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Acute Renal Failure After Cardiopulmonary Bypass: A Possible Association With Drugs of the Fibrate Group

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Background: Renal failure is a recognized, but infrequent, complication following cardiac surgery. The causes for this condition are multifactorial, and a major concern is that the occurrence of postoperative acute renal failure is still associated with a high mortality rate.
Methods and Materials: We report unexpected acute renal failure occurring in 4 patients after uncomplicated cardiac surgery. Each patient was taking a fibric acid derivative at the time of surgery. Renal failure occurred rapidly within 3 days of surgery and was associated with increased concentrations of skeletal muscle-derived creatine kinase (CK). One patient developed myoglobinuria, and another developed a malignant hyperthermia-like syndrome.
Conclusions: These cases show that patients receiving lipid lowering medications could be at higher risk of developing acute renal failure after cardiac surgery. This association merits careful evaluation in large prospective studies and, if proved, would suggest that patients taking either statins or fibrates should discontinue doing so before cardiac surgery.
Key words: acute renal failure, rhabdomyolysis, fibrates, statins.

The beneficial effects of treatment of hyperlipidemia in the secondary prevention of ischemic heart disease are well established (1–5). Although lipid-lowering agents, such as fibric acid derivatives (fibrates) and 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are generally well tolerated and have a good safety profile, they are rarely associated with development of significant myopathy, which may result in rhabdomyolysis and acute renal failure. Here we report 4 patients undergoing uncomplicated cardiac surgery who developed unexpected acute renal failure in the early postoperative period, which was associated with markedly elevated levels of creatine kinase (CK). One other feature common to all these patients was that all were taking fibric acid derivatives before surgery.

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Case Reports

Case 1

A 61-year-old asymptomatic man with combined hypercholesterolemia was admitted for elective coronary artery bypass grafting after coronary angiography, done 7 months before the surgery, which had shown severe triple vessel disease. Echocardiography confirmed good left ventricular function. He had been taking ciprofibrate 100 mg/d during the 4 months before surgery. The operation, with a left internal mammary graft to the left anterior descending artery and saphenous vein graft to the right coronary artery, was uneventful. However, he became hypotensive during the first postoperative night, with a systolic blood pressure of 80 mm Hg and oliguria (urine output 12 mL/h), despite adequate central venous pressure of 12 cm H_2O. His subsequent management included infusion with dopamine, colloid, mannitol, and frusemide. Over the course of the first and second postoperative days, he had continuing oliguria, and during the evening of the second postoperative day he suffered a respiratory arrest. Results of arterial blood gas analysis

immediately before this event on 0.7 FiO_2 were pH 7.19; PO_2, 9.5 kpa; PCO_2, 4.4 kpa; and base deficit, −13.5. Pulmonary artery catheterization indicated pulmonary artery pressure of 21 mm Hg (systolic) and 7 mm Hg (diastolic) with a pulmonary artery wedge capillary pressure of 9 mm Hg, and the cardiac output was 4.31 L/min, cardiac index was 2.4 L/min/m^2, and systemic vascular resistance was 480 dynes · sec · cm^{-5} (normal range, 900–1400). He required inotropic support with noradrenaline and was commenced on hemofiltration. On the third postoperative day, the CK was greater than 10 times the upper limit of normal, and a day later myoglobin was detected in the urine. He went on to make a full recovery. Results of his investigations are summarized in Figure 1. He was discharged from hospital taking ciprofibrate 100 mg daily with a recorded CK level of 261 IU/L. When ciprofibrate was increased to 200 mg/d (before this dose was withdrawn from the market), there was an asymptomatic increase in CK, which fell to normal when the dose was reduced to 100 mg/d. He was subsequently changed to simvastatin, an HMG-CoA reductase inhibitor that he tolerated well, and he has had no further problems.

Case 2

A 58-year-old woman with long-standing type 1 diabetes mellitus and obesity (body mass index, 41) presented with unstable angina. Eight months before surgery, she had had an anterior myocardial infarction. Coronary angiography, done 6 months before the operation, confirmed 2-vessel disease, and echocardiography showed good left ventricular function. She also had combined hypercholesterolemia, which had been treated for 3 months with bezafibrate 200 mg twice daily. Six days before surgery, she suffered an episode of severe chest pain, and a CK of 600 IU/L was noted. The operation, with a left internal mammary graft to the proximal left anterior descending coronary artery together with a saphenous vein graft to the first obtuse marginal branch of the circumflex coronary artery, was uneventful. At the time of transfer from bypass, she had a left atrial pressure of 14 mm Hg, a right atrial pressure of 12 mm Hg, and a systolic blood pressure of 100 mm Hg. In the early postoperative period, her blood pressure dropped to 75/50 mm Hg, and she became hemodynamically unstable, requiring an infusion of up to 5 μg/min of

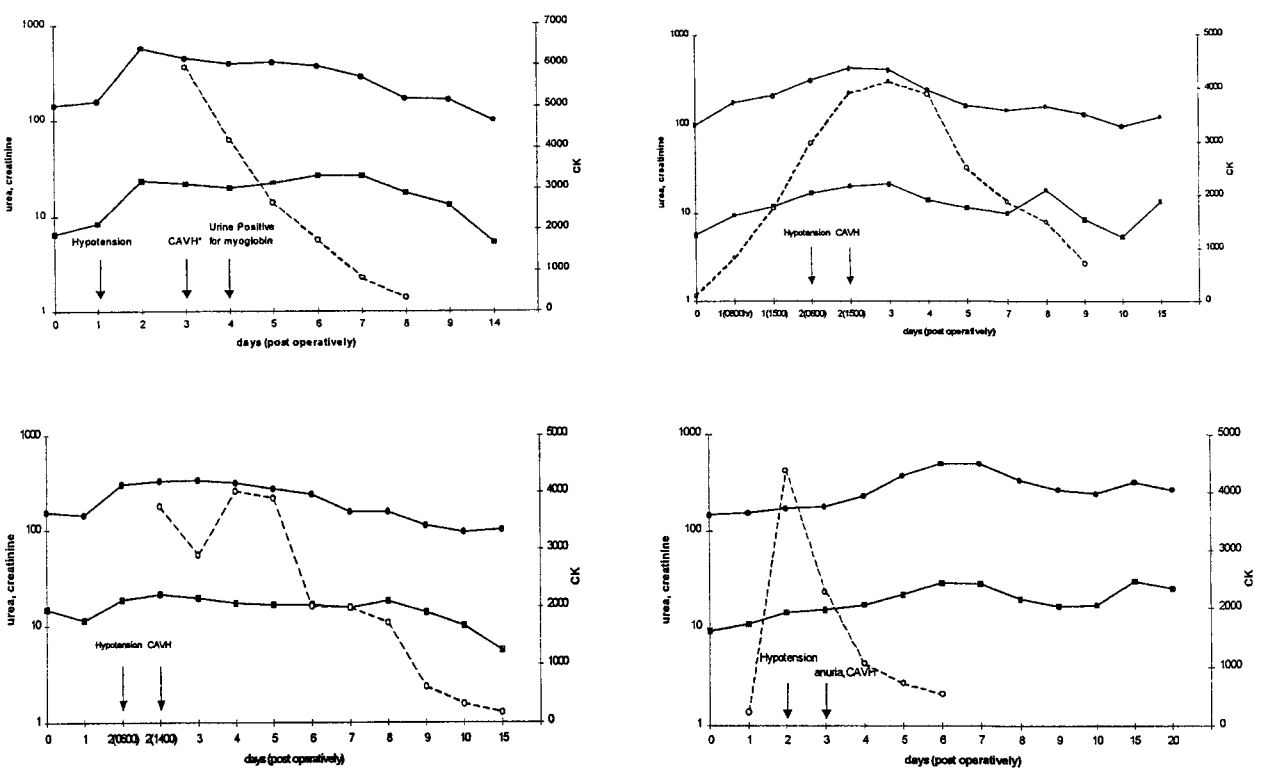

Fig. 1. Postoperative changes in urea, creatinine, and CK levels in four patients. Normal range for urea (2.5–8 mmol/L), creatinine (60–110 μmol/L), CK (30–250 IU/L in males and 30–180 in females). [BUN: 8–22 mg/dl, creatinine: 0.6–1.2 mg/dl] Note that, in all patients, isoform analysis showed low proportions (<15%) of CK-MB, indicating that the increased activity reflected skeletal muscle damage. *CAVH, Continuous Arteriovenous Hemofiltration.

adrenaline. Her urine output was initially well maintained between 30 and 100 mL/h. Pulmonary artery catheterization on the first postoperative day showed a pulmonary artery pressure of 42 mm Hg (systolic) and 19 mm Hg (diastolic) (mean, 26 mm Hg), and the cardiac output was 3.81 beats/min with a cardiac index of 2.11 beats/min/m^2. Systemic vascular resistance was 1220 dynes · second · cm^{-5}, and pulmonary vascular resistance was 126 dynes · second · cm^{-5} (normal range, 150–250). Despite an adequate central venous pressure, she became oliguric (urine output, <20 mL/h) and required hemofiltration. On the second postoperative day, the CK increased to more than 10 times the upper limit of normal (Fig. 1). She made a good initial progress, and hemofiltration was discontinued on the fifth postoperative day. However, 2 days later, she developed mediastinitis and sternal dehiscence and required a muscle flap to close the sternal defect. The results of her investigations are shown in Figure 1.

Case 3

A 69-year-old man presented with aortic stenosis with a gradient of 65 mm Hg and triple-vessel coronary artery disease. He had a 10-year history of type 2 diabetes mellitus and had required insulin for the preceding 18 months. He had peripheral vascular disease and previously had undergone angioplasty of several peripheral arteries, and 2 percutaneous transluminal coronary angioplasties, one of which had included rotablation. Cardiac angiography immediately before surgery showed a residual 40% stenosis in the right coronary artery, minor residual left anterior descending coronary artery disease, and a blocked small circumflex coronary artery. He had been noted to have combined hypercholesterolemia, which was treated with ciprofibrate 200 mg/d during the 8 months before surgery (that was before withdrawal of ciprofibrate 200 mg from the formulary). At operation, the aortic valve was replaced with a 25-mm Carpentier Edwards porcine xenograft using antegrade cold blood cardioplegia with mild hypothermia to 28°C. Dopamine (at 3.5 μg/kg/min) was used while he was on bypass and continued for 24 hours postoperatively. Twenty-four hours later, he became hypotensive (systolic blood pressure, 85 mm Hg) with oliguria (urine output, <30 mL/h) despite an adequate central venous pressure and without evidence of blood loss. He also complained of severe chest pain, breathlessness, and generalized muscle aches, which were associated with a serum CK level of 3758 IU/L. At this time, arterial blood gas analysis showed a metabolic acidosis with pH 7.31 and base deficit −7.8. The serum creatinine was noted to have increased twofold when compared with the previous preoperative values, reaching 326 mmol/L, and serum potassium was 7.2 mmol/L. His liver transaminases were noted to increase more than 20-fold the upper level of normal. He underwent hemofiltration, and dopamine infusion was restarted. Echocardiography showed good biventricular function with no pericardial effusion. Pulmonary artery catheterization showed him to be well perfused with a central venous pressure of 16 cm H_2O. He subsequently made a full recovery, and his liver enzymes returned to normal. The results of his investigations are shown in Figure 1.

Case 4

A 61-year-old man was admitted for elective coronary artery bypass grafting. Coronary angiography, done 5 months before the operation, showed triple-vessel disease with good left ventricular function. During the 3 months before surgery, he had been taking warfarin after a deep vein thrombosis of the left leg. He also had a combined hypercholesterolemia, for which he was taking ciprofibrate 100 mg/d. He underwent coronary artery bypass grafting with left internal mammary artery grafting to the left anterior descending artery and short saphenous vein grafts to the first obtuse marginal and right coronary arteries. He came off bypass uneventfully, but it was noted that he required more colloid than expected to maintain an adequate central venous pressure in the early postoperative period. On the second postoperative day, he became pyrexial (38.2°C), confused, and complained of lower back pain. He then suffered a respiratory arrest and was ventilated after resuscitation. Initially he was thought to be in septic shock, because cardiac output studies indicated a cardiac output of 10 L/min with a systemic vascular resistance of 300 dynes · second · cm^{-5}. He required up to 34 μg/min noradrenaline and 13.3 μg/min adrenaline to maintain systolic blood pressure above 100 mm Hg and rapidly developed renal failure. Echocardiography showed good left ventricular function, and ultrasound examination of the kidneys and pancreas was normal. Microbiological investigations failed to identify any significant pathogenic organisms. He remained pyrexial with a temperature over 40.2°C despite administration of broad spectrum antibiotics. Retrospective analysis of blood from the second

postoperative day showed CK was 4383 IU/L. Urine myoglobin could not be measured, because he had become anuric before the diagnosis of rhabdomyolysis was considered. He underwent hemofiltration, and his pyrexia settled. His investigations are summarized in Figure 1. Deterioration in renal function between days 10 and 15 was caused by sepsis associated with an indwelling urinary catheter. He subsequently recovered and was discharged without further events.

Discussion

The prevalence of acute renal failure (ARF) after cardiac surgery varies from 2.5% to 7%, with mortality from 24% to 70% (6,7). In our Renal Unit, in 1998, the incidence of acute renal failure requiring continuous arteriovenous hemofiltration (CAVH) in patients undergoing cardiac surgery was only 2%. Because CAVH was initiated rapidly in all of the patients reported here, this precluded confirmatory measurement of other urinary indices of ARF such as the fractional excretion of sodium, urine osmolality/plasma osmolality, and urine creatinine/serum creatinine. Previous studies have identified a number of factors associated with an increased risk of developing postoperative ARF in patients undergoing cardiac surgery. These include diabetes mellitus, preexisting renal impairment, advanced age, low intraoperative urine output, and preoperative low cardiac output requiring inotropic support and emergency surgery (7,8).

Rhabdomyolysis associated with acute renal failure is a recognized severe complication of cardiopulmonary bypass surgery but can occur in patients in whom an aortic balloon pump was used during the operation (9). Other contributory factors may be the low cardiac output syndrome and the alpha vasoconstrictor effect of high-dose continuous intravenous infusion of epinephrine. However, intravenous epinephrine is reported to cause rhabdomyolysis in cardiac surgery only where there is direct cannulation of the femoral artery for the cardiopulmonary bypass, and it also correlates with prolonged extracorporeal circulation during surgery, which might cause leg ischemia/reperfusion–induced injury (9). These conditions did not pertain to patients 2 and 4, who received epinephrine postoperatively. Furthermore, an elevated CK was reported in patient 4 before intravenous epinephrine was commenced.

Atheroembolic renal disease is another potential cause for renal failure after vascular surgery, and it is associated with eosinophilia, which is a diagnostic clue reported previously in many patients (10,11). The absence of this latter feature in our patients makes this cause of renal failure unlikely. However, the definitive diagnosis can only be made by renal biopsy, which was not appropriate in our patients who recovered fully from ARF.

Even though all reported patients appeared to have at least 1 of the risk factors for developing postoperative ARF, as do many patients who require cardiac surgery, no single risk factor would account for the massive elevation of CK, which was a common feature to all and the development of rhabdomyolysis in patient 1.

Measurement of circulating CK is a sensitive indicator of muscle damage. Human tissues contain 3 forms of CK, which are made up of dimers of the muscle (M) and brain (B) isoforms: MM, BB, and MB. Skeletal muscle contains mostly CK-MM, with less than 15% CK-MB. In the myocardium, most CK is CK-MB.

At the time of surgery, all of our patients described were taking fibrates (ciprofibrate or bezafibrate) as treatment for combined hypercholesterolemia. The principal mechanism of action of fibrates is to lower plasma triglyceride (TG) by the promotion of lipolysis of TG-rich lipoprotein and restricting availability of free fatty acids for synthesis of TG in the liver (12). The plasma half-life of individual fibrates varies. The half-life of bezafibrate is 2 to 4 hours, whereas for ciprofibrate it is much longer (80–120 hours) (13). In most instances, evidence of muscle damage, whether in the form of myalgic symptoms or as elevation in CK, appears within 2 months of commencement of therapy, although delays of 5, 6, 8, or even 24 months have been described (14).

The precise mechanism whereby fibrates cause muscle damage is not known; however, the risk of developing myopathy is increased in certain circumstances. Renal insufficiency increases the risk of myopathy because fibrates are principally eliminated by the kidneys. Three of our patients had preexisting but mild renal impairment. It has been established that ciprofibrate at a dosage of 200 mg or more per day is believed to be associated with increased risk of rhabdomyolysis and has been withdrawn at this dose. Only one of our patients (patient 3) had been taking ciprofibrate 200 mg/d before surgery. Another (patient 1) developed an asymptomatic elevation in plasma CK when rechallenged with ciprofibrate at a dose of 200 mg/d but not when given 100 mg/d.

Fibrate metabolites are predominantly (greater than 90%) plasma protein bound in the blood (13). In the presence of other drugs that are plasma protein bound, there is a possibility that these metabolites may be displaced, perhaps increasing their activity. In clinical practice, only the interaction between fibrates and coumarin derivatives such as warfarin is believed to be of significance (15), although there was one reported case of rhabdomyolysis when ciprofibrate was given in conjunction with ibuprofen (16). In addition to ciprofibrate, patient 4 had been taking warfarin for a deep vein thrombosis before surgery, and it is possible that the pharmacokinetics of the fibrate could have been altered as a consequence of this. Similarly, in hypoproteinemic states such as nephrotic syndrome, the risk of fibrate-induced myopathy is increased (17,18), because less protein is available to bind the active metabolites, thus increasing the levels of free active drug (13). Hypothyroidism is also believed to increase the risk of development of myopathy in association with fibrates (19–22). There was no clinical evidence of hypothyroidism in any of our patients, and one (patient 1, who developed rhabdomyolysis) had documented normal thyroid function tests 6 months previously.

There are reported cases in the literature of rhabdomyolysis associated with drug monotherapy of either the fibrate or statin group or with a combination of these drugs (23–35). However, the risk appears to be rare in that approximately 1 case has been reported for every 100,000 treatment-years (36). Table 1 shows the number of recorded cases and the incidence of rhabdomyolysis with individual drugs according to postmarketing surveillance.

There were notable interactions when statins were used in conjunction with other drugs that are metabolized in a similar manner. Deterioration of renal function and rhabdomyolysis secondary to administration of statins with drugs such as erythromycin (37), itraconazole (38), and nefazodone (39) is now well established. This is because statins are metabolized in the liver by the microsomal cytochrome P450 located in the smooth endoplasmic reticulum of the hepatocytes (40). Thus, an increased likelihood of adverse events might be expected if statins are coadministered with any agent that inhibits the activity of the CYP 3A4 isoenzyme.

In the absence of any other identifiable factor that might account for the clinical events and the rise in the measured circulating CK, the only factor common to all 4 patients was the fibrate medication. Each patient was operated on by a different combination of surgeons and under different consultant practices. The agents used in induction and during anesthesia varied. Two patients (patients 2 and 4) received suxamethonium at induction, an agent known to cause transient 2- to 3-fold elevation in CK, and has been rarely associated with rhabdomyolysis (41,42). However, this serious complication usually occurs in patients with preexisting muscle disease (42,43). Both intermittent ischemic arrest and cold blood cardioplegic arrest were employed intraoperatively. Oxygenators varied throughout this period. Agents used for postoperative sedation varied, but none received muscle paralysis in the initial postoperative period. There is no reported association between fibrates, statins, and general anesthetic agents, which might be relevant to the patients in this report. The policy of the Unit at the time was that all patients received a single dose of intravenous cefuroxime with the induction of anesthesia as prophylaxis against wound infection, but none of the patients were taking any nephrotoxic antibiotics before surgery. Thus, drug-induced acute interstitial nephritis does not apply to any of the patients.

Table 1. The Number of Reported Cases and the Incidence of Rhabdomyolysis for Different Fibrates and Statins

Drugs	Total No. of Cases	Incidence per Patient Years
Fenofibrate	—	3.6 cases for 1 million patient years since 1979 (Figures based on 20 million patient years of fenofibrate use)
Bezafibrate	—	223 cases in 10.1 million patient years (Figures includes rhabdomyolysis and myopathy)
Ciprofibrate	103*	—
Fluvastatin	—	13 cases for every 700,000 patient years
Cerivastatin	8	—
Simvastatin	—	1 case for every 100,000 patient years

NOTE. These are world-wide figures and were obtained through personal contact with the drug companies.
* This figure includes cases from 1985 to 1995 (31 involved ciprofibrate 100 mg and 71 involved ciprofibrate 200 mg) La Revue Prescrire 1995; 151.

In conclusion, although each patient had characteristics that might have placed them at an increased risk of postoperative renal failure, these are characteristics of many patients undergoing cardiac surgery, most of whom do not develop these complications overtly (7,8). It is likely that our patients developed renal failure as a result of fibrate therapy. We report this possible association in 4 patients between the administration of lipid-lowering agents of the fibrate class and the development of acute renal failure with elevated levels of skeletal-derived CK after cardiac surgery. This association warrants further investigation because, if established in future cases, it would suggest that patients taking lipid-lowering medications should discontinue them before undergoing cardiac surgery. However, it would seem reasonable, until there is further evidence, to recommend that all statins and fibrates should be discontinued before surgery and restarted when the patient has recommenced a low-cholesterol diet. The events in these 4 patients have been reported to the Committee on the Safety of Medicines. We plan to undertake a study in the future to confirm or refute this hypothesis.

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