Original Articles

Orlistat, an under-recognised cause of progressive renal impairment

Andrew K. Coutinho¹ and Gerald R. Glancey²

¹Renal Specialist Registrar, Renal Unit, Ipswich General Hospital, The Ipswich Hospital NHS Trust, Ipswich, Suffolk, UK
²Renal Consultant, Renal Unit, Ipswich General Hospital, The Ipswich Hospital NHS Trust, Ipswich, Suffolk, UK

Correspondence and offprint requests to: Andrew K. Coutinho; E-mail: andrewcoutinho@yahoo.com

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ABSTRACT

Obesity is an emerging risk factor for chronic kidney disease (CKD) in the developed world. Orlistat, an intestinal lipase inhibitor, used in the treatment of obesity is available as an over-the-counter medication across the European union and in many countries worldwide. It is associated with acute kidney injury (AKI). We present three adults, followed up from 1 to 6 years, who developed de novo or worsening renal impairment while on orlistat. Stopping the drug halted progression, but did not reverse the degree of renal impairment at presentation.

BACKGROUND

Obesity is increasing in prevalence [1, 2]. Orlistat, a specific inhibitor of intestinal lipases, is a recognized treatment [3, 4], but in rare instances has been associated with acute kidney injury (AKI). What is not well recognized is the insidious development of chronic renal impairment due to orlistat. We describe three adult cases of chronic renal impairment which were associated with orlistat usage.

CASE REPORT

Patient A, a 54-year-old female, with type 2 diabetes mellitus (DM), essential hypertension, hypothyroidism, depression and urinary stress incontinence was seen in May 2006 because of deteriorating renal function. She was otherwise well and clinical examination was unremarkable apart from a body mass index (BMI) of 28 kg/m². At the time, her medication consisted of metformin, perindopril, levothyroxine, clomipramine, atenolol, aspirin and estradiol. She also took orlistat at a dose of 120 mg thrice daily (tds) from August 2005 till April 2006. Her serum creatinine (SCr) level had been 83 µmol/L 1 year prior to referral. On presentation, her SCr level was 224 µmol/L, estimated glomerular filtration rate (eGFR) 20 mL/min, urinary protein 0.33 g/day. Patients B and C were a married couple. The wife (B) was a 66-year-old with obesity, type 2 DM, essential hypertension, hypothyroidism, depression and chronic kidney disease (CKD) diagnosed as stage IIIa in 2008. At referral in January 2011, she had been well with a normal clinical examination apart from a BMI of 37 kg/m². Her medication consisted of metformin, levothyroxine, lisinopril, rosuvastatin, furosemide, gliclazide, omeprazole, fluoxetine and lercanidipine. She had taken orlistat intermittently from October 2006 to mid-2008 and regularly from March 2010 until it was stopped in March 2011 at a dose of 120 mg tds. Her SCr level had been 103 µmol/L a year earlier. At review, her SCr was 327 µmol/L, eGFR 12 mL/min and urinary protein creatinine ratio (PCR) 38 mg/mmol. Patient C was 68 years old with obesity, osteoarthritis, had undergone lumbar spine decompression surgery (complicated by the development of a neuropathic bladder in 2005) and had CKD Stage IIIa in 2008. At referral in March 2011 for declining renal function, clinical examination was unremarkable apart from a BMI of 37 kg/m². His medication consisted of quinine sulphate, temazepam and terazosin. He had taken orlistat at 120 mgs tds from 2007 to 2009 and from April 2010 until January 2011. His SCr level was 267 µmol/L, which had been 149 µmol/L a year earlier, and the urine PCR was 38 mg/mmol. Renal tract ultrasound of patient C showed slight renal cortical thinning but was normal in the other two patients. Magnetic resonance angiography of the renal...
arteries in Patient A was normal. The three patients had no history or family history of stone disease or gastrointestinal fat malabsorption disorders. Apart from orlistat, the other medications are not known to be associated with oxalate nephropathy. They had all received dietetic advice about a low calorie diet.

Renal biopsies (Figure 1) on two patients were done 5 months (patient C) and 9 months (patient A) after orlistat was stopped. Both showed extensive tubular atrophy and interstitial fibrosis. In Patient B, the biopsy was done within a week after stopping orlistat. This biopsy showed tubular atrophy, interstitial fibrosis and calcium oxalate (CaOx) crystals in the tubules.

**DISCUSSION**

There is increasing evidence that obesity can initiate and accelerate progression of kidney disease [5]. Obesity is shown to create an inflammatory milieu within the body due to synthesis and release of bioactive substances and pro-inflammatory cytokines. This environment can predispose to and exacerbate pre-existing renal injury [6]. In healthy volunteers, orlistat inhibits gastric and pancreatic lipases [4] and reduces the absorption of dietary fats. Unabsorbed fat binds to calcium in the intestinal lumen, limiting the amount of free calcium available to bind oxalate leading to an increase in intestinal oxalate absorption. Enteric hyperoxaluria is the commonest cause of secondary hyperoxaluria and can lead to nephrocalcinosis. Nephrocalcinosis or recurrent urolithiasis can lead to parenchymal inflammation and fibrosis and eventually to end-stage renal disease [7]. In vitro studies demonstrate that CaOx crystals trigger proinflammatory cytokine IL-1β secretion from intrarenal dendritic cells and that this process contributes to CaOx-induced tissue inflammation [8]. Another study showed that oxalate crystals provoke a biphasic initial inflammatory response in proximal tubular cells, leading to the exfoliation of necrotic crystal-containing cells followed by non-necrotic crystal-containing cells gradually being eliminated [9]. There have been previous reports of AKI associated with orlistat use [10–13]. Singh et al. [11] presented a 57-year old female with type 2 DM with AKI. An initial biopsy showed calcium oxalate crystals in the tubules which were absent a month later on. A Canadian epidemiological study found a significant increase in AKI events over 1 year in a group of new orlistat users when compared with the year before starting orlistat [14].

The three adult cases we present developed significant tubular atrophy and interstitial fibrosis while using orlistat.
were followed up from 1 to 6 years after stopping the drug. In all cases, stopping orlistat halted the decline in renal function but no reversal of renal impairment was observed (Figure 2). All three cases exhibited factors predisposing to kidney injury including obesity, hypertension and pre-existing CKD.

In summary, our case series highlights orlistat as a potential cause of insidious and irreversible renal impairment. Prior to the manufacturing issues which currently limit the supply of the drug, orlistat was available as an over-the-counter medication in many European countries at a dose of 60 mg tds which is lower than the dose taken by the patients in our series. Nevertheless, in light of its potential for causing serious renal impairment, we recommend orlistat be sold as a prescription only medicine and that regular monitoring of renal function is mandatory.

CONFICT OF INTEREST STATEMENT

We declare that the results presented in this paper have not been published previously in whole or part.


REFERENCES


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