CASE REPORT

Orlistat-induced oxalate nephropathy: an under-recognised cause of chronic kidney disease

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SUMMARY

Two patients developed kidney failure due to oxalate deposition in the kidney while taking orlistat. Cessation of orlistat was followed by partial recovery of kidney function. The mechanism by which orlistat causes hyperoxaluria and the management of orlistat-induced oxalate nephropathy is reviewed. We suggest that all patients taking orlistat are at risk of this condition, which may develop insidiously and is easily overlooked. Monitoring of kidney function of patients taking orlistat is warranted.

BACKGROUND

Obesity is a global health concern.¹ The National Institute for Health and Care Excellence (NICE) advises that pharmacological intervention may be considered for people who do not reach their target weight loss with dietary, activity and behavioural changes.² Orlistat is a potent, long-acting oral gastrointestinal lipase inhibitor indicated for adults who are overweight, specifically those with a body mass index (BMI) greater than 30 kg/m² or greater than 28 kg/m² with associated risk factors.^{2,3} It acts in the lumen of the stomach and small intestine by forming a covalent bond with gastric and pancreatic lipases reducing the absorption of dietary fat.³ The most commonly reported side effects are gastrointestinal in nature and include abdominal pain, flatulence, faecal incontinence and oily stools.⁴ There have also been reports of acute kidney

injury due to hyperoxaluria and associated oxalate nephropathy.^{5–14} Although this is recognised in the nephrology literature, the consequences of orlistat-associated hyperoxaluria are less well appreciated by the general prescriber. We describe two cases of oxalate nephropathy due to orlistat, review the mechanism of orlistat-induced oxalate nephropathy and highlight learning points for clinical practice.

CASE PRESENTATION**Case 1**

A 65-year-old man with hypertension, type 2 diabetes mellitus, ischaemic heart disease and obesity was referred for assessment of renal impairment. He complained of lethargy and breathlessness. His general practitioner confirmed that he had received orlistat 120mg three times per day for 10 months. His other medications included aspirin, furosemide, metformin, atorvastatin, perindopril, betahistine, gliclazide, sitagliptin, spironolactone, citalopram, bisoprolol and lansoprazole. He had not taken antibiotics, non-steroidal anti-inflammatory drugs, ascorbic acid, naftidrofuryl or herbal products, nor had he ingested ethylene glycol. Blood pressure was 142/60 mm Hg. Heart sounds and abdominal examination were normal. A chest radiograph demonstrated a right-sided pleural effusion. Investigations included a serum creatinine of 423 compared with 106 µmol/L a year earlier. Haemoglobin was 8.1 g/dL. Liver function, bone profile, serum immunoglobulins, protein electrophoresis and antineutrophil cytoplasmic antibody were normal or negative. Urinalysis showed +1 blood, but no protein. Urinary oxalate–creatinine ratio was 160 µmol/mmol (normal <33 µmol/mmol). A CT scan demonstrated a normal left kidney, a parapelvic cyst and several non-obstructing renal calculi in the lower pole of the right kidney, but no evidence of hydronephrosis. Pleural aspirate was a transudate. Renal biopsy revealed moderate chronic interstitial inflammatory infiltration with patchy fibrosis and tubular atrophy (figure 1). Several tubules contained oxalate crystals, and blood vessels showed hyperplastic change. Two months after stopping orlistat, his oxalate–creatinine ratio had fallen to 26 µmol/mmol. His serum creatinine decreased marginally to 316 µmol/L (figure 2).

Figure 1 Case 1 H&E section showing oxalate crystals in a renal tubule with associated inflammatory change. Inset confirms birefringence of refractile material on polarised light microscopy.

Case 2

A 65-year-old woman was referred for assessment of renal impairment. She had chronic obstructive

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Figure 2 Case 1 serum creatinine and eGFR. eGFR, estimated glomerular filtration rate.

pulmonary disease, type 2 diabetes mellitus, obesity and osteoarthritis. She was short of breath on exertion. Her general practitioner confirmed that she had been prescribed orlistat 120 mg three times per day intermittently for 8 years. Her other medication comprised atorvastatin, carbocisteine, clonidine, escitalopram, gabapentin, linagliptin, omeprazole and salbutamol, symbicort and tiotropium inhalers. She had not taken ascorbic acid, naftidrofuryl or herbal products, nor had she ingested ethylene glycol. She weighed 89.1 kg with a BMI of 36 kg/m². Blood pressure was 158/80 mm Hg. Physical examination was normal. Urinalysis did not demonstrate blood or protein. Investigation results included: urea 15.3 mmol/L, creatinine 284 µmol/L, urinary albumin-creatinine ratio <2 mg/mmol and haemoglobin A1c 45 mmol/mol. Urine oxalate concentration was 680 µmol/L at her first clinic visit before cessation of orlistat. Twenty-four-hour urinary oxalate was 411 µmol (normal 40–320 µmol), and the urinary oxalate

concentration was 168 µmol/L 1 day after stopping orlistat. Ultrasound of the kidneys showed loss of corticomedullary differentiation, but no hydronephrosis. Renal biopsy (figure 3) contained nine normal glomeruli. There was evidence of mild tubular atrophy, focal acute tubular necrosis and mild interstitial fibrosis. Many tubules contained oxalate crystals. Her serum creatinine fell to 191 after stopping orlistat compared with 75 µmol/L 2 years earlier (figure 4).

DISCUSSION

The decision to prescribe orlistat is governed by the balance of risks and benefits. Orlistat has been associated with a 2.8% absolute and 37% relative risk reduction for the development of diabetes mellitus and 2.7 kg weight loss when compared with placebo over 4 years.¹⁵ Accordingly, orlistat is an effective pharmacological intervention for those who are overweight and at risk of obesity-related complications, though the absolute benefit is small. As with any medication, it is important to consider the associated risks of adverse events.

Animal experiments and human observations have demonstrated that orlistat causes hyperoxaluria. Ferraz *et al* studied rats administered a standard and oxalate-supplemented diet.¹⁶ The

Figure 3 Case 2 H&E section showing oxalate crystals in a renal tubule with associated inflammatory change. Inset confirms birefringence of refractile material on polarised light microscopy.

Figure 4 Case 2 serum creatinine and eGFR. eGFR, estimated glomerular filtration rate.

Table 1 Summary of published case reports

Case report	Gender and age	BMI (kg/m ²)	Orlistat dose	Orlistat duration	Presenting symptoms	Creatinine (µmol/L)			Ultrasound	Evidence of hyperoxaluria	Renal biopsy findings
						Baseline	Presentation	Last reported			
Humayun <i>et al</i> ⁵	F76	29.5	120mg three times a day	6 weeks	N/A	164	427	178	Multiple non-obstructing stones	54.6 mg/day (9.7–40.5)	'Calcium oxalate crystals within tubular lumens with interstitial inflammation and features of acute tubular necrosis'.
Kwan <i>et al</i> ⁶	F60	N/A	120mg three times a day	N/A	Malaise, anorexia and oliguria	100	726	Improved	Normal kidneys	815 µmol/day (<100–500)	'Mild interstitial fibrosis, a sparse lymphocytic infiltrate and oxalate crystals deposited in the tubular lumen'.
Coutinho and Glancey ⁷	F54	28	120mg three times a day	8 months	Clinically well	83	224	≈190	Normal kidneys	N/A	'Extensive tubular atrophy and interstitial fibrosis'. Nine months after presentation.
	F66	37	120mg three times a day	Intermittent use; estimated 31 months	Clinically well	103	327	≈290	Normal kidneys	N/A	'Tubular atrophy, interstitial fibrosis and calcium oxalate crystals in the tubules'. One week after presentation.
	M68	34	120mg three times a day	Intermittent use; estimated 33 months	N/A	149	267	≈180	Slight cortical thinning	N/A	'Extensive tubular atrophy and interstitial fibrosis'. Five months after presentation.
Hinchliffe <i>et al</i> ¹⁰	N/A	N/A	N/A	N/A	N/A	N/A	590	N/A	N/A	N/A	Image only.
Karamadoukis <i>et al</i> ¹¹	N/A	N/A	N/A	N/A	N/A	N/A	Acute Tubular Necrosis	Died	N/A	N/A	Acute tubular necrosis and calcium oxalate crystals.
	N/A	N/A	N/A	N/A	N/A	N/A	Acute Tubular Necrosis	Recovered	N/A	N/A	Acute tubular necrosis and calcium oxalate crystals.
Singh <i>et al</i> ¹²	F57	N/A	120mg three times a day	N/A	Malaise, weakness and loose oily stools	221	336	221	Slightly echogenic non-hydronephrotic kidneys	1.64 mmol/day (<0.55)	Several calcium oxalate crystals within tubules and interstitium. Diffuse chronic interstitial fibrosis. Additional features of hypertensive nephrosclerosis.

Continued

Table 1 Continued

Case report	Gender and age	BMI (kg/m ²)	Orlistat dose	Orlistat duration	Presenting symptoms	Creatinine (µmol/L)			Last reported	Ultrasound	Evidence of hyperoxaluria	Renal biopsy findings
						Baseline	Presentation					
Courtney <i>et al</i> ³	F55	35	N/A	5 months	N/A	141	626		Dialysis dependent at 24 months	Normal kidneys	N/A	'Diabetic nephropathy with moderate interstitial scarring and widespread glomerulosclerosis. There was extensive, superimposed, intratubular deposition of calcium oxalate crystals in the kidney, with mild to moderate tubulointerstitial inflammation'.
Chaudhari <i>et al</i> ⁸	F56	N/A	N/A	N/A	Fatigue	71	583		N/A	Medullary nephrocalcinosis	N/A	'Severe interstitial nephritis with tubular atrophy, moderate presence of oxalate crystals in tubules'.
Dossabhoy <i>et al</i> ⁹	M61	35	120 mg three times a day	4 years	Nausea, vomiting and reduced oral intake	<88	548	203	N/A	N/A	54 mg/day (7-44)	Acute tubular necrosis, oxalate crystals in tubules.

BMI, body mass index.

authors demonstrated that orlistat increased urinary oxalate and urinary calcium oxalate product and decreased urinary calcium in most experimental groups.¹⁶ Sarica *et al* compared patients administered orlistat to controls and observed an increase in urinary oxalate.¹⁷ Though the risk of gastrointestinal disturbances with orlistat is well recognised, our experience and review of the literature suggests that the consequences of hyperoxaluria are less well known.^{4 14 18}

Orlistat inhibits the action of gastric and pancreatic lipases within the gastrointestinal tract, enzymes that are essential for the hydrolysis of dietary fat.^{3 19} This reduces the absorption of fatty acids and bile salts, which become available to bind to calcium in the gastrointestinal tract.²⁰ This leads to increased oxalate absorption via two mechanisms. First, less luminal calcium is available to bind to oxalate to form insoluble calcium oxalate.²⁰ Second, the non-absorbed bile salts may increase colonic permeability to oxalate.²⁰ The oxalate absorbed from gastrointestinal tract is filtered at the glomerulus causing hyperoxaluria.²⁰ This process is termed 'enteric hyperoxaluria' and occurs in the setting of other malabsorption syndromes such as inflammatory bowel disease or surgical bowel resection (including bariatric surgery).^{21–23}

How does hyperoxaluria lead to renal impairment? Oxalate in solution probably does no harm to the kidney, but urinary oxalate supersaturation leads to the precipitation of calcium oxalate that causes crystal deposition, nephrocalcinosis or nephrolithiasis.^{24 25} First, mechanical obstruction may directly injure tubules and cause acute kidney injury.²⁶ Second, calcium oxalate crystals in renal tubules cause renal antigen presenting cells to release proinflammatory interleukin 1 β via the intracellular signalling pathway, nucleotide-binding domain, leucine-rich repeat-containing family protein 3 inflammasome/apoptosis-associated speck-like protein containing caspase activation and recruitment domain/caspase-1 axis.^{27 28} Third, the calcium oxalate activates nicotinamide adenine dinucleotide phosphate oxidase leading to the release of excess reactive oxygen species.²⁹ These processes ultimately lead to interstitial fibrosis and chronic kidney disease.

The majority of reported cases had multiple small intratubular oxalate crystals demonstrated histologically. Fewer had large stones visible on imaging. The reason for the difference is not certain, but this may be related to the product of crystallisation. Crystallisation in the kidney is determined by the tubular fluid oxalate and calcium concentrations and various inhibitors and promoters. In conditions when the urine is heavily supersaturated with oxalate, multiple small crystals may form rapidly in the tubules throughout the kidney, but the process may be slower when the concentration of oxalate is lower. Larger stones form when there is time for the precipitation of calcium oxalate around a nidus.

Our and other cases demonstrate a similar natural history (table 1).^{5–14} Kidney failure developed insidiously and was detected incidentally when blood tests were performed for another reason. The patients had no or non-specific symptoms such as fatigue and breathlessness. Urinalysis was benign. Imaging showed calculi in a few patients, but most had normal ultrasound scans. Renal biopsy showed oxalate crystals in renal tubules except in two cases when biopsy was undertaken several months after stopping orlistat and showed tubular atrophy with interstitial fibrosis.⁷ Cessation of orlistat was followed by stabilisation or improvement of kidney function, but recovery was incomplete.

Diagnosis hinges on awareness, demonstration of hyperoxaluria (which resolves after stopping orlistat) and biopsy. Patients prescribed orlistat are often at risk of kidney failure for other

reasons such as pre-existing renal impairment, diabetes mellitus and hypertension. Obesity itself is associated with nephrolithiasis and accelerates progression of chronic kidney disease.^{30 31} Many patients taking orlistat who present with renal impairment may not be biopsied as the cause of renal impairment is deemed to be related to one of the above diagnoses and as the procedure is often considered too high risk in overweight patients. Thus, patients taking orlistat may be among those with kidney disease least likely to be biopsied.

Twenty-four-hour urinary oxalate or oxalate-creatinine ratio may demonstrate hyperoxaluria, but these are not reliable criteria because urinary oxalate decreases in renal failure and may vary with dietary preference and seasonal variation. Furthermore, urinary oxalate levels may fall promptly and no longer be abnormal after cessation of orlistat, as demonstrated in both cases.

Risk is probably greatest in patients with impaired kidney function, because plasma oxalate may increase and be filtered through fewer nephrons. By analogy, systemic oxalosis accelerates as glomerular filtration declines in primary hyperoxaluria. Furthermore, damage in patients with good kidney function may be difficult to detect, because serum creatinine does not increase until there is significant impairment. The orlistat datasheet includes hyperoxaluria among side effects and advises caution in chronic kidney disease, but does not define this, recommend modification of dose or specify monitoring.

Cessation is recommended after 3 months if there is no weight loss. NICE advises that the decision to use drug treatment for longer than 12 months should only be made after discussion with the patient, but does not prohibit long-term use.² Risk may be related to therapy duration, but the case reports suggest that acute kidney injury may develop within a few weeks of starting orlistat or after many months in those established and apparently stable on treatment. We suggest that monitoring of kidney function is warranted in all patients for as long as they take orlistat.

Orlistat is available over the counter and the internet. It seems unlikely that patients would appreciate the risk. Although dietary oxalate restriction may reduce risk, this is difficult and unlikely to be successful in patients who overeat.

The amount of oxalate that is absorbed from the gut is influenced by whether it is in a soluble or insoluble form. Oxalic acid and sodium oxalate are soluble, whereas calcium oxalate and magnesium oxalate are insoluble. In a mouse model of enteric hyperoxaluria, a diet deficient in calcium was associated with acute kidney injury, which was prevented by the addition of calcium carbonate.²⁸ There is less evidence in humans, but a diet unrestricted in calcium and a calcium supplement such as calcium carbonate between 1 and 4 g daily may increase calcium oxalate precipitation in the bowel.³² A high fluid intake to dilute urine may be beneficial.

The Medicines and Healthcare Products Regulatory Agency report 123 UK suspected adverse drug reactions of renal and urinary abnormalities.³³ These include tubulointerstitial nephritis, crystal nephropathy, nephropathy, renal tubular atrophy, kidney fibrosis, acute kidney injury, chronic kidney disease, renal failure, renal impairment, nephrolithiasis and hyperoxaluria.³³ Varying nomenclature is difficult to interpret, but many of these reports may describe the same phenomenon.

We suggest that oxalate nephropathy, secondary to orlistat, is under-recognised and the use of orlistat including availability over the counter and internet be reviewed. Prescribing physicians should be vigilant. Precautionary measures and monitoring of kidney function of all patients taking orlistat are warranted.

Learning points

- Orlistat use can cause oxalate kidney stones or oxalate nephropathy.
- Oxalate nephropathy due to orlistat is often asymptomatic and develops insidiously.
- Recovery of kidney function after stopping orlistat may be incomplete with resultant chronic kidney disease.
- Diagnosis requires an appropriate clinical history, demonstration of hyperoxaluria that resolves after stopping orlistat, kidney biopsy and exclusion of other causes of hyperoxaluria.
- All patients taking orlistat may be at risk, and monitoring of kidney function throughout therapy is warranted.

Contributors LRS looked after the patients, made the diagnosis and wrote much of the report. BN reported the histopathology. LO contributed to patient care and wrote parts of the report. ACN wrote parts of the paper.

Competing interests None declared.

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