l, calcium 2.1 mmol/l and phosphate 2.17 mmol/l. Serum creatine kinase was 3000 IU/l and later peaked to a value of 12,852 IU/l. Total protein was 66 g/l, aspartate aminotransferase 1089 U/l, alanine aminotransferase 355 U/l, alkaline phosphatase 51 U/l and lactate dehydrogenase 2376 U/l. Haemoglobin was 8.8 gm/dl and white cell count 10,300/mm³. Urine myoglobin was negative. The urine analysis was normal. The coagulation tests and thyroid function test were normal. Auto antibody screening was negative. Chest radiograph was normal. Ultrasound of the kidneys showed normal parenchymal echogenicity with no evidence of obstruction.

A diagnosis of acute renal failure secondary to drug-induced rhabdomyolysis was made. He was hydrated with normal saline and underwent alkaline diuresis. In view of the increasing trend of plasma urea and creatinine the patient was treated with peritoneal dialysis. Within two weeks the creatine kinase level decreased to 30 IU/l and hepatic transaminases decreased to near normal levels. The plasma urea and

Table I. Summary of patient characteristics, investigation results, management and outcome.

	Case 1	Case 2
Age (years)	64	64
Sex	male	male
Bezafibrate dose (mg/d)	600	800
Peak creatine kinase (IU/L)	10,000	12,852
Urine myoglobin	positive	negative
Aspartate aminotransferase (U/L)	1496	1089
Alanine aminotransferase (U/L)	363	355
Lactate dehydrogenase (U/L)	4576	2376
Creatinine		
baseline	254	140
on admission	477	544
maximal	999	850
Baseline creatinine clearance (ml/min)	21	52
Treatment	haemodialysis	peritoneal dialysis
Outcome	died	survived

creatinine level upon discharge were 7.7 mmol/l and 203 micromol/l respectively. He was discharged after three weeks of hospital stay.

DISCUSSION

Drug-induced myopathy is now a well recognised potential adverse effect of fibric acid derivatives⁽²⁻⁹⁾ and statins⁽¹²⁻¹⁴⁾. Nicotinic acid has also been implicated⁽¹⁵⁾. The risk of developing drug-induced myopathy may be greater in patients with pre-existing impaired renal function^(10,11) or concomitant use of certain drugs. These factors may reduce excretion of the drug or increase the non protein bound portion of the drug or its metabolite^(12,13).

Early reports, primarily published in the 1980s confirmed muscle damage with elevated creatine kinase (CK) levels associated with use of the fibric acid derivative bezafibrate^(5,6). Gemfibrozil is a newer fibric acid derivative initially marketed in 1982. Adverse effects such as myopathy⁽⁸⁾, myositis⁽⁹⁾ and rhabdomyolysis^(10,16) have been reported when it is administered in conjunction with hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors. However, rhabdomyolysis and acute renal failure have also been reported in patients receiving this drug alone⁽⁷⁾. Most of these patients had some degree of renal impairment^(3,5,11) and this predisposed to the complication since fibric acid derivatives and their metabolites are eliminated primarily via the renal route. The fibrate drugs are excreted predominantly as glucuronide conjugates; 60% to 90% of an oral dose is excreted in the urine, with smaller amounts appearing in the faeces. Excretion of these drugs is impaired in renal failure, though excretion of gemfibrozil was reported to be less severely compromised in renal insufficiency than excretion of other fibrates⁽¹⁷⁾. According to the information leaflet by the drug manufacturers, approximately 70% of administered dose of gemfibrozil is excreted in the urine with less than 2% excreted unchanged. Bezafibrate however, is mostly excreted in the urine with 50% excreted unchanged.

Both patients reported here are elderly patients with underlying renal impairment. They have been taking gemfibrozil at a dose of 1200 mg daily (maximum dosage recommended for patients with normal renal function) for a period of one year without any problems. However, when the treatment was changed to bezafibrate, symptoms of myotoxicity developed almost immediately. This may be explained by the dosage of bezafibrate prescribed as well as the severity of pre-existing renal impairment. The first patient had a moderately severe degree of chronic renal failure (creatinine clearance of 21 ml/min).

However he only developed rhabdomyolysis after the introduction of bezafibrate at a dose of 600 mg daily. A possible explanation for the development of rhabdomyolysis with bezafibrate but not with an equivalent dosage of gemfibrozil in this case may be the different degrees of propensity for myotoxicities amongst drugs belonging to the same group and the fact that excretion of bezafibrate is more severely compromised compared to gemfibrozil in the presence of renal insufficiency⁽¹⁷⁾. Myotoxicity that developed in the second patient who had a milder degree of renal impairment (creatinine clearance of 52 ml/min) could be explained by the fact that the dose of bezafibrate which he received (800 mg daily) was higher than the dose recommended for normal individuals. None of the other drugs co-ingested by both patients have been reported to potentiate the myotoxic effect of both fibrates. It is also interesting to note that both patients have elevated levels of aminotransferases and lactate dehydrogenase. This has also been reported in rhabdomyolysis associated with other fibric acid derivatives & statins^(7,10,12). High levels of aminotransferases and alkaline phosphatase have been reported as toxicity due to fibric acid derivatives unrelated to rhabdomyolysis⁽¹⁸⁾. The negative urine myoglobin result found in the second patient was somewhat surprising considering he had frank rhabdomyolysis. The semi-quantitative method used for urine analysis of myoglobin in our laboratory may render it liable to observer's error.

The pathogenesis of myopathy associated with fibrates and statins is unknown. Pierce and colleagues of the Food and Drug Administration⁽¹⁰⁾ reported several patients with rhabdomyolysis due to combination lovastatin - gemfibrozil treatment who underwent skeletal muscle biopsy but none of them had an appreciable inflammatory cell infiltrate. These patients were found to have muscle fibre necrosis and fragmentation with type II muscle fibre atrophy without evidence of frank myopathy or inflammation. This makes immune mechanism a less likely cause of the myopathy. Drug-induced membrane destabilizing effects leading to myofibrillar degeneration have been postulated to account for clofibrate-induced myopathy⁽¹⁹⁾ but it is not readily apparent why skeletal muscle should be a target tissue. No clear evidence exists of combined cardiac and skeletal muscle injury among the reported cases of severe myopathy associated with gemfibrozil-lovastatin therapy. However, one patient in the report by Pierce & colleagues⁽¹⁰⁾ showed 44% CK MB isoenzyme fraction, without a diagnosis of acute myocardial infarction being made. The first patient reported here died of an acute coronary event but no CK MB assay

was done. The haemodialysis treatment he received may have aggravated myocardial ischaemia or he may have suffered from myocardial toxicity.

Two critical factors which predispose to myohaemoglobinuric acute renal failure in rhabdomyolysis are hypovolaemia/dehydration and aciduria⁽²⁰⁾. At the nephronal level, three basic mechanisms underlie haem protein toxicity : renal vasoconstriction, intraluminal cast formation and direct haem protein-induced cytotoxicity leading to acute tubular necrosis⁽²¹⁾. Recent animal studies have shown that the deposition of myoglobin in the kidney is associated with lipid peroxidation, initiated by the haem iron of myoglobin. A study by Holt et al⁽¹⁾ has also demonstrated increased lipid peroxidation in humans with rhabdomyolysis and renal impairment due to various different causes.

Since intravascular volume status has such a profound impact on the development of experimental haem protein-induced acute renal failure, rigorous intravenous fluid therapy, often administered with mannitol and sodium bicarbonate, is a mainstay in the early management of rhabdomyolysis or severe intravascular haemolysis. Although no prospective clinical trials have proven their efficacy, retrospective analysis by Better and co-workers⁽²²⁾ provided overwhelming support for their use. Alkalinisation is hypothesised to improve renal function in rhabdomyolysis by stabilizing the highly reactive ferryl Mb preventing lipid peroxidation⁽¹⁾, and not by enhancing solubility and excretion of Mb as originally proposed^(20,23).

In this report the first patient died despite receiving lower dose of bezafibrate. This could be explained by his more severe degree of underlying renal impairment. Similarly, his peak serum creatinine was higher (see Table I) before dialysis was initiated indicating a more severe degree of uraemia. Adequate fluid resuscitation for the first patient was also limited by oliguria. The management was complicated by underlying ischaemic heart disease which made haemodialysis less suitable. The systemic heparinization which he received may have contributed to the bleeding manifestations and aggravated his clinical condition. The second patient had a better renal function and was non oliguric, enabling fluid resuscitation and urinary alkalization to proceed without much complications and he had a better clinical outcome.

The presence of renal impairment is not an absolute contraindication against the use of fibrates, only caution is advised in most drug formularies. However no clear guidelines have been laid as to the precise level of serum creatinine or creatinine clearance above or below which fibrates should not be used at

all. For gemfibrozil, it is recommended that the dose is reduced to 50% when GFR is between 10-50 ml/min and 25% when GFR is less than 10 ml/min⁽²⁴⁾.

Detection of myopathy during treatment with fibric acid derivatives could be done through periodic CK monitoring. Patients on combination of an HMG-CoA reductase inhibitor and gemfibrozil are suggested to be followed at 6-week intervals with careful history and determination of CK values until a stable pattern is established⁽²⁵⁾. However, as rhabdomyolysis may develop suddenly after a few days to weeks or months of treatment, and continue to worsen (as reflected in further rises of CK blood levels) for several days after discontinuation of the drug, there can be no assurance that periodic plasma CK level monitoring of patients receiving the drug would allow early identification of drug-induced myopathy in time to prevent progression to frank rhabdomyolysis⁽¹⁰⁾. Therefore, it is difficult to suggest a fixed duration of follow up interval while patients are on bezafibrate therapy. In general, physicians should be alert to symptoms and signs of possible drug- induced myopathy in patients receiving fibric acid derivatives. Renal function tests should be carried out before initiating therapy and periodically when using bezafibrate and the dose adjusted if necessary. A rise in the creatinine level may occur in patients with existing renal insufficiency and if the dosage is not reduced myotoxicity may develop. As a conclusion, fibric acid derivatives should be prescribed with great caution in patients with underlying renal impairment, as failure to follow dosage guidelines (as illustrated in these two cases) would result in myotoxicity.

ACKNOWLEDGEMENT

To Associate Professor Dr Zabidi A.M. Hussin, who has kindly reviewed this manuscript and made valuable comments.

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