CASE REPORT

Ciprofloxacin and statin interaction: a cautionary tale of rhabdomyolysis

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SUMMARY

A 62-year-old woman presented to hospital, on general practitioner (GP) advice, with a 15-day history of slowly progressing muscle weakness. Results showed newly deranged liver function and creatine kinase (CK) of >24 000. Prior medical history includes previous myocardial infarction and recurrent urinary tract infection. 4 days prior to symptom onset, the patient developed typical urinary tract infection symptoms, treated with ciprofloxacin. The patient had been taking simvastatin (40 mg nocte) for 13 years and had never previously taken ciprofloxacin. Initial management included intravenous crystalloid fluids and discontinuation of simvastatin. CK level fell, liver function slowly improved and renal function remained stable. Muscle weakness improved and the patient became independently able to perform activities of daily living. While the interactions between statins and other antibiotics are well documented, the interaction between statins and ciprofloxacin is less so. The consequences of this interaction can have potentially serious outcomes.

BACKGROUND

Statins and ciprofloxacin are both commonly prescribed drugs.^{1 2} While the interactions between statins and other antibiotics are well documented,³ the interaction between statins and ciprofloxacin is less so.⁴⁻⁶ The consequences of this interaction can have potentially serious outcomes and be detrimental to patient well-being.

CASE PRESENTATION

A 62-year-old woman presented to hospital, on general practitioner (GP) advice, with a 15-day history of slowly progressing muscle weakness and a 10-day history of dark brown, frothy urine. The patient had attended her GP a day before, who took routine blood tests (including creatine kinase, CK) and on receipt of results (including CK=16 070 U/L), advised seeking urgent medical advice.

Medical history includes previous myocardial infarction (MI) and recurrent urinary tract infection. Four days prior to the onset of muscle weakness, the patient developed typical urinary tract infection symptoms (including foul smelling urine, dysuria and haematuria) and was treated with ciprofloxacin. The patient had been taking simvastatin (40 mg nocte) for 13 years and had never previously taken ciprofloxacin. She is a non-smoker and drinks alcohol occasionally. There was no history of recreational drug use. Other medication includes nicorandil (10 mg BD), aspirin (75 mg

OD), bisoprolol (5 mg OD) and glycerol trinitrate (400 µg PRN) with no recent changes.

Four days after starting ciprofloxacin therapy, the patient noted increased weakness in her limbs (lower limbs>upper limbs) and progressive difficulty completing activities of daily living. Limb weakness progressed over the antibiotic course and continued following its completion. At the time of initial GP presentation, antibiotic course had been completed. A change in urine colour from red to darker brown was noted, and as urine colour became darker, limb weakness became more severe, leading her to seek medical advice in the community. There was no history of injury or immobilisation. On arrival to hospital, CK had risen to 24 514 U/L and liver function was deranged (AST 870 U/L, ALT 240 U/L). Calcium level was normal. There were no infective symptoms to suggest viral aetiology. On examination, there was markedly reduced power, especially in the lower limbs (proximal>distal) with no evidence of compartment syndrome.

INVESTIGATIONS

Initial investigations included blood tests, which showed markedly elevated CK, elevated transaminases and preserved renal function. Venous gas showed no evidence of acidosis and inflammatory markers were unremarkable. We discussed the case with renal colleagues who advised to monitor calcium level to ensure hypocalcaemia did not result and check urate level (which was normal). We monitored CK and liver function, which dramatically improved over the course of admission. To exclude any liver pathology, we arranged an abdominal ultrasound, which was unremarkable other than an incidental small left renal angiomyolipoma.

DIFFERENTIAL DIAGNOSIS

Statin induced rhabdomyolysis, due to interaction with ciprofloxacin.

TREATMENT

Management with intravenous crystalloid fluids and urinary catheterisation to allow careful observation of urine output. Simvastatin was discontinued on initial presentation to GP. We discussed the case with renal colleagues, to ensure optimal management and make them aware should renal function deteriorated requiring dialysis.

OUTCOME AND FOLLOW-UP

CK level and liver function slowly improved and renal function remained stable. On admission, the

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patient had borderline hypocalcaemia, but this resolved without need for intervention. Muscle weakness improved and the patient was able to independently mobilise around the ward and perform activities of daily living. We requested that CK and liver function be rechecked in the community 1 week after discharge to ensure complete resolution. At the time of discharge, simvastatin had been discontinued for over 1 week. The patient decided against restarting an alternative statin, avoiding any potential drug interactions and the GP is now considering alternative non-statin therapies such as ezetimibe. Owing to recurrent urinary tract infections, we started prophylactic trimethoprim therapy and advised that the GP seek urology input should this remain an ongoing issue.

DISCUSSION

Statins (3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors) are effective in both the primary and secondary prevention of ischaemic heart disease and are generally well tolerated. The two most important adverse effects are elevation of liver enzymes and skeletal muscle abnormalities, ranging from benign myalgias to life-threatening rhabdomyolysis. Statin-related rhabdomyolysis occurs infrequently when compared with myopathy or myalgias, with estimated incidence around 0.01% for 5-year therapy.^{6 7} Adverse effects with statins are frequently associated with drug interactions owing to their long-term use in older patients who are likely to be exposed to polypharmacy.⁸ In fact, around 50% of cases of statin-related rhabdomyolysis could be precipitated by an interaction between the statin and a new prescribed drug believed to interfere with statin metabolism.^{9 10} Previous literature suggests that myopathy is a direct consequence of HMG-CoA reductase inhibition,¹¹ is dose-dependent and is most likely to occur when statins are administered with other myotoxic drugs or ones which can elevate statin concentrations into a toxic range. Potential mechanisms of how ciprofloxacin could feasibly disturb the metabolism of simvastatin^{4 6} as well as other statins⁵ have previously been outlined in prior case reports. Interactions between statins and other drugs on the CYP3A4 metabolic pathway are recognised and ciprofloxacin is a known weak inhibitor of CYP3A4, implying that it may consequently inhibit simvastatin metabolism, by increasing myotoxicity. Alternative mechanisms have been proposed but not confirmed. Some have proposed that the inhibition of glycoprotein P (P-gp) (an active tissue-specific drug transporter belonging to the ATP-binding cassette (ABC) superfamily) could play a role. Acting as an efflux pump, it avoids cellular uptake of several drugs and toxins, preventing their absorption. Simvastatin is an inhibitor and a substrate of the P-gp; therefore, any inhibition of P-gp by other drugs may increase serum levels of simvastatin when coadministered.¹² P-gp inhibition may also occur with β -blockers.¹³ Whether ciprofloxacin could be a substrate of P-gp or not remains uncertain.¹⁴ Another theory surrounds the role of the multiple drug protein-2 (a membrane transport protein from the ABC superfamily excreting toxins into bile), since simvastatin is a substrate of this transporter.¹⁵ Finally, there are several genetic factors that may also predispose one to statin-related toxicity¹⁶ or

genetic mutations (eg, involving CYP2C8) which may be relevant in a statin–ciprofloxacin interaction.⁵

This case report wishes to raise awareness of this drug interaction, as although it may be relatively uncommon and incompletely understood, the potential outcome to patients is very serious indeed.

Learning points

- ▶ Statins can cause deranged liver function and myopathies.
- ▶ The likelihood of these side effects are increased by concomitant drug therapy.
- ▶ A potential mechanism for ciprofloxacin to increase the concentration of statins exists.
- ▶ Caution must therefore be taken when prescribing ciprofloxacin to patients taking statins.

Competing interests None declared.

Patient consent Obtained.

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