Nimesulide and acute renal failure caused by oxalate precipitation

Sir,

Acute renal failure (ARF) seen with non-steroidal anti-inflammatory drugs (NSAIDs) is mainly haemodynamically mediated due to inhibition of the synthesis of renal prostaglandins (PGs) [1]. Nimesulide is a new generation NSAID that differs from conventional NSAIDs in structure and pharmacological profile, claiming fewer side effects due to the specificity for the COX-2 enzyme [2]. We describe a patient presenting ARF following intake of several tablets of nimesulide.

Case. A 40-year-old man was admitted with right-sided loin pain, asthenia, and gastrointestinal complaints of 1 week. One month before admission he had a torsio of the right ankle for which nimesulide was prescribed in a dose of two tablets of 200 mg/day. In total, the patient had taken 28 tablets or 5600 mg nimesulide. No other medication or vitamins have been taken. Medical history revealed the presence of microscopic haematuria since the age of 20, discovered on routine medical examination during duty. However, a clinical investigation was never performed. There was no history of familial nephropathy. Physical examination showed a well-fed, well-hydrated, ill-looking man. The patient was normotensive, had no fever nor adenopathies or rash. Ankle oedema was absent, but fluid retention was suspected as the patient reported a weight gain of 7 kg during the last two weeks. Initial laboratory tests showed ARF (s-creatinine 10.86 mg/dl (normal levels 0.5–1.5 mg/dl), urea 142 mg/dl (normal levels 15–40 mg/dl), normal potassium). Fibrinogen was 488 mg/dl (normal levels 180–400 mg/dl), C-reactive protein 21 mg/l (normal level up to 4 mg/l) and elevated sedimentation rate 35 mm/h (normal levels 0–10 mm/h). White blood cell (WBC) count and total number of eosinophils were within the normal range. Urine analysis disclosed rare WBC, numerous RBC, no casts. Urine culture was negative. Creatinine clearance was 6 ml/min. The test for urinary myoglobin was negative. Proteinuria was 0.82 g/day and glucosuria was absent. Hyperuricaemia of 16 mg/dl was noted (normal levels 3.4–7.0 mg/dl), but with low urinary uric acid concentration: 71 mg/24 h (normal levels 250–750 mg/24 h). The urinary uric acid to creatinine ratio was less than 1 (FEUA = 0.48). Bacterial and viral infection was excluded by appropriate testing. Complement study and serum-IgA were in the normal range and nuclear antibodies and ANCA were negative. Despite severe renal failure oxaluria was still 18 mg/day. In subjects with normal renal function and on a normal diet, oxalate excretion ranges from 10 to 45 mg/day. Renal ultra sonography revealed no abnormalities even as the plain X-ray of the abdomen. Histology of a renal biopsy showed normal glomeruli and blood vessels. Interstitium was focally infiltrated by lymphocytes, plasma cells and eosinophilic polymorphonuclear (PMN) cells. Some of the tubules were dilated and showed signs of tubular distress (e.g. desquamation of cells, attenuation of the epithelium). In several tubular lumina, PMN cells and protein casts were observed. Multiple crystals were present in the tubules despite fixation in Bouin. These crystals were surrounded by desquamated tubular cells and giant cells. They were identified as calcium oxalate crystals by the Pizzolato method (Figure 1) [3]. The immunofluorescence study showed tubular casts of IgA, IgG, and Kappa and mesangial deposits of C3, but no positivity in glomerular or tubular cells. The patient did not receive corticosteroid treatment, only fluid and electrolytes balance were carefully managed. Five days after admission, a decrease of s-creatinine was noted (and the patient was discharged 2 days later with a s-creatinine of 9.36 mg/dl). Two weeks after admission, s-creatinine had further declined to 2.56 mg/dl and proteinuria was absent. His flank pain gradually decreased in severity. Eight weeks after admission, renal function was completely normalized and he refused further investigation. Calcium and oxalate excretion were not repeated.

Comment. Both acute and chronic renal failure has been observed in patients treated with non-specific NSAIDs [1]. In the present case of haemodynamically mediated renal failure, the renal biopsy did not show structural lesions and renal function recovered upon withdrawal of the drug. First generation NSAIDs are non-specific inhibitors of both constitutive COX-1 and inducible COX-2 forms of cyclooxygenase. COX-2 is expressed in endothelial and smooth muscle cells and recent studies in humans detected COX-2 also in both the macula densa and medullary interstitial cells [1,4]. COX-2 is induced by pro-inflammatory cytokines and is responsible for the increased production of PGs in inflammatory tissues [4]. Nimesulide, another COX-2 inhibitor is claimed to have few renal side effects compared with the non-selective NSAIDs [2]. The increase of urinary Tamm–Horsfall glycoprotein (THG) and β-N-acetyl glucosaminidase, which has been noted in normal subjects after repeated doses suggests that nimesulide is potentially nephrotoxic [5]. Nimesulide may also induce an acute transient fall of renal blood flow in healthy men when furosemide is concomitantly given. When the glomerular filtration rate becomes dependent of PGs, the administration of nimesulide may attenuate the diuretic, kaliuretic and natriuretic effects of furosemide [6]. Our patient presented with ARF characterized by obstruction of the tubuli by oxalate crystals. Many drugs eliminated by the kidney may form crystals in the urine. Crystallization depends on the urinary pH and is enhanced by a high concentration of the drug and a low urinary volume. Precipitation is prevented mostly by inducing alkaline diuresis. In our patient the crystals could be identified as calcium oxalate. Oxalate nephropathy may be observed in primary as well as in secondary oxalosis [7]. Acute oxalate crystalluria and acute oxalate renal failure commonly arise from ethylene glycol poisoning. This ethylene glycol is metabolized to glyoxylic acid and then to oxalic acid, which may lead to the deposition of calcium oxalate crystals [7]. Oxalate crystalluria has also been reported following the inappropriate use of diethylene glycol in paracetamol elixirs, following i.v. administration of naftidrofuryloxalate and of high doses of vitamin C, and following oral administration of piridoxilate, an association of glyoxylic acid and pyridoxine [8]. In some cases the iatrogenic oxalate nephropathy leads to end-stage renal failure. In our patient, fortunately, renal
function recovered completely. This observation indicates that nimesulide can provoke acute renal failure as a result of an obstructive crystalline nephropathy.

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