Influenza vaccine—a possible trigger of rhabdomyolysis induced acute renal failure due to the combined use of cerivastatin and bezafibrate

Sir,

Muscle toxicity is one of the major adverse effects of both HMGCoA reductase inhibitors (statins) and fibrates. Although rarely associated with the use of these drugs as monotherapy, combined therapy carries a significant risk of rhabdomyolysis [1–5]. Acute viral illnesses may cause myopathic syndromes ranging from myalgias to frank rhabdomyolysis. However, to the best of our knowledge, vaccinations against common viral infections have not been previously implicated as a contributory cause of rhabdomyolysis induced acute renal failure (ARF). We present a patient treated with both cerivastatin and bezafibrate, who developed ARF due to rhabdomyolysis only after being administered an influenza vaccine.

Case. A 68-year-old man was referred to Casualty complaining of extreme weakness and diffuse muscle pain. He had a history of previous myocardial infarction, stable angina pectoris and hyperlipidaemia. His medication included isosorbide mononitrate, aspirin, simvastatin 40 mg/day, and bezafibrate 200 mg/day. Two months prior to hospitalization cerivastatin at a dose of 0.9 mg/day was substituted for simvastatin. Two weeks before admission routine laboratory data showed a serum creatinine of 1.1 mg/dl, creatine phosphokinase (CPK) 70 U/l, total cholesterol 210 mg/dl, HDL 22 mg/dl, LDL 154 mg/dl and triglycerides 172 mg/dl. Five days prior to being seen in Casualty he was vaccinated with influenza vaccine. Within 24 h following the vaccination, the patient began to complain of diffuse myalgia. He attributed this to the vaccination. However, his symptoms worsened accompanied by increasing muscular weakness. On admission to Casualty, physical examination was unremarkable except for generalised muscle tenderness. Laboratory data revealed a serum CPK value of 93 000 U/l, an initial serum creatinine of 3.5 mg/dl, urea 149 mg/dl, Na 138 mEq/l, K 5.2 mEq/l, Ca 9.0 mg/dl, Pi 6.9 mg/dl and albumin 38 g/l.

Dipstick examination of the urine showed a positive orthotoluidine test. Serum and urine myoglobin were 43 400 and 18 600 µg/l respectively. Treatment with forced diuresis and alkalization of the urine was commenced. Serum creatinine peaked at 5.7 mg/dl. Renal function returned to normal within the following days.

Comment. Combined lipid lowering therapy with statins and fibrates is an attractive option because of the more favourable lipid profile achieved compared to the use of either drug on its own [5,6]. Such a therapeutic regimen is, however, associated with an increased risk of muscle toxicity. Rhabdomyolysis has most often been reported with a statin/fibric acid combination [1–5]. Enhanced susceptibility to myopathy is encountered in patients with reduced renal function or those on concurrent drugs, notably, cyclosporin A, macrolide antibiotics and certain calcium channel blockers. These drugs share with the statins the hepatic catabolic pathway CYP3A4 resulting in a marked increase in reductase inhibitory activity when used simultaneously [3]. Cerivastatin, a third generation HMG CoA reductase inhibitor, is actually metabolized via a dual pathway, the CYP3A4 and CYP2C8 hepatic isoenzymes [5]. One might anticipate, therefore, a reduced risk of drug–drug interactions with cerivastatin. Indeed, pharmacological studies have shown that CYP3A4 inhibitors have only minor effects (<1.5-fold) on the drug’s pharmacokinetics [7]. However, the risk of myopathy of statin/fibrate combination therapy may be unrelated to CYP activity. Gemfibrozil and clofibrate have been documented as inducing myopathy independent of statins suggesting direct muscle toxicity. The additive risk of statins may occur at the level of the myocyte by a mechanism, as yet, unknown.

A literature review has revealed only one case of rhabdomyolysis associated with cerivastatin, this in a patient on combined cerivastatin (0.3 mg/day) and gemfibrozil (600 mg b.i.d) treatment [5]. As in our case, this patient had normal baseline renal function. Our patient was administered cerivastatin at a high dose (0.9 mg/day). In a recently published study of 28 subjects given cerivastatin 0.8 mg daily for 4 weeks only two developed CPK values three times the upper limit of normal [8]. Despite being treated with this high dosage of cerivastatin in conjunction with bezafibrate, no myopathic complications were seen in our patient for approximately a 2-month period. Only after being vaccinated for influenza, did he begin to complain of myalgias. He sought medical attention when progressive muscular weakness rendered him unable to get out of bed, 3 days post-vaccination.

Muscle syndromes associated with acute viral infections range from commonly experienced myalgias through myositis to rhabdomyolysis. Mild to moderate diffuse myalgias frequently occur during the prodrome or early phase of any acute viral illness. Myositis consisting of marked muscle pain and tenderness with elevated muscle enzymes (up to 30 times normal) is primarily seen in children infected with either influenza A or B. Myoglobinuric ARF does not, however, occur in this setting. Massive rhabdomyolysis with ARF has been reported with the following viruses: influenza A and B, coxsackie, Epstein–Barr virus, herpes simplex virus, parainfluenza, adenovirus, echovirus, cytomegalovirus and human immunodeficiency virus [9]. The aetiology of muscle injury in viral infections is unclear. Possibilities include direct invasion of muscle tissue by the virus, release of myotoxic cytokines or other immunologic processes. Given the time course of events in our patient, we hypothesize that the influenza vaccine acted as the trigger to the development of rhabdomyolysis on a background of combined cerivastatin/bezafibrate therapy. Of note, the myalgias experienced by the patient were understandably attributed by him to the vaccine, a fact which disguised the true nature of his condition.

Statin/fibrate combination therapy should be undertaken cautiously, particularly when a high dose of either statin or fibrate is employed. In addition, our report sounds a warning
note to patients on this regimen who intend to be vaccinated against common viruses.

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8. Stein E, Isaacsohn J, Stoltz R et al. Pharmacodynamics, safety, tolerability and pharmacokinetics of the 0.8 mg dose of cerivastatin in patients with primary hypercholesterolemia. *Am J Cardiol* 1999; 83: 1433–1436