Acute rhabdomyolysis caused by combination therapy with atorvastatin and warfarin

Introduction

Atorvastatin and warfarin are commonly prescribed in combination. Acute rhabdomyolysis is a rare but recognized side effect of atorvastatin occurring within a few weeks of initiation. This article presents a case of a 69-year-old man, on stable atorvastatin therapy, who developed acute rhabdomyolysis following initiation of warfarin. Rising international normalized ratio is a well-recognized feature of interaction between warfarin and various statins (fluvastatin, lovastatin and simva-statin). There has only been one previous similar case of acute rhabdomyolysis following the commencement of warfarin, reported in a patient on stable simvastatin therapy. To the authors' knowledge, no similar case has been reported with atorvastatin.

Both atorvastatin and warfarin are metabolized via the hepatic cytochrome P450 system, specifically by CYP3A4, thus the introduction of warfarin in this patient inhibited atorvastatin metabolism, increasing its bioavailability and resulting in acute rhabdomyolysis. The recommendation that atorvastatin is the preferred statin in patients receiving warfarin therapy must therefore be interpreted with caution.

Discussion

Atorvastatin is one of several 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) used in the treatment of hypercholesterolaemia. While myalgia and myositis are common and well-recognized side effects of statin therapy, acute rhabdomyolysis is rare. Statins are metabolized by the hepatic cytochrome

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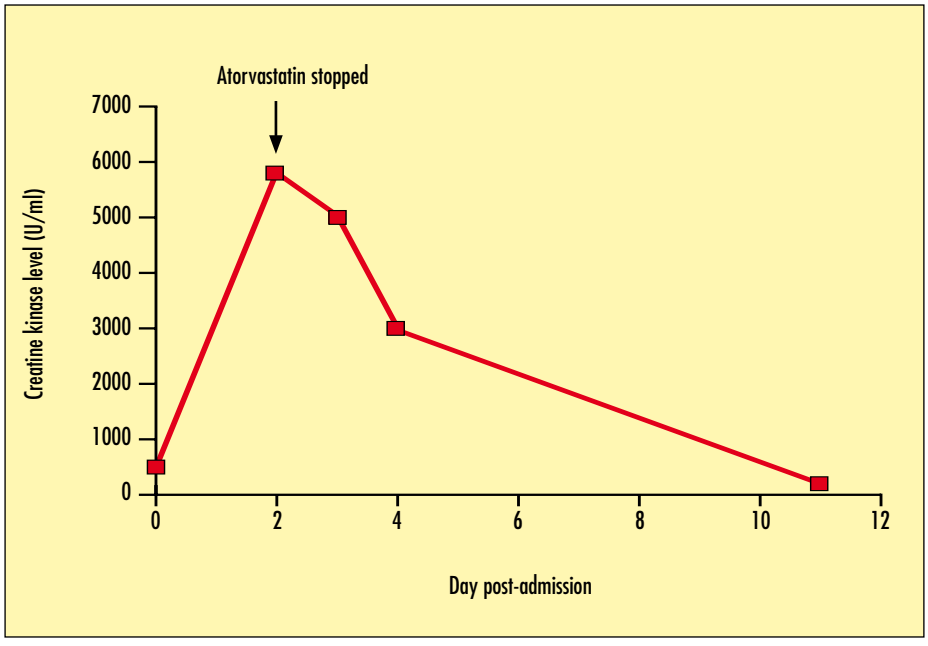
Figure 1. Plasma creatine kinase levels during admission.



Case Report

A 69-year-old man presented with a sudden onset of generalized muscle aches, mild confusion, malaise and weakness. He denied any chest pain, dyspnoea, palpitations, had not noticed any new rashes and had no relevant travel history. One week before this presentation, the patient had been diagnosed with paroxysmal atrial fibrillation by his GP, and had been started on warfarin. His past medical history included transient ischaemic attack 3 years previously, hypertension, hypercholesterolaemia, polymyalgia rheumatica (symptomatically well controlled on oral steroids) and Duke's B colonic adenocarcinoma, fully resected 6 years previously. He was an ex-smoker with a 30 pack year history and drank 30 units of alcohol per week. There was no recent history of strenuous exercise or injury. The patient's regular medications included atorvastatin (10 mg once daily), aspirin (75 mg once daily), bisoprolol (2.5 mg once daily) and prednisolone (4 mg once daily). On examination the patient was haemodynamically stable and apyrexial, with oxygen saturations of 95% on ambient air. He had significant proximal muscle weakness and generalized muscle tenderness. Systemic examination was otherwise unremarkable.

His initial biochemistry showed a raised plasma creatine kinase level of 482 units/litre (normal range 55–170 units/litre) but normal renal function (urea 4.1 mmol/litre, creatinine 73 μmol/litre), normal full blood count with an erythrocyte sedimentation rate of 27 mm/1st hour (normal range <22 mm/1st hour), and an international normalized ratio of 1.95. An electrocardiogram showed no acute changes and his troponin I level was not raised. There was no immediate explanation for his severe symptoms so he was admitted for observation. Two days post admission his creatine kinase level had risen to 5855 units/litre (*Figure 1*). As his erythrocyte sedimentation rate was not markedly raised, it was felt that his symptoms could not be attributed to a flare-up of his polymyalgia rheumatica, and rhabdomyolysis secondary to statin therapy was diagnosed. At this point, atorvastatin was stopped. The patient was treated with intravenous fluid therapy. His renal function remained within normal limits, and his serum creatine kinase level began to fall (*Figure 1*). His symptoms improved and he was discharged 4 days post-admission.

P450 system, and thus have the potential to interact with other drugs metabolized by this route. One such drug is the oral anticoagulant warfarin, a vitamin K epoxide reductase inhibitor.

Co-prescribing of statins and warfarin is common (for example in patients with a history of ischaemic heart disease and atrial fibrillation), and there are several case reports and other studies describing the interactions between the two drugs (Iliadis and Konwinski, 1995; Trilli et al, 1996; Lin et al, 1999; Andrus, 2004). The most commonly reported interaction is a raised international normalized ratio in patients on stable warfarin therapy following the start of statin therapy. However, a study looking specifically at the interaction between atorvastatin and warfarin in 12 patients did not demonstrate any significant change in international normalized ratio (Stern et al, 1997).

To the best of the authors' knowledge there is only one case report describing rhabdomyolysis as the result of an interaction between statins and warfarin. This occurred in an 82-year-old man on stable simvastatin therapy who had recently been started on warfarin (Moyogorosi et al, 1999). The US Food and Drug Administration adverse event report on statin-associated rhabdomyolysis mentions 33 reports of warfarin as a 'potentially interacting drug' (Omar and Wilson, 2002), but no further details of these cases have been published to date.

Some statins interact with warfarin more commonly than others. This is probably in part a result of structural differences between the statins which affect the particular cytochrome P450 enzyme via which they are metabolized. Lovastatin, simvastatin and atorvastatin are metabolized by the CYP3A4 isoenzyme, whereas fluvastatin is metabolized by CYP2C9. These statins undergo phase 1 metabolism through conversion to more hydrophilic compounds, and are then excreted from the body. Pravastatin is not significantly metabolized by the cytochrome P450 system but directly conjugated for phase 2 metabolism (Transon et al, 1996). Warfarin is a racemic mixture of R and S stereoisomers. The S isomer has been estimated to be five times as potent at inhibiting vitamin K epoxide reductase, and is mainly metabolized by the cytochrome P450 isoenzymes CYP2C9, CYP2C19 and CYP2C18, whereas the less active R isomer is mainly metabolized by CYP1A2 and CYP3A4.

The basis for the interaction between atorvastatin and warfarin can be explained, at least in part, by the use of a common metabolic pathway (CYP3A4). The introduction of warfarin resulted in competitive inhibition of CYP3A4-mediated atorvastatin metabolism, resulting in increased bioavailability of atorvastatin to a level sufficient to cause rhabdomyolysis.

While the recommendation that atorvastatin is the preferred statin for patients on warfarin therapy can be understood from previous studies looking at interactions between these drugs (Stern et al, 1997; Andrus, 2004), further reports of rhabdomyolysis resulting from the introduction of warfarin in patients receiving atorva-statin therapy may lead to reconsideration of this recommendation.

Conclusions

This article has presented a case of a 69-year-old man on stable atorvastatin therapy who developed acute rhabdomyolysis following the initiation of warfarin. This interaction has not been previously described with atorvastatin. Vigilance is required when co-prescribing warfarin with any statin. **BJHM**

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LEARNING POINTS

- Prescribers should be aware of the potential interaction between warfarin and statins in general.
- Although atorvastatin has been described as the statin of choice for use in patients on warfarin therapy, prescribers should be aware that both drugs are metabolized by the same cytochrome P450 isoenzyme (CYP3A4), and thus there is the potential for increased bioavailability of either drug.
- Statin-induced myositis or rhabdomyolysis is usually manifest in the period following commencement of statin therapy. However, this side effect is still possible in patients on stable therapy when warfarin or other potentially interacting drugs are added.
- If a diagnosis of rhabdomyolysis is considered, it is important to measure serial serum creatine kinase levels as the rise may not be immediately apparent at presentation.