Case Report

Renal tubular toxicity of HMG-CoA reductase inhibitors

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Introduction

A patient developed direct renal tubular toxicity on high-dose HMG-CoA reductase inhibitor (statin) therapy. Considerable renal damage was present by the time the injury became apparent. Urine abnormalities regressed after stopping the drug and reappeared after about 2 weeks following re-challenge. Although tubular damage may be slight and relatively difficult to detect, it is possible that cumulative injury in susceptible individuals over a period of years may result in significant renal damage.

HMG-CoA reductase inhibitors (statins) reduce morbidity and mortality from coronary heart disease, prevent strokes and possibly reduce renal disease as the result of cholesterol lowering, improved endothelial function, reduced inflammation and reduced oxidative stress [1].

Significant side effects associated with statins are infrequent. Myalgia and arthralgia are common (1–7%) but frank rhabdomyolysis is rare and is generally associated with concurrent fibrate use [2]. Liver enzyme abnormalities may occur but are generally mild and transient. Minor alimentary tract disturbance and neuropathy are infrequent [3].

Mechanisms of toxicity are poorly understood and potentially include interruption of a wide variety of metabolic functions including membrane glycoprotein composition and fluidity, chloride channel activation and impaired mitochondrial function by reduced ubiquinone synthesis that may render lipoproteins more susceptible to oxidation injury [4]. Renal damage associated with the use of statins is generally due to associated rhabdomyolysis causing acute tubular necrosis. To the best of our knowledge, direct renal tubular damage by statins has not been described. The case we describe appears to have developed dose-related tubular toxicity.

Case

Familial hypercholesterolaemia was diagnosed in 1990 when the 58-year-old man (weight 66 kg) presented with a plasma cholesterol level of 442 mg/dl (11.5 mmol/l). Simvastatin was started and increased until substantial lowering of cholesterol was obtained at a dose of 40 mg/day. Atorvastatin was started in 1997 with doses increasing from 20 to 80 mg/day. In December 1999, rosuvastatin was started and the dose progressively increased to 80 mg/day by April 2000. Apart from stasis leg ulcers, he was clinically well and on no chronic medication other than the ‘statin’ and 150 mg aspirin per day. Urinalysis by dipstick and plasma creatinine had been normal at commencement of the study.

In November 2001, it was noted that his plasma creatinine had risen from 0.89 mg/dl (79 mmol/l) to 1.59 mg/dl (141 mmol/l) and that proteinuria had developed. Although clinical examination was normal, his urine was macroscopically ‘cloudy’ due to the presence of innumerable renal tubular casts, as illustrated in Figure 1a. Most of the casts had a coarse granular appearance but there were also some cellular, fine granular and very occasional hyaline casts. Moderate numbers of renal tubular cells and very occasional red cells were seen. ‘Dipstick’ examination showed 1+ protein and 3+ blood.

Special investigations revealed normal haemoglobin, white cell and platelet counts but an ESR of 31 mm in the first hour. Hepatitis surface antigen, hepatitis C antibody and antinuclear factor were negative. Protein electrophoresis was normal. Total serum protein was 8 g/dl, albumin 4.4 g/dl, ALT 69 units/l (normal range 1–41) and alkaline phosphatase 124 units/l (normal range 39–117). Creatinine clearance was 42 ml/min, urine protein excretion 1.6 g/day, plasma creatinine 1.58 mg/dl (140 mmol/l) and urea 37.2 mg/dl.
Creatine phosphokinase (CPK) levels during the preceding 2 years as well as those following our investigations and subsequent interventions were never significantly raised (Figure 2).

Renal biopsy showed acute as well as chronic tubulointerstitial nephritis. There was an increase in fibrous tissue with tubular atrophy and occasional inflammatory cells were present. Casts were seen in some dilated tubules and contained detached renal tubular cells. The glomeruli were normal by light and electron microscopy. Immunofluorescent microscopy showed some IgM and very little C3 deposition in the glomeruli, probably the result of non-specific ‘trapping’. Blood vessels were entirely normal. Electron microscopy showed increased size of many of the mitochondria of the proximal tubules.

Statin therapy was stopped, resulting in a total disappearance of casts (Figure 1b). Over 3 weeks the haematuria resolved and proteinuria was reduced to within normal levels (80 mg/24 h). Plasma creatinine dropped to 1.28 mg/dl (113 mmol/l) and urea to 38.4 mg/dl (6.4 mmol/l); creatinine clearance improved to 48 ml/min.
The need for cholesterol lowering and the initial uncertainty regarding the association of the drug with the renal abnormalities justified re-challenge with the drug at full dose with urine examination at 2 day intervals. Initially, the urinalysis remained normal on microscopy as well as dipstick examination. After 2 weeks the abnormalities reappeared (Figure 1c). The casts were present in large numbers but not quite to the extent noted on initial presentation (Figure 1a).

The drug was again stopped and the urine sediment and proteinuria returned to normal. As the need for long-term statin therapy remained, the patient was started on 40 mg/day of atorvastatin in June 2002, with similar monitoring. Urine abnormalities reappeared but casts were fewer and predominantly hyaline. Some casts were remarkable in that they contained up to four apparently intact tubular cells imbedded in the hyaline matrix of the cast. Proteinuria increased slightly from the average baseline of 128 (three estimations) to 190 mg/day (six estimations). These findings further improved on reduction of Atorvastatin to 20 mg/day and did not recur on Simvastatin 40 mg/day.

**Discussion**

The findings and clinical course are highly suggestive of direct tubular damage by both statins at high dosage. The time taken following re-introduction of rosuvastatin to manifest with acute tubular abnormalities suggests that the injury might relate to cumulative metabolic effects of the statin on tubular cells rather than an idiosyncratic allergic reaction or direct chemical toxicity. Rhabdomyolysis was effectively excluded by frequent CPK estimations; these were never significantly elevated.

Evidence of acute tubular toxicity was noted in the form of irregular vacuolated renal tubular cells, loss of tubular cells with denudation of tubular basement membranes as well as tubular cell casts seen both on histology and in the urine. The enlargement of mitochondria on electron microscopy was also in support of recent damage and might reflect abnormalities of energy metabolism possibly similar to those noted in patients with statin-induced oxidative muscle injury [5]. Although chronic tubulointerstitial damage is likely to have resulted from continuing injury, the effect of previous disease or drug therapy cannot be excluded.

The reappearance of renal tubular abnormalities with atorvastatin suggests that the injury is a class effect and its milder nature suggests that it may be dose-related. At low doses, statins might produce tubular damage only detectable by small increments in protein excretion or by abnormal casts only detectable on direct urine microscopy by an experienced observer. Cumulative damage over years may similarly only manifest with relatively modest proteinuria. Once an elevation of plasma creatinine is noted, substantial chronic damage would already be present.

Further studies are required to fully define the nature and prevalence of this adverse reaction as well as its implications for the management of patients on long-term statin therapy.

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Conflict of interest statement. The authors declare that although Dr J. Firth and Professor D. Marais have been involved in sponsored clinical trials involving rosuvastatin, neither has a conflict of interest in relation to this case, which was managed independently by Professor R. van Zyl-Smit, a clinical nephrologist.

References


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