CASE REPORT

Risk of statin-induced rhabdomyolysis in patients with hepatic impairment

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SUMMARY

We describe a case of a 54-year-old man with a 2-month history of biliary colic associated with a common bile duct stone. He underwent laparoscopic cholecystectomy and developed postoperative acute kidney injury stage 3. A renal biopsy was performed and demonstrated myoglobin in the renal tubules. Retrospective creatine kinase analysis was suggestive of rhabdomyolysis. It is thought this was precipitated by simvastatin accumulation in the context of a period of hepatic impairment and elevated liver enzymes.

BACKGROUND

Although statin-induced rhabdomyolysis is well recognised, it often goes unnoticed in the setting of hepatic impairment. Elevation of liver enzymes, particularly in the setting of biliary disease, should prompt consideration of withholding statin therapy to reduce this risk.

CASE PRESENTATION

The patient is a 54-year-old man with hypertension and diet-controlled type 2 diabetes mellitus. His regular medications included simvastatin, bendroflumethiazide and ramipril. He initially presented to his general practitioner with intermittent, dull, postprandial epigastric pain. An abdominal ultrasound scan demonstrated a gallbladder with a diffusely thickened irregular wall and internal septations. There appeared to be a 10 mm stone in the common bile duct. The patient's symptoms had resolved so a 2-month interval scan was arranged. This showed mildly improved appearances of the gallbladder but the previously identified stone could not be visualised. By this point, the patient had experienced a recurrence of his upper abdominal pain and was now jaundiced, anorexic, febrile with pruritus, had dark urine and pale stools and was readmitted to hospital. His investigations included bilirubin of 245 µmol/L, alkaline phosphatase 318 IU/L, γ-glutamyl transferase (γ GT) 1070 IU/L and an alanine transaminase (ALT) 201 IU/L. His urine protein/creatinine ratio was 60 mg/mmol. His full blood count showed haemoglobin of 16.3 g/dL, a white cell count of $6.5 \times 10^9/L$ and a platelet count of $246 \times 10^9/L$. At that point his renal function was normal with a serum creatinine of 91 µmol/L. An intravenous contrast-enhanced CT scan confirmed a 9 mm stone in the common bile duct. He was clinically well and was discharged with an arrangement for laparoscopic cholecystectomy and bile duct exploration. This was performed uneventfully but he was readmitted 11 days postoperatively with

anorexia and lethargy but without any pain or fever. He had been drinking fluids normally. His jaundice had not improved. His blood pressure was 130/70 mm Hg with a pulse rate of 75/min. His serum creatinine was 161 µmol/L. His haemoglobin had fallen to $10.4 \times 10^9/L$ with a white cell count of $6.9 \times 10^9/L$ and platelets of $3340 \times 10^9/L$. His liver function tests remained elevated with a bilirubin of 229 µmol/L, alkaline phosphatase of 214 IU/L, γ-GT 127 IU/L and an ALT 510 IU/L. He was treated with intravenous cefuroxime and metronidazole for possible sepsis. A contrast-enhanced CT scan showed a small collection in the gallbladder fossa, aspiration of which yielded no growth on bacterial culture. His liver function tests improved (with serum bilirubin falling from 446 to 108 µmol/L) but he developed acute kidney injury stage 3 with a peak creatinine of 601 µmol/L. His urine output was maintained between 1125 and 2450 mL/24 h during this period. Urinalysis showed blood 3+ and protein 1+. Urine protein/creatinine ratio was 60 mg/mmol. It was suspected his acute kidney injury was probably due to acute tubular necrosis from dehydration and intravenous contrast use in the setting of continued ACE inhibitor and diuretic use. His ramipril and bendroflumethiazide were discontinued. He was aggressively rehydrated with intravenous fluids but serum creatinine did not fall promptly. A renal biopsy was performed on the seventh day, which demonstrated acute tubular necrosis (figure 1) with some positive tubular staining to myoglobin (figure 2). Retrospective analysis of blood sample at the time of admission revealed serum creatine kinase to be significantly elevated at 7400 IU/L. Creatine kinase had decreased after kidney biopsy to

Figure 1 Renal biopsy specimen with H&E staining, demonstrating acute tubular injury.

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Figure 2 Renal biopsy specimen with immunoperoxidase staining for myoglobin in renal tubule.

1415 IU/L, implicating clinically silent rhabdomyolysis as a cause of his acute kidney injury. Simvastatin was discontinued in light of the biopsy findings.

INVESTIGATIONS

Prior to admission

Creatinine 87 $\mu\text{mol/L}$, alkaline phosphatase 362 IU/L, $\gamma\text{-GT}$ 505 IU/L, ALT 63 IU/L and bilirubin 446 $\mu\text{mol/L}$.

At the time of the admission when acute kidney injury developed

Creatinine 161 $\mu\text{mol/L}$, alkaline phosphatase 214 IU/L, $\gamma\text{-GT}$ 127 IU/L, ALT 510 IU/L and bilirubin 229 $\mu\text{mol/L}$.

At the time of peak creatinine

Creatinine 601 $\mu\text{mol/L}$, alkaline phosphatase 173 IU/L, $\gamma\text{-GT}$ 174 IU/L, ALT 432 IU/L and bilirubin 81 $\mu\text{mol/L}$.

At transfer back to secondary care

Creatinine 480 $\mu\text{mol/L}$, alkaline phosphatase 115 IU/L, $\gamma\text{-GT}$ 113 IU/L, ALT 256 IU/L and bilirubin 59 $\mu\text{mol/L}$.

At 3-month follow-up

Creatinine 156 $\mu\text{mol/L}$, alkaline phosphatase 54 IU/L, ALT 22 IU/L and bilirubin 14 $\mu\text{mol/L}$.

At 6-month follow-up

Creatinine 160 $\mu\text{mol/L}$.

DIFFERENTIAL DIAGNOSIS

- ▶ Acute tubular necrosis secondary to dehydration and contrast
- ▶ Tubulointerstitial nephritis secondary to bendrofluthiazide

TREATMENT

Supportive treatment with intravenous fluids and stopping of potential nephrotoxic medications—ramipril, bendroflumethiazide and simvastatin.

OUTCOME AND FOLLOW-UP

The patient's acute kidney injury resolved without the need for renal replacement therapy. Two months following the onset of his acute kidney injury his serum creatinine had fallen to 180 $\mu\text{mol/L}$. Long-term follow-up identified with residual

chronic kidney disease stage 3b with a serum creatinine of 169 $\mu\text{mol/L}$ and estimated glomerular filtration rate of 37 ml/minute 12 months following the onset of his acute kidney injury.

DISCUSSION

Normally, statin therapy is monitored by measuring serum creatine kinase in presence of appropriate clinical symptoms. Statin-induced rhabdomyolysis is well described,¹ although the causative mechanism has not been clearly established. As well as inhibiting the conversion of HMG-coenzyme A to mevalonic acid, statins can also inhibit the synthesis of coenzyme Q10 (ubiquinone), which is involved in myocyte energy production,² although studies are conflicting about the extent of this.

Critical illness markedly impairs statin metabolism,² leading to elevated systemic levels and increased susceptibility to myocyte toxicity and rhabdomyolysis. The risk of statin-induced rhabdomyolysis is increased in the presence of renal and hepatic impairment and in diabetes. In this case, deranged liver function over a period of months probably led to impaired statin metabolism, increased systemic drug levels and a propensity to rhabdomyolysis leading to acute kidney injury, which can progress rapidly through various stages as shown in table 1.

The mortality risk from rhabdomyolysis is approximately 0.3/100 000 person-years, and the risks of non-fatal rhabdomyolysis and of putative statin-attributable peripheral neuropathy is approximately 3 and 12 events, respectively, per 100 000 person-years.³ The more immediate pleiotropic effects of statins in the proinflammatory and prothrombotic environment of the perioperative period are thought to include improved endothelial function (antithrombotic function and vasomotor function in response to ischaemic stress), enhanced stability of atherosclerotic plaques, decreased oxidative stress and decreased vascular inflammation.^{4–6} It is therefore important to individualise treatment decisions based on a patient's specific cardiac risk profile.

Rhabdomyolysis results in acute kidney injury due to intraluminal myoglobin cast formation, haem protein nephrotoxicity and renal vasoconstriction.⁷ As in this case, specific symptoms may be minimal or overlooked.

Table 1 Kidney Disease Informing Global Outcome (KDIGO) classification of acute kidney injury (AKI)

AKI stage	Serum creatinine criteria	Urine output criteria
Stage 1	Increase in creatinine of ≥ 26.4 $\mu\text{mol/L}$ (or 1.5–2-fold) from baseline, which is known or presumed to have occurred within the prior 7 days	Less than 0.5 mL/kg/h for more than 6 h
Stage 2	Increase in serum creatinine to more than 200–300% (>2 –3-fold) from baseline	Less than 0.5 mL/kg/h for more than 12 h
Stage 3	Increase in serum creatinine to more than 300% ($>$ threefold) from baseline (or serum creatinine of ≥ 354 $\mu\text{mol/L}$ with an acute increase of 44 $\mu\text{mol/L}$). Or initiation of renal replacement therapy	Less than 0.3 mL/kg/h for 24 h or anuria for 12 h

AKI is defined as an increase in creatinine of ≥ 26.4 $\mu\text{mol/L}$ or increase in serum creatinine to ≥ 1.5 times the baseline, which is known or presumed to have occurred within prior 7 days.

Patient's perspective

Statins are widely prescribed and potentially serious side effects can occur after many years due to serious interactions either with other medications or organ dysfunction.

Learning points

- ▶ Maintain a high index of suspicion for rhabdomyolysis in patients treated with statins, even in the absence of myalgia.
- ▶ Include a creatine kinase assay in the initial laboratory screen for acute kidney injury.
- ▶ Consider the risks and benefits of continuing statin therapy in patients with intercurrent illness associated with deranged liver function or biliary disease.

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Competing interests None.

Patient consent Obtained.

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