Allopurinol hypersensitivity

Allopurinol (4-hydroxypryprazolo[3,4-d]pyrimidine) is the mainstay of treatment for gout. A common side effect is rash or gastrointestinal upset, but xanthine stones, hepatic granulomas, agranulocytosis, reversible leucopenia, and aloplopia may occur. Hypersensitivity with vasculitis has been reported, mostly in patients with hyperuricaemia secondary to diuretic treatment—usually thiadiazides for hypertension—and often with mild renal impairment. The following case probably occurred in primary gout, though secondary hyperuricaemia cannot be excluded.

Case report

A West Indian aged 34 was diagnosed by his general practitioner as having gout by a nephropathy because of acute pain in the first metatarsophalangeal joint, a serum urate concentration of 0.52 mmol/l (8.7 mg/100 ml), and a serum urea concentration of 8-5 mmol/l (51-2 mg/100 ml). Results of urine analysis are not available. Blood count was normal but erythrocyte sedimentation rate (ESR) was 41 mm in the first hour. On 4 August 1978 he began allopurinol 300 mg daily. On 13 September he noticed an intensely pruritic rash in the groins, which progressed over the next week with fever, sweats, leucocytopaenia and anaemia. He was admitted on 21 September.

Examination showed an ill man with fever (38-5°C), generalised maculopapular rash, and cervical and axillary lymphadenopathy. Blood pressure was 120/70 mm Hg, haemoglobin concentration was 13-4 g/dl; white cell count 13-1 x 10^9/l (13 100/mm^3), 15% eosinophils; ESR 42 mm in first hour; serum albumin concentration 29 g/l; serum aspartate aminotransferase activity 2778 IU/l; serum alanine aminotransferase activity 2222 IU/l; serum lactate dehydrogenase activity 6213 IU/l; serum alkaline phosphatase activity 133 IU/l; serum bilirubin concentration 16 μmol/l (0-9 mg/100 ml); serum urica concentration 22 mmol/l (135 mg/100 ml); serum creatinine concentration 290 μmol/l (3-2 mg/100 ml); and serum urate concentration 0-54 mmol/l (9 1 mg/100 ml). Urine contained 6 x 10^5 red cells and 6 x 10^5 white cells/l with granular casts; 24-hour collection yielded 3 g protein. Chest radiograph and electrocardiogram were normal. Blood cultures grew no pathogens. Serum IgA concentration was raised (6-5 g/l); IgG and IgM concentrations were normal. Serum C3 concentration was 1-60 g/l (normal 0-70-1-61) and C4 concentration 0-73 g/l (0-15-0-45). Antinuclear factor was not detected. Tests for soluble immune complexes and allopurinol sensitivity by lymphocyte transformation and migration inhibition were negative. Biopsy showed dermal vasculitis, and immunofluorescence staining disclosed granular deposits of IgG and IgM with complement around small dermal blood vessels.

Prednisolone 60 mg daily was instituted on 25 September. The patient improved, but on 13 October, when the dose was reduced to 10 mg daily, rash and fever recurred. He was discharged on 23 October taking 30 mg daily. Blood count and liver enzyme values were normal. ESR was 26 mm in first hour; serum albumin concentration 28 g/l; serum urate concentration 9-0 mg/100 ml; serum creatinine concentration 190 μmol/l (2-1 mg/100 ml).

Renal biopsy performed in February 1979 (Dr B H B Robinson) because of persistent renal impairment (creatinine 300 mg/l in the mainstay of treatment for gout), demonstrated glomerular fibrosis with extensive tubular atrophy and chronic inflammation of the interstitium consistent with an “allergic” glomerulonephritis.

Comment

The syndrome of allopurinol hypersensitivity consists of maculopapular rash, nephritis, hepatitis, fever, and eosinophilia. Although probably mediated by immune complexes, its precise mechanism is not understood. Allopurinol has a serum half life of 1-25 hours but its active metabolite oxypurinol has a life half of 18-30 hours. Oxypurinol is handled in a similar way to uric acid, being retained in patients taking thiazide diuretics and with renal impairment; thus sensitivity to this metabolite or possibly allopurinol ribonucleotide, whose fate is unknown, may be the cause. Alternatively, a persistent immunological reaction, sometimes necessitating prolonged steroid treatment, may reflect “cross-reaction with normal purines, ribonucleotides, or nucleic acids.

In other reported cases symptoms occurred four to six weeks after starting allopurinol 200–400 mg daily, and in one case after only seven days. Over a third of these patients died from renal failure, infection, and gastrointestinal haemorrhage. Treated promptly most patients recover, although prolonged steroid treatment may be required. The hazards of allopurinol should be considered, particularly before prescribing for secondary hyperuricaemia without clinical gout, as both thiazides and renal impairment appear to be predisposing factors.

1 Savage, M O, Hibble, A G, and Pickering, D, Archives of Disease in Childhood, 1975, 50, 393.

(Accepted 16 February 1979)