

Rhabdomyolysis following co-prescription of fusidic acid and atorvastatin

¹S Teckchandani, ²S Robertson, ³A Almond, ⁴K Donaldson, ⁵C Isles

¹Specialty Registrar; ^{2,3}Associate Specialist; ^{4,5}Consultant Physician, Renal Unit, Dumfries and Galloway Royal Infirmary, Dumfries, UK

ABSTRACT The placebo-corrected incidence of rhabdomyolysis in a systematic review of 20 statin trials was 1.6/100,000 per year. It is likely to be higher than this in everyday clinical practice when statins are knowingly or inadvertently co-prescribed with drugs that interfere with their metabolism. We report a case of rhabdomyolysis causing muscle weakness and prolonging an episode of dialysis-dependent acute kidney injury, which occurred when fusidic acid was co-prescribed with atorvastatin. Renal function and muscle power recovered when both drugs were withdrawn. We found four other cases of rhabdomyolysis with fusidic acid and atorvastatin and three with fusidic acid and simvastatin in the literature, a review of which suggests that the risks of rhabdomyolysis vary with the extent to which an individual statin is dependent for its metabolism on the cytochrome P450 3A4 isoenzyme and the degree to which this isoenzyme's activity is inhibited by a particular antimicrobial. Of note, the interaction between statins and fusidic acid did not feature in seven of eight recent reviews of statin toxicity. Our case report highlights the importance of close monitoring of patients on statins, especially when new drugs are started or if patients become unwell, by checking creatine kinase and liver function tests and by examining for new muscle weakness. Our review of statin–antimicrobial drug interactions suggests that fusidic acid is another CYP450 3A4 enzyme inhibitor with the potential to cause rhabdomyolysis when co-prescribed with simvastatin and atorvastatin.

Correspondence to S Teckchandani, Ward 43, Glasgow Royal Infirmary, 1053 Great Western Road, Glasgow G12 0NR, UK

tel. +44 (0)7916 273061

e-mail suneetatec@doctors.org.uk

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INTRODUCTION

Hydroxymethyl glutamyl coenzyme A reductase inhibitors (statins) reduce vascular risk and are widely prescribed for patients with, or likely to develop, ischaemic heart disease. These drugs are generally well tolerated¹ but have two uncommon and potentially serious adverse effects: elevation of liver enzymes, which are usually asymptomatic,¹ and skeletal muscle disorders. The effects on skeletal muscle range from benign myalgias and myopathy to rhabdomyolysis. Myopathy may be defined by a ten-fold elevation in creatine kinase (CK) with muscle pain or weakness, while rhabdomyolysis is usually associated with CK >10,000 international units per litre (IU/l) and acute kidney injury, which may be life-threatening.^{1–3}

The placebo-corrected incidence of rhabdomyolysis in a systematic review of 20 statin trials was 1.6/100,000 per year,⁹ but the incidence is likely to be higher than this in everyday clinical practice when statins are knowingly or inadvertently co-prescribed with drugs that inhibit their metabolism.¹⁰ Against this background we wish to report a case of rhabdomyolysis that occurred when fusidic acid was co-prescribed with atorvastatin, potentiating the toxicity of both drugs. We also review the literature on statin–antimicrobial drug interactions.

CASE REPORT

A 69-year-old male presented with multi-organ failure secondary to left lower lobe consolidation, for which he required ventilation, dialysis and inotropic support. One week previously he had been prescribed flucloxacillin (2 g per day) and fusidic acid (2.25 g per day), following the excision of an infected hip prosthesis. His medical history included myocardial infarction, hypertension and hyperlipidaemia, and his routine medications were ramipril (10 mg per day), atenolol (50 mg per day), atorvastatin (40 mg per day), ezetimibe (10 mg per day), aspirin (75 mg per day) and diclofenac (100 mg per day).

We were able to withdraw ventilatory and circulatory support after three days, although the patient remained dialysis-dependent and slow to mobilise. We observed at this point that he could not sit up unaided and demonstrated proximal muscle weakness with CK 21,652 IU/l (normal range 0–195). Liver function tests were also deranged, with bilirubin 60 mmol/l, aspartate aminotransferase (AST) 618 IU/l (normal range 0–42), alanine aminotransferase (ALT) 177 IU/l (normal range 0–50), gamma GT 213 IU/l (normal range 0–50) and alkaline phosphatase 175 IU/l (normal range 35–130). Atorvastatin, ezetimibe and fusidic acid were stopped.

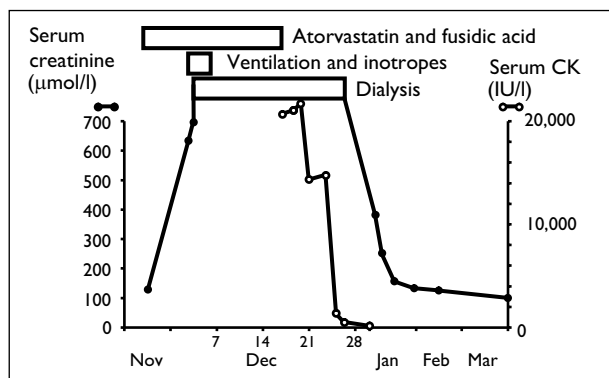


FIGURE 1 Clinical course of a patient whose acute renal failure was caused initially by pneumonia with multi-organ failure and subsequently by rhabdomyolysis due to an interaction between atorvastatin and fusidic acid.

The patient was unable to walk for a further four days and remained dialysis-dependent for another ten days (Figure 1). When reviewed at the clinic two months after his initial presentation, muscle power had returned to normal and serum creatinine was 105 $\mu\text{mol/l}$. We subsequently reported our findings to the Medicines and Healthcare products Regulatory Agency.

DISCUSSION

Evidence of a statin–fusidic acid interaction

Our patient's presentation with pneumonia and multi-organ failure may well have led to a delay in the recognition of his rhabdomyolysis, which we did not consider until he complained of muscle weakness after ventilatory and circulatory support were no longer needed. Had severe organ failure caused rhabdomyolysis, we would have expected our patient to present with muscle weakness rather than develop this later in the course of his illness, at a time when his respiratory and circulatory function had recovered.

We also felt that the statin–ezetimibe combination was unlikely to have been responsible: a recent review has suggested that ezetimibe is safe when given in combination with high-dose statins,⁴ and our patient had been on these drugs for several years without untoward effects. We were unaware at the time of his presentation of an interaction between fusidic acid and statins, but subsequently learned that fusidic acid inhibits the CYP3A4 enzyme system and that this particular drug combination is likely to potentiate the toxicities of both drugs.^{11,12} We later found seven case reports of rhabdomyolysis due to a fusidic acid–statin interaction, including four of fusidic acid with atorvastatin^{13–16} and three of fusidic acid with simvastatin.^{17–19} Fusidic acid was the only CYP3A4 inhibitor prescribed in five of these reports. Despite this, the risk of an interaction between statins and fusidic acid is mentioned in only one¹ of eight recent reviews of statin toxicity.^{1–8}

Other statin–antimicrobial interactions

The statins, the antimicrobials and the cytochrome P450 isoenzymes responsible for their metabolism are shown in Table 1.^{20–43} Simvastatin is mainly metabolised and atorvastatin partly metabolised by CYP3A4, while fluvastatin is metabolised by CYP2C9 with contributions from CYP2C8 and CYP3A4 (summarised by Bellosta et al.¹). Rosuvastatin is not extensively metabolised but has some interaction with CYP2C9 and CYP2C19 isoenzymes.⁴⁴ It will be apparent from Table 1 that the risks of rhabdomyolysis may vary both with the statin and with the antimicrobial. Simvastatin 80 mg daily caused more rhabdomyolysis than atorvastatin 80 mg daily in the statin trials that compared more intensive with less intensive treatment (summarised by Armitage⁵), and is probably more likely than atorvastatin to cause rhabdomyolysis when given in combination with macrolide antibiotics⁴⁵ and azole antifungals.^{46,47}

TABLE 1 Statins, antimicrobials and risks of rhabdomyolysis*

	Clarithromycin 3A4	Erythromycin 3A4	Ketoconazole 3A4	Fluconazole 2C9, 2C19	Fusidic acid 3A4
Pravastatin Not significantly metabolised by P450	Caution ²⁰	Caution	Should be safe ²¹	Should be safe ²²	Should be safe
Fluvastatin Mainly metabolised by 2C9, partly by 2C8 and 3A4	Should be safe	Should be safe ²³	Should be safe ²³	Omit ²²	Should be safe
Simvastatin Mainly metabolised by 3A4	Omit ^{24–29}	Omit ^{29,30}	Omit ^{31–34}	Caution ^{35–37}	Omit
Atorvastatin Partly metabolised by 3A4	Omit or max dose 20 mg ^{20, 38, 39}	Omit or max dose 10 mg ⁴⁰	Omit or max dose 40 mg ⁴¹	Should be safe	Omit or max dose 10 mg
Rosuvastatin Less than 10% metabolised by 2C9 and 2C19	Should be safe	Should be safe ⁴²	Should be safe	Omit or max dose 10 mg ⁴³	Should be safe

*This table shows the cytochrome P450 isoenzymes responsible for the metabolism of statins and inhibited by five commonly used antibiotics. Advice to omit or limit the dose of statin is based on case reports or increase in the area under curve (AUC) likely to arise as a result of cytochrome P450 interaction. 'Caution' means case report or increase in AUC independent of cytochrome P450 enzyme system. 'Should be safe' means no case report found and no interaction anticipated. Superscript references denote the papers providing evidence for the advice given in each box.

There were no cases of rhabdomyolysis reported with pravastatin in the Prospective Pravastatin Pooling Project,⁴⁸ possibly reflecting the fact that this drug is not metabolised by cytochrome P450. Rhabdomyolysis has nevertheless been reported with pravastatin,⁴⁹ indicating that other mechanisms must be responsible. Saito et al. have suggested that P-glycoproteins and organic anion transporter polypeptides may be responsible for statin–drug interactions at a pharmacokinetic level.⁵⁰ There are fewer data on the safety of rosuvastatin, the most potent of the statins and the newest to be licensed for use in the treatment of hyperlipidaemia. Pre- and post-marketing surveillance suggests a myopathy rate similar to that of the other statins,⁵¹ while head-to-head comparisons of rosuvastatin with atorvastatin in 25 studies of 19,621 patients have shown no significant differences in side effects between 5–40 mg rosuvastatin and 10–80 mg atorvastatin.⁵² Other patient risk factors that may increase the possibility of rhabdomyolysis with statins are advanced age, chronic kidney disease, muscular disorders, endocrine disorders, hepatic impairment, prolonged seizures, debilitated status and severe infections.⁴

CONCLUSION

The increasing tendency to treat older patients to more demanding lipid targets and the fact that statins are frequently co-prescribed with interacting drugs⁵³ means that the risk of rhabdomyolysis in patients taking statins can only increase. Our case report highlights the importance of close monitoring of patients on statins, especially when new drugs are started or patients become unwell, by checking creatine kinase and liver function tests and by examining for new muscle weakness. Our review of statin–antimicrobial drug interactions suggests that fusidic acid is another CYP450 3A4 enzyme inhibitor with the potential to cause rhabdomyolysis when co-prescribed with simvastatin and atorvastatin.

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