A Note To Cardiothoracic Surgeons: Statins Can Interact With Ciprofloxacillin And Fusidic Acid To Cause Rhabdomyolysis And Myoglobinuric Renal Failure

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Citation

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Abstract

Statins are widely used to decrease cholesterol and improve morbidity and mortality associated with coronary artery disease. The incidence of rhabdomyolysis increases dramatically when statins are co-administered with drugs that inhibit their hepatic transformation such as cyclosporine or azoles.

We present a case of early rhabdomyolysis in an MRSA positive patient post coronary artery bypass grafting on Atorvastatin, who was given Ciprofloxacillin and Fusidic acid for a sternotomy wound infection.

Most cardiac surgery patients are on statins. Drug induced rhabdomyolysis is rare in cardiac surgery patients but is preventable and can result in acute renal failure and death. High level of suspicion and early aggressive treatment can prevent acute renal failure.

INTRODUCTION

The patient is a 58yr old gentleman known to be methicillin-resistant staphylococcus aureus (MRSA) positive; past medical history included an appendicectomy, myocardial infarction with stenting of his left anterior descending coronary artery, hypertension and hypercholesterolemia.

Medication (over 5yrs) included Bisoprolol 5mg OD, Frusemide 20mg OD, Atorvastatin 40mg nocte and Aspirin 75mg OD.

He had uncomplicated coronary artery bypass grafting, was discharged on day 8 and readmitted a week later with a sternotomy wound infection and mediastinitis confirmed by contrast enhanced CT scanning. He was treated initially with Teicoplanin and Vancomycin intravenously, then Fusidic acid and Ciprofloxacillin orally. He eventually required debridement of his sternotomy wound and treatment with a V.A.C (Vacuum Assisted Closure) dressing; there was good response to treatment and he was discharged on oral Fusidic acid 500mg TID and Ciprofloxacillin 500mg BD to be reviewed at the wound clinic.

He presented to the wound clinic a week later complaining of fatigue and feeling weak. He was unable to get out of the wheelchair he had started needing. He had a pain in his calf and had been feeling short of breath over the last few days. He had no chest pain and no productive cough.

On examination he was of slim build and found to have cold and mottled extremities. He had a heart rate of 74 which was regular, blood pressure of 137/70 mmHg, oxygen saturations of 87%, temperature 35.6 centigrade and ECG showed sinus rhythm with multiple ventricular ectopics. Inspection of his sternotomy wound was unremarkable, sternum was stable, auscultation revealed normal heart sounds and clear lung fields. Abdominal examination was unremarkable and a neurological examination revealed no gross abnormality. A trans-thoracic echocardiogram showed mild left ventricular dysfunction and no other abnormality. Doppler ultrasound of his legs showed no thrombus in the deep veins.

He did not have the characteristic dark urine but was found to have urinary myoglobin on a sample of urine. Blood tests were taken which revealed CK-MB 662, CK 56500, AST 1652, ALT 404 and LDH 4110. His full blood count, urea

and electrolytes and coagulation screen were normal.

Atorvastatin, Ciproxin and Fusidic acid were discontinued. He was started on a therapeutic dose of clexane, catheterised and his fluid status was closely monitored and he had daily renal function blood tests to monitor serum electrolytes and renal function.

Rhabdomyolysis is characterised by muscle cell necrosis and release of muscle cell components into the circulation, most notably creatine phosphokinase (CK) and myoglobin.

The primary mechanism through which muscle damage occurs in rhabdomyolysis is sarcoplasmic calcium overload leading to activation of degradative enzymes. This may occur secondary to a number of processes including ATP depletion and increased intracellular sodium concentration, and direct sarcolemmal injury [1]. Common causes of rhabdomyolysis include: trauma, infection, drugs, toxins and rare causes like exertional activity.

The presentation of rhabdomyolysis varies. Typically the muscle disorder is self-limiting and resolves within days to weeks. Muscular signs and symptoms include pain, weakness, muscle tenderness and contractures. The most frequently involved muscle groups are the calves and lower back [1].

Rhabdomyolysis may present as malaise, fever, tachycardia, nausea and vomiting. Hyperuricaemia may lead to encephalopathy with depression of respiration, hypoxia and respiratory acidosis; Hypovolaemia due to haemorrhage and influx of fluid into necrotic muscle may occur; Hyperkalaemia can cause severe arrhythmias resulting in cardiac arrest; Deposition of calcium in necrotic muscle worsens the toxicity of hyperkalaemia; disseminated intravascular coagulation is common [2].

Acute renal failure is said to occur in about 30% of patients [3], the mechanisms of myoglobinuric acute renal failure include; renal vasoconstriction/hypoperfusion, haem protein cast formation, ischaemic tubular injury, haem iron induced oxidant stress [4].

The most reliable laboratory indicator is serum Creatinine Kinase (CK). CK levels 5 times higher than normal suggests rhabdomyolysis and are frequently 100 times above normal or even higher. Failure of CK to decrease suggests ongoing muscle injury. Plasma and urinary myoglobin is also helpful as well as a full blood count, urea and electrolytes, coagulation screen and liver function tests [4].

In this case, we think rhabdomyolysis was as a result of his medication i.e. Atorvastatin and his antibiotics i.e. Ciproxin and Fusidic acid. Rhabdomyolysis has been noted in patients being treated with Quinolones e.g. Ciprofloxacillin [5].

There have also been reported cases of rhabdomyolysis as a result of interaction between HMG CoA-reductase inhibitors (e.g. statins) and Fusidic acid [6,7,8,9].

Fusidic acid, like Atorvastatin, undergoes extensive first-pass metabolism in the liver. Atorvastatin is metabolised via the cytochrome P3A4 enzyme system. It is known that, if given concomitantly with inhibitors of this system (e.g. macrolides and azole derivatives), statin concentrations can become elevated and lead to an increased likelihood of adverse effects such as rhabdomyolysis [10].

Patients in cardiac surgery or cardiology are usually on a statin. Reported drug interactions from statins causing rhabdomyolysis in cardiac surgery are rare but should be looked out for as acute renal failure occurs in up to 10% of patients after cardiac surgery. Early diagnosis by picking up the subtle signs and treatment reduces morbidity and mortality and is more cost effective by preventing renal failure requiring dialysis.

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