

Oral desensitization in patients with chronic tophaceous gout and allopurinol hypersensitivity

SIR, The difficulties of treating gout in renal and cardiac transplant patients, whose urate excretion may be impaired by renal insufficiency and by treatment with diuretics and cyclosporin A, have recently been highlighted [1]. The management of gout in chronic renal insufficiency can also be complicated by hypersensitivity to allopurinol, which occurs more frequently in these patients [2]. We report two patients with chronic tophaceous gout, renal insufficiency and cardiac disease requiring long-term diuretics in whom cutaneous hypersensitivity reactions forced discontinuation of allopurinol therapy. Subsequent reintroduction of allopurinol in an oral desensitization regime was well tolerated and led to symptomatic improvement.

Case 1 was a 69-yr-old woman with a 14 yr history of recurrent gouty arthritis with formation of tophi during the latter 5 yr. Her past medical history included rheumatic carditis as a child with subsequent aortic and mitral valve replacements at the ages of 52 and 56 yr, respectively. She required long-term treatment with diuretics (frusemide 40 mg daily) and digoxin, with the addition of warfarin since her first cardiac surgery. On her initial presentation, treatment with allopurinol was commenced, but had to be discontinued due to vomiting, flu-like symptoms and a mild rash. She had been unable to tolerate probenecid due to dyspepsia, and despite continuous treatment with colchicine 500 μg twice daily she suffered frequent episodes of gout with serum urate levels varying from 500 to 800 $\mu\text{mol/l}$ (normal range 160–420). Azapropazone and sulphinpyrazone were avoided in view of the patient's cardiac disease and concomitant anticoagulation. In recent months, she was noted to have proteinuria with a slightly raised serum creatinine of 120 $\mu\text{mol/l}$.

In view of persistent symptoms and concern over the possibility of gouty nephritis, allopurinol was re-

commenced in a desensitization regime (Table 1). Suspensions were prepared by mixing powdered allopurinol with equal parts of distilled water and Keltrol A® solution (Nova Labs Ltd). Two different concentrations of allopurinol suspensions were used (0.5 and 5 mg/ml), depending on the dose required. The regime was tolerated well up to a dose of 200 mg daily, when the patient developed a mild, macular rash. This settled after reducing the dose to 100 mg daily, which was continued thereafter. Serum urate levels were restored to normal and over the next 2 yr the patient suffered no further episodes of acute gout with gradual resorption of her tophi. Unfortunately, the patient died from a cerebrovascular accident following further cardiac surgery to replace a leaking mitral valve.

Case 2 was a 77-yr-old woman with a 5 yr history of gout who was referred to the rheumatology department with increasing frequency of acute gouty arthritis. She too had prosthetic mitral and aortic valves, and required long-term diuretic therapy with frusemide and anticoagulation with warfarin. The previous year she had been admitted with a widespread, erythematous rash accompanied by oral ulceration following 6 weeks of allopurinol therapy. The rash had settled after discontinuation of allopurinol. At the time of referral to the rheumatology department, she had multiple tophi over the small joints of the hands, the right knee and the left foot with active synovitis of the right wrist. Serum urate and creatinine were elevated at 617 and 132 $\mu\text{mol/l}$, respectively. After resolution of the acute attack, allopurinol was commenced in the desensitization regime. A mild rash occurred over the feet and ankles when a dose of 100 mg daily was reached, and this faded over the subsequent 3 weeks following discontinuation of allopurinol. Allopurinol was subsequently reintroduced in a modified regime, which involved doubling the time intervals between dose increments, to reach a maintenance dose of 100 mg daily. In the 18 months of follow-up, there has been symptomatic improvement of her gout with normalization of serum urate levels, although there has been no obvious dissolution of her tophi. The rash has not recurred.

Both our cases had chronic tophaceous gout that was extremely debilitating. In addition, both had evidence of renal impairment, possibly due to gouty nephritis. As such, we considered that allopurinol was the drug of choice and that reintroduction in a desensitization regime was expedient. The first case was intolerant of probenecid and, indeed, uricosurics have generally been considered ineffective for patients with renal impairment and gout [3]. In addition, both cases had cardiac disease and required anticoagulation. In view of their effects on salt and water retention, and possible interactions with warfarin, azapropazone and sulphinyprazole were avoided.

There have been a number of reports of desensitization following allopurinol hypersensitivity, the majority in patients with renal impairment. In the largest series by Fam *et al.* [4], nine patients successfully tolerated the allopurinol desensitization protocol. Four patients developed early mild cutaneous reactions, but this did not preclude reintroduction of allopurinol in a modified protocol. Early cutaneous reactions also occurred in our two patients and, similarly, allopurinol was successfully reintroduced.

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TABLE 1. Oral allopurinol desensitization protocol adapted from [4]

Days	Dose of allopurinol (mg)	Amount of suspension 1 (0.5 mg/ml) given (ml)
1–3	0.05	0.1
4–6	0.1	0.2
7–9	0.2	0.4
10–12	0.5	1
13–18	1	2
16–18	5	10
		Amount of suspension 2 (5 mg/ml) given (ml)
19–21	10	2
22–24	25	5
25–27 ^a	50	10

Small doses may be diluted with water before being administered.

^a100 mg allopurinol tablet daily from 28 days onwards.