Conflict of interest statement. The Weight Management Programme was established with unrestricted educational grants from Roche Products Ltd and Amgen Ltd.

Department of Nutrition and Dietetics and Department of Renal Medicine
King’s College Hospital
London SE5 9RS, UK
Email: helen.mclaughlin@kch.nhs.uk


doi:10.1093/ndt/gfm203

Advance Access publication 21 May 2007

Reply—Orlistat and renal failure

Sir,

We welcome the interest of MacLaughlin and Macdougall in the use of the gastrointestinal lipase inhibitor orlistat in patients with chronic kidney disease (CKD).

We previously reported the rapid, non-recoverable decline of renal function in a patient with diabetic nephropathy, that coincided temporally with the successful use of orlistat for weight reduction [1]. There was histological evidence of extensive intratubular calcium oxalate crystal deposition.

The report by MacLaughlin and Macdougall of 33 patients with stage 3 or 4 CKD, who were treated with orlistat for >6 months as part of a weight management programme, provides some reassurance about the safety of this medication in CKD patients. Interestingly, the average weight reduction was 6.6% at 6 months, with no acceleration of CKD progression in the majority of patients. There was, however, a reduction in eGFR exceeding 10 ml/min at 6 months in 6/33 (18%). It is reasonable to suggest that the risk of hyperoxaluria will parallel the degree of weight reduction if both are due to malabsorption (our patient had an 11% weight loss after 5 months). It would be useful to determine the percentage weight loss in those patients with a more rapid decline in renal function, if there was an alternative clinical explanation for this, and the outcome of those that exhibited continued decline.

The conclusion that in the presence of a normal dietary fat intake the addition of orlistat does not make a significant difference to urinary oxalate levels in rodents is misleading. We reference directly to the results of Ferraz et al [2] ‘compared to baseline, urinary oxalate increased significantly after [standard] diet + orlistat in controls’. However, we acknowledge that the extrapolation of the results from rodent models is inherently limited for several reasons, including the dose/kg ratio and differing pathophysiology (for example, calcium oxalate urolithiasis is not a spontaneous phenomenon in rats).

The mechanism of action of gastrointestinal lipase inhibitors, the temporal association of accelerated renal function decline with the commencement of orlistat, the high degree of compliance and weight reduction, the pathological findings and the absence of an alternative plausible explanation support our proposition that intrarenal precipitation of calcium oxalate triggered the acute deterioration in kidney function in our patient [1].

The data from MacLaughlin and Macdougall support our conclusion that the majority of patients prescribed a gastrointestinal lipase inhibitor do not develop clinically significant hyperoxaluria and that additional dietary restrictions are unnecessary. Nevertheless, we would advise careful monitoring of renal function in CKD patients prescribed orlistat. The risk of accelerated loss of renal function may be particularly high in compliant patients with the most rapid weight loss.

Conflict of interest statement. None declared.

Regional Nephrology Unit
Belfast City Hospital
Lisburn Road, Belfast, BT9 7AB
Email: aecourtney@doctors.org.uk


doi:10.1093/ndt/gfm211

Letters

Advance Access publication 17 May 2007

Probeneic-induced membranous nephropathy

Sir,

Nephrotic syndrome (NS) associated with probenecid therapy for gout has been previously reported [1–4]. Minimal or no abnormalities were seen on renal tissue examination. We report the first case of membranous nephropathy (MN) induced by probenecid therapy.

A 79-year-old white man was admitted for pitting oedema. His past history was remarkable for familial gout. He had been treated for the previous year with probenecid (500 mg twice daily), because of allopurinol intolerance. Serum acid uric level decreased from 10.92 mg/l to 5.88 mg/l. He denied taking any other drugs and was not exposed to industrial chemicals. One month previously, routine examination revealed blood pressure 120/70 mmHg, negative urinalysis and serum creatinine level 1.1 mg/dl, but an increase in serum uric acid to 8.4 mg/l. Probeneic daily dose was increased to 1500 mg. Two weeks later, his weight had further increased, and gross pitting oedema was noted. Urinalysis revealed a ++++ test for protein and a negative test for red blood cell. Other laboratory studies included a 24h protein excretion of 5.5g and serum albumin 2.2g/dl. Renal biopsy was done with the diagnosis of MN (Figure 1). There was no evidence of any disease (negative check-up for thoracoabdominal CT scan, cystoscopy, colonoscopy and immunological tests) or drug therapy usually associated with MN, and no other evidence of an allergic response to probenecid. Drug was discontinued and within 6 weeks, the urine was free of protein and the patient was oedema-free.
NS associated with probenecid therapy for gout has been described previously in five patients [1–4]. Ferris et al. [1] described the case of a man who within 4 months of starting treatment with probenecid developed NS, which disappeared when the drug was stopped. NS reappeared and recovered on two occasions, when probenecid was re-introduced and withdrawn, successively. Renal biopsy was not performed. Sokol et al. [2] described a similar patient who developed NS 3 months after starting probenecid. Recovery followed withdrawal, and the same sequence was repeated when probenecid was re-introduced. Renal biopsy showed no abnormality apart from precipitated protein in Bowman’s spaces and in the convoluted tubules. Scott and O’Brien [3] reported two patients who developed oedema and proteinuria 8 and 15 months after starting treatment with probenecid. In one patient, rapid recovery from a full NS followed withdrawal of probenecid. Renal biopsy showed a few foci of tubular atrophy and fibrosis without crystal spaces. The second patient continued to take the drug and died in renal failure. Post-mortem examination revealed widespread dilatation of cortical tubule and crystals were found in collecting tubules and in the interstitium. No glomerular abnormalities were seen in any of these patients. Finally, Hertz et al. [4] described the case of a man who within 5 months of starting treatment with probenecid developed NS, which disappeared 3 weeks after the drug was stopped. Minimal change nephropathy was suspected on electron microscopy, showing a coalescence of foot processes over normal glomerular basement membranes. In our patient, NS developed 1 year after probenecid therapy started, but 2 weeks after increasing the daily dose. As in four of the five previously reported cases, the nephrosis disappeared soon after administration of the drug was stopped. In our patient case, the nephrotic syndrome remission might be explained by the natural evolution of MN. However, the fact that proteinuria appeared 15 days following the introduction of treatment, and disappeared 6 weeks after stopping, leads us to believe that a cause–effect relationship between the drug and the clinical profile exists. We deemed it unethical to re-introduce the molecule to test for imputability.

Drug-induced MN included gold salts, D-penicillamine and high-dose captopril [5]. Probenecid should be added to this list. However, the drug has been in widespread use for over half a century and renal complications remain very rare.

Conflict of interest statement. None declared.

1Department of Nephrology
2Department of Pathology
Pitie-Salpetriere Hospital
Paris, France
Email: hassan.izzedine@psl.aphp.fr


doi:10.1093/ndt/gfl798