Oliguric Renal Failure Associated with Benoxaprofen

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Sir,

Benoxaprofen was withdrawn in Britain in August 1982 following reports of over 3,500 adverse reactions including 61 deaths accumulated since its introduction in 1980. Fatal cases of cholestatic jaundice and renal failure were among these reactions, predominantly affecting elderly patients [1–3]. In none of these cases was renal failure attributed to a tubulo-interstitial nephritis. We would like to document a further case of acute renal failure due to allergic interstitial nephritis, associated with blood eosinophilia, skin rash and mouth ulceration, which followed exposure to benoxaprofen.

Case Report

A 60-year-old widow with long-standing seronegative arthritis was started on benoxaprofen 600 mg daily with much improvement in her symptoms. Her previous history included a partial gastrectomy and vagotomy for chronic duodenal ulceration, a total right hip arthro-plasty for a femoral neck fracture, and severe grief reaction and depression for which she had been receiving fluphenazine and maprotiline for 2 years. 2 weeks after starting benoxaprofen she was admitted into her local hospital with a history of dysuria, dark urine and a pruritic rash. Physical examination showed a generalised morbilli-form rash, mouth ulceration and pyrexia of 37.5 °C. She passed only 480 ml of blood-stained urine in the ensuing 24 h. A midstream urine culture confirmed a coliform urinary infection. Her haemoglobin was 10.9 g/dl, white cell count $5.5 \times 10^3/\mu\text{l}$ with 35% eosinophils (total = 1,925, normal = 40–400/ μl), and platelet count $200 \times 10^3/\mu\text{l}$. Plasma sodium was 136 mmol/l, potassium 5.0 mmol/l, bicarbonate 21 mmol/l and urea 9.8 mmol/l. Benoxaprofen, fluphenazine and maprotiline were discontinued and she was treated with chlorpheniramine for the rash and amoxycillin for the urinary infection, and discharged. 1 week later she was readmitted as an emergency with anuria of 48 h duration and promptly transferred to our renal unit. Examination showed a resolving skin rash, mouth ulcers and oedema of both legs. Blood pressure was 130/70 mm Hg. Haemoglobin was 8.4 g/dl, white cell count $5.9 \times 10^3/\mu\text{l}$ with 10% eosinophils (total = 590), platelet count $250 \times 10^3/\mu\text{l}$, plasma sodium 136 mmol/l, potassium 8.6 mmol/l, urea 50.5 mmol/l, serum creatinine 1.3 mmol/l, calcium 2.0 mmol/l, phosphate 2.2 mmol/l and urate 0.4 mmol/l. Peritoneal dialysis was commenced immediately. Her 24-hour

Fig.1. Histological appearance of the kidney showing interstitial oedema, interstitial inflammatory infiltrate of lymphocytes, plasma cells and eosinophils, a histiocytic granuloma, and extensive tubular damage. Glomeruli show only minimal changes. HE. $\times 10$.

urine volume was now only 130 ml. A high-dose excretory urogram showed unobstructed normal-sized kidneys concentrating poorly. An isotope renogram demonstrated bilateral delay in isotope clearance with a half-life of 43 min (normal $\approx$ 15–25 min). The following other investigations were normal or negative – blood sugar, liver function, immunoglobulins, complement, coagulation screen, autoantibodies, antinuclear factor, DNA antibodies, antistreptolysin titre, chest X-ray, repeat midstream urine, and serum protein electrophoresis. The renal biopsy (fig. 1,2) revealed extensive tubular damage with some evidence of regeneration. The interstitium was oedematous and contained an inflammatory infiltrate of lymphocytes, plasma cells, eosinophils and several histiocytic granulomata. Only minor glomerular changes were seen. Ziehl-Neelson stain was negative for acid-fast bacilli. Her urine output gradually improved to over 2 litres on her 8th hospital day. Three early morning urine samples were negative for acid-fast bacilli. Her rash faded gradually and renal function improved progressively, plasma creatinine falling to 0.15 mmol/l with a clearance of 30 ml/min on discharge at 1 month. When she was reassessed 6 months later, her blood eosinophil count and urine output were now normal but her creatinine clearance was still only 30 ml/min. A second renal biopsy specimen (slide not shown) showed a fine interstitial fibrosis, more severe vascular pathol-

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Fig. 2. Similar changes as in figure 1 under $\times$ 25. HE.

ogy with ischaemic glomerular changes, very little residual interstitial infiltrate and no granulomata. Direct immunofluorescent staining was negative for immunoglobulins, complement, fibrin and albumin. The electron microscopic examination showed no evidence to support immunological glomerular damage. Prednisolone 60 mg daily was commenced, tailing down to 20 mg daily. 6 months later she was symptom-free but her creatinine clearance remained low at 35 ml/min.

Comment

Non-steroidal anti-inflammatory drugs have been widely reported to cause allergic interstitial nephritis [4–7]. To our knowledge this complication has not been documented with benoxaprofen. Neither fluphenazine nor ma-protiline – both of which our patient had taken for 2 years without incident – is known to cause allergic interstitial nephritis.

Her residual renal impairment 1 year after the initial insult is unlikely to be due to pre-existing renal failure (initial blood urea was 9.8 mmol/l). Evidence from the accumulated literature indicates that complete recovery of renal function is the usual outcome in patients with drug-induced allergic interstitial nephritis if the condition is recognized and the offending drug is withdrawn. Occasionally, the renal failure may be quite severe and prolonged [8], may be progressive [9] and may leave the patient with significant residual renal impairment even after prompt withdrawal of the offending drug [8,10].

Whether or not treatment with steroids hastens recovery or improves prognosis in acute interstitial nephritis remains uncertain. Galpin et al. [11] treated 8 (out of 14) patients with methicillin-induced acute interstitial nephritis with prednisolone 60 mg daily after withdrawal of the

drug. Of these 8 patients serum creatinine returned to previous normal levels in 6, and stabilized after an average of 9.3 days. In contrast, in the 6 patients who did not receive prednisolone,

serum creatinine returned to control values in only 2, and stable concentrations were obtained only after 54 days.

To the long list of drugs known to cause acute allergic interstitial nephritis – aspirin, indomethacin, tolectin, naproxen, ibuprofen, fenoprofen, phenylbutazone, methi-cillin, penicillin, ampicillin, rifampicin, sulphonamides, cotrimoxazole, phenindione, phenytoin, furosemide, cephalosporins, allopurinol, ethambutol, and several others – can now be added benoxaprofen.

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