RHABDOMYOLYSIS DUE TO AN UNCOMMON INTERACTION OF CIPROFLOXACIN WITH SIMVASTATIN

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ABSTRACT

A case report of a ciprofloxacin and simvastatin interaction is presented. The addition of ciprofloxacin to chronic simvastatin therapy led to the development of rhabdomyolysis. As ciprofloxacin is a weak inhibitor of CYP3A4, it is very likely that other mechanisms involving the ATP-binding cassette drug efflux transporter family played a role in this drug interaction.

Key Words: *Simvastatin, ciprofloxacin, rhabdomyolysis, elderly, polypharmacy*

CASE REPORT

A 77-year-old woman was admitted to hospital with symptoms of severe muscle weakness and generalised muscle aches for 4 days, and dark discoloration of her urine. Five days prior to her presentation she had been diagnosed with a urinary tract infection and started on ciprofloxacin. Her muscle symptoms began after receiving 2 doses of ciprofloxacin.

Her past medical history included a coronary artery bypass operation 11 years earlier. She had hypertension and hypothyroidism, which were adequately controlled. During the past 7 years she has been taking isosorbide mononitrate 20 mg BD, pindolol 2.5 mg OD, cimetidine 400 mg OD, nicorandil 10 mg BD, aspirin 75 mg, furosemide 40 mg, levothyroxine 100 mcg and simvastatin 40 mg.

On physical examination she was apyrexial, pulse 68 beats per minute and blood pressure 197/68 mm Hg. There was no skin rash or clubbing. Her muscles were tender to touch. She had grade 3 power proximally and grade 4 distally. She was unable to stand up from a chair.

Haemochemistry analysis: Hb 10.2 gm/dL, WBC 9.3 x $10^3/mm^3$, Platelets 235 x $10^3/mm^3$, ESR 80 mm/hr, urea 20.8 mmol/L, creatinine 121umol/L, CRP 20mg/L, creatinine kinase 28,980 U/L, bilirubin 7 umol/L, alkaline phosphatise 78 U/L, alanine transaminase 212 U/L. Urine dipstick showed 4 + blood. Serum electrolytes and thyroid function were normal. Autoimmune screen, including anticentromere and anti SCL antibody, was negative.

The differential diagnosis included either statin induced rhabdomyolysis due to interaction with ciprofloxacin or polymyositis. The simvastatin and ciprofloxacin were discontinued. She was hydrated with intravenous fluids and treated with high dose methyl prednisolone for 3 days pending results of the autoimmune screen. Creatinine kinase levels returned to normal (166 U/L) on day 14. The muscle biopsy showed very few lymphocytes and was not suggestive of polymyositis. Physiotherapy and confidence building measures produced marked clinical improvement. The patient was able to walk with a Zimmer frame on day 23.

DISCUSSION

Most drug interactions have a pharmacokinetic or pharmacodynamic basis, or both.[1] The inhibition or induction of hepatic drug metabolism is a major source of variability in drug response and forms the basis of many adverse drug interactions.[2] Hepatic metabolism is served by a large family of

mono-oxygenases. These CYP450 enzymes have broad and overlapping substrate specificity and an ability to interact with almost any chemical species.[3] However, the role of ATP-binding cassette (ABC) drug efflux transporter family [p-glycoproteins (p-gp) and MRPs (multiple drug resistance associated proteins)] and solute carriers (SLCs) [organic anion transport proteins (OATPs)] is increasingly being recognised in metabolism and interaction of various drugs.

The HMG-CoA reductase inhibitors (statins) are associated with 2 uncommon, but important, adverse effects, asymptomatic elevation in liver enzymes and myopathy. The incidence of myopathy in patients taking statins alone is estimated to be 0.1 to 0.2 % in clinical trials[4,5] and rhabdomyolysis is exceedingly rare.[4,6] Nevertheless, in clinical practice muscular pains and weaknesses are reported more frequently, 7% of patients on statin monotherapy. Myalgia has contributed up to 25% of the adverse events that are associated with statin use.[7]

Evidence suggests that myopathy is a direct consequence of HMG-CoA reductase inhibition [7] and is dose-dependent. Myopathy is most likely to occur when statins are administered with other drugs or chemicals that are themselves myotoxic or that can elevate the concentrations of the statin into a toxic range. The incidence of muscle disorders increases over 10-fold when statins are given with gemfibrozil, niacin, erythromycin, itraconazole, cyclosporine and diltiazem.[5]

More than 80% of simvastatin is metabolised in the liver by CYP3A4. Approximately 20% of the drug is metabolised by the CYP2C8 enzyme.[8] Simvastatin, an inactive lactone pro-drug, is metabolised to simvastatin acid, which is an active metabolite. P-gp and MRP2 located at biliary canaliculi are responsible for high hepatic excretion of simvastatin. Statins act as substrates and competitive inhibitors of p-gp and MRP efflux mechanism.[9] The fluroquinolone ciprofloxacin is partially metabolised in liver. It is a strong inhibitor of CYP1A2 and weak inhibitor of CYP3A4. Multiple ABC transporters located in the gut wall and renal tubules contribute to the efflux of ciprofloxacin. Ciprofloxacin is a substrate for p-gp and MRP.[10]

As ciprofloxacin is a weak inhibitor of CYP3A4, it is likely that other mechanisms (involving p-gp or MRP) contributed to the observed drug interaction in this case report. The addition of ciprofloxacin disturbed the metabolism of simvastatin and lead to its toxicity. Prescribers and pharmacist need to be aware of the potential for a simvastatin and ciprofloxacin interaction. This interaction has been reported to the MHRA, UK [GB-MHRA-EYC 00001164].

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