

Renal failure as a suspected adverse reaction to benoxaprofen

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Summary

A 77-year-old woman suffering from osteoarthritis was treated with benoxaprofen. She developed diarrhoea, skin rash and renal failure.

Renal failure has not been reported before as an adverse reaction to benoxaprofen.

The case is discussed in the context of multisystem and immunological response to benoxaprofen.

Introduction

Benoxaprofen (Opren) is a recently introduced non-steroidal anti-inflammatory (NSAI) drug. Its mode of action differs from that of other NSAI drugs since the anti-inflammatory effect is mediated not by the suppression of prostaglandin synthesis but by inhibition of the movement of mononuclear cells into arthritic joints (Dawson, 1980). Since decreased platelet adhesiveness and the tendency to microbleeding that occurs with other NSAI drugs is thought to be due to impaired prostaglandin synthesis in mucosa, platelets and vessel walls, it was anticipated that gastro-intestinal bleeding would be less likely with benoxaprofen than with other NSAI drugs and this has been borne out in practice (Ridolfo *et al.*, 1980; Mihulaschek, 1980). Skin photosensitivity and oncholysis however, are common, occurring in just under 10% of cases (Mihulaschek, 1980). A persistently elevated serum lactic dehydrogenase may also occur.

Renal failure has not yet been described as a complication of treatment with benoxaprofen.

Case report

A 77-year-old woman with osteoarthritis for 25 years, especially severe in the left knee and ankle and lumbar spine, had been treated with benorylate, indomethacin and ibuprofen over the years. In February 1981, because of an exacerbation of her symptoms she was given benoxaprofen 600 mg daily. After a fortnight's treatment she reported considerable pain relief. Five weeks after the start of treatment she developed a generalized itchy rash. She had

ulceration of her mouth and this was associated with an unpleasant taste, anorexia and nausea. Her nails became brittle and she felt generally unwell. Benoxaprofen was therefore stopped and she was commenced by her general practitioner on a reducing dose of prednisolone, starting with 5 mg four times daily and tailing off over a week and chlorpheniramine 2 mg three times daily. A week later she was feeling better and the rash had settled. Two days after this, the rash returned and she felt considerably worse and was therefore admitted to Newsham General Hospital. At the time of admission she had in addition developed diarrhoea, which was not stained with blood or mucus.

On examination she looked ill and was pyrexial with a temperature of 37.5°C. She was not dehydrated. She had oncholysis and a skin eruption associated with marked erythema confluent on the face and outer thighs, but affecting also the trunk and upper limbs, and extensive exfoliation. She had a tachycardia and was normotensive.

Results

Investigation showed Hb 13.9 g/dl, WBC $13.1 \times 10^9/l$ (2% eosinophils), ESR 5 mm/hr, platelets $70 \times 10^9/l$, blood urea 18.8 mmol/l, creatinine 345 $\mu\text{mol/l}$, total protein 62 g/l, albumin 29 g/l, plasma protein electrophoretic strip no other significant abnormality. A mid-stream specimen of urine showed: 1 white blood cell per high powered field, no casts, protein 0.3 g/l, no organisms, no Bence-Jones protein. Stool and blood cultures were negative.

A diagnosis of a drug sensitivity reaction was made. She remained unwell, initially with a pyrexia and then with a tendency to hypothermia due to heat loss from her erythema, continuing malaise and occasional diarrhoea. The rash did not improve in spite of local corticosteroids and it was noted that she had become oliguric, though she was well-hydrated. The blood urea began to rise sharply until one week after admission it was 76

mmol/l and her creatinine had risen to 1320 μ mol/l. Liver enzymes, initially slightly elevated, rose further, the alkaline phosphatase rising to 282 u./l, lactic dehydrogenase (LDH) to 695 u./l and aspartate transaminase (AST) to 166 u./l. The serum bilirubin remained normal. The initial high white count persisted and a 37% eosinophilia prompted a search for L.E. cells, which was positive. Anti-DNA factor was negative. The value of her C3 was normal, but C4 at 0.08 g/l was greatly reduced.

The usual measures for combating acute renal failure, including high dose i.v. frusemide were commenced. Prednisolone 20 mg three times daily was given, and one week later urine output was back to normal, the blood urea was falling and the other indices of renal and hepatic dysfunction were rapidly improving. L.E. cells were no longer seen in the peripheral blood and the eosinophil count fell. When the urea had fallen sufficiently, an intravenous urogram (IVU) was carried out to which the patient developed hypotension and acryanosia associated with shivering which lasted for several hours, from which she spontaneously improved. The kidneys were of normal size and there was only a minimal delay in the appearance of the nephrogram phase. There was no evidence of obstruction in the lower renal tract. Examination of the urine on 3 and 4 April showed protein 1 g/l.

In May 1981 the patient was clinically much improved, but had residual lower limb oedema, the blood urea, creatinine and liver enzymes were normal, and there was only a trace of protein in the urine.

Discussion

The combination of skin rash, diarrhoea and renal failure in this patient indicated a multisystem disease. The presence of eosinophils and L.E. cells in conjunction with a low C4 level, strongly suggests that this was due to an immune response. The fact that the illness began approximately 5 weeks after commencing benoxaprofen and that it was associated with a skin rash and oncholysis, both of which are known to occur in about 10% of patients taking benoxaprofen, supports the suspicion that the illness was an adverse reaction to this drug. It is

interesting that the patient described her rash as initially being like measles: morbilliform rashes have been described as a side effect of other NSAID drugs (Mihulaschek, 1980). There were no features in the patient's past history to suggest pre-existing renal impairment; moreover the IVU was essentially normal and the patient's recovery to normal renal function would make a pre-existing chronic renal failure highly unlikely.

Recently the phenylalkanoic acids—fenoprofen and naproxen—have been implicated in the rapid development of interstitial nephritis, leading to acute renal failure sometimes accompanied by the nephrotic syndrome. This can be rapidly reversed on discontinuing the drug (Brezin *et al.*, 1979). The mechanism of the side effect may be related to decreased renal synthesis and urinary excretion of prostaglandin E, though an allergic mechanism has also been invoked (Brezin *et al.*, 1979; Kimberley *et al.*, 1978). Clearly the latter would seem to be more likely in the case of this patient's reaction to benoxaprofen.

In view of our experience of this drug, which extensive clinical trials have hitherto indicated to be at least as safe as other NSAID drugs (Dawson, 1980; Mihulaschek, 1980) it would seem reasonable to reserve benoxaprofen for those patients who have severe symptoms, as the use of the drug might possibly have an adverse effect upon the kidneys in addition to its other more widely known complications.

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