BRIEF COMMUNICATION

Reinstitution of allopurinol therapy for gouty arthritis after cutaneous reactions

ADEL G. FAM, MD, FRCP[C], FACP; THOMAS W. PATON, PHARM D; ABE CHAITON, MD, FRCP[C]

Allopurinol is highly effective in the treatment of hyperuricemia.[1] Adverse reactions are relatively rare.[1,2] Toxic effects on the skin are the most common and are more frequent in patients with renal insufficiency.[1-4] In the presence of renal failure uricosuric drugs are generally ineffective and allopurinol is preferred.[4-6]

This report describes a patient with chronic tophaceous gouty arthritis, renal insufficiency and allopurinol dermatitis. Therapy with allopurinol was reinstituted by means of a schedule of gradually increasing doses.

Case report

A 67-year-old man had had intermittent gouty arthritis for 28 years and tophaceous deposits on the feet, hands and elbows for 10 years. Colchicine and phenylbutazone had been given for acute attacks. Alcoholism and congestive heart failure had been present for 6 years.

The arthritis had increased in severity in the last 2 years. The serum uric acid level was 0.68 mmol/l (11.5 mg/dl), the blood urea nitrogen level 12.1 mmol/l (34 mg/dl) and the serum creatinine level 124 μmol/l (1.4 mg/dl). Therapy with allopurinol, 300 mg/d, was started. Fourteen days thereafter a generalized pruritic, maculopapular, erythematous rash associated with fever and eosinophilia developed. The drug was discontinued, the patient was given hydroxyzine hydrochloride (Atarax) and the rash resolved over a 6-week period. Suppressive therapy with colchicine was substituted.

Eighteen months later the patient was transferred from another hospital for management of severe gout and progressive renal failure. The blood urea nitrogen level had risen 2 months earlier to 17.8 mmol/l (50 mg/dl) and the serum creatinine level to 389 μmol/l (4.4 mg/dl). He had no history of nephrolithiasis or renal infection. There were numerous large tophi on the hands, elbows and feet, some with sinuses discharging urate, as well as several acutely inflamed joints, including both knees, the left ankle and the right wrist. Monosodium urate crystals were identified in aspirates from the left knee and from the left olecranon bursa.

The hemoglobin level was 11.9 g/dl, the leukocyte count 8.9 × 10^9/l with a normal differential count, the serum uric acid level 0.59 to 0.77 mmol/l (9.9 to 12.9 mg/dl) and the 24-hour urinary excretion of uric acid 1.22 to 2.68 mmol (205 to 450 mg). The blood urea nitrogen level was 25.0 mmol/l (70 mg/dl), the serum creatinine level 433 μmol/l (4.9 mg/dl) and the creatinine clearance 10 ml/min. The urine was sterile and contained only 3+ protein; the total 24-hour urinary excretion of protein was 1.3 to 3.0 g. Rheumatoid and antinuclear factors were not detected. An intravenous pyelogram revealed poorly functioning, normal-sized kidneys without stones.

Ibuprofen was given to control exacerbations of gout, and an attempt was made to reinstitute allopurinol therapy. Allopurinol solution was prepared by dissolving 50 mg of allopurinol powder (supplied by Burroughs Wellcome Ltd.) in 500 ml of distilled water, for a final concentration of 0.1 mg/ml. In the first attempt 10 ml of the solution (1 mg of allopurinol) was given daily for 2 days, then 50 ml

Table I—Dosage of allopurinol

Days	Daily dose (mg)	Preparation
1–5	0.05	0.5-ml solution
6–9	0.10	1-ml solution
10–12	0.20	2-ml solution
13–15	0.50	5-ml solution
16–18	1	10-ml solution
19–21	5	50-ml solution
22–24	10	100-ml solution
25–27	25	250-ml solution
28–30	50	Half a 100-mg tablet
31–33	100	100-mg tablet
34 and on	300	300-mg tablet

From the departments of medicine and pharmacy, University of Toronto, Sunnybrook Medical Centre, Toronto

Reprint requests to: Dr. Adel G. Fam, Rheumatic disease unit, Sunnybrook Medical Centre, 2075 Bayview Ave., Toronto, Ont. M4N 3M5

(5 mg) was given daily for 4 days. On the seventh day fever and a generalized erythematous, itchy eruption developed and the drug was discontinued. Hydroxyzine hydrochloride was administered and the rash resolved within 5 days. In the second attempt allopurinol was administered as indicated in Table I. The daily dose of 300 mg has been continued since, with no ill effects. By day 90 the serum uric acid level had dropped to 0.39 mmol/l (6.5 mg/dl), drainage from the sinuses had ceased and attacks of gout had become less frequent.

Discussion

Cutaneous reactions have been reported in 2.1% to 4.4% of patients receiving allopurinol.[2,7] In the presence of renal failure they occur more frequently,[1-4] likely owing to reduced renal clearance, leading to excessively high plasma levels of allopurinol and its metabolite, oxipurinol.[3] Most skin reactions are relatively mild and reversible,[2] but occasionally a severe hypersensitivity reaction, with fever, eosinophilia, renal failure and severe dermatitis, may occur, particularly when administration of the drug is continued after the initial rash appears.[8]

Our patient had severe chronic tophaceous gouty arthritis, renal impairment and recurrent allopurinol dermatitis. Patients with gout, urate nephropathy and renal insufficiency respond poorly or not at all to uricosuric agents.[4,5] Not only is allopurinol effective in this situation, but also it may arrest further renal deterioration[1,5,6] and, in some instances, improve renal function.[9]

In our patient the rash recurred upon challenge with as little as 5 mg of allopurinol, but with further challenge, of a minute dose and then slowly increasing doses, it was possible to reinstitute therapy. Allopurinol therapy was reinstituted by means of a similar dosing schedule in one other case.[10] The reason for the success of this method of reinstituting therapy is at present unknown, although antibody-mediated hyposensitization may be the mechanism.

Conclusion

On the basis of these preliminary data we can conclude that allopurinol dermatitis does not necessarily preclude further treatment with the drug. Cautious reintroduction of the drug may be attempted if equally effective alternative drugs are not available.

We thank Mrs. Cynthia Brown and Mrs. Janet Hays for secretarial assistance.

References

1. Rundles RW, Metz EN, Silberman HR: Allopurinol in the treatment of gout. *Ann Intern Med* 64: 229, 1966

2. Frisch JM, Lovatt GE, Sproit ARM, et al: The adverse reaction profile of allopurinol, in *Frontiers of Internal Medicine, 1974*, Blondheim SH (ed), Karger, Basel, 1975, pp 412-19

3. Elion GB, Yü T-F, Gutman AB, et al: Renal clearance of oxipurinol, the chief metabolite of allopurinol. *Am J Med* 45: 69, 1968

4. Wilson JD, Simmonds HA, North JDK: Allopurinol in the treatment of uraemic patients with gout. *Ann Rheum Dis* 26: 136, 1967

5. Wyngaarden JB, Kelley WN (eds): Treatment of hyperuricemia and tophaceous gout, in *Gout and Hyperuricemia*, Grune, New York, 1976, pp 472-90

6. Boss GR, Seegmiller JE: Hyperuricemia and gout: classification, complications and management. *N Engl J Med* 300: 1459, 1979

7. Boston Collaborative Drug Surveillance Program, Boston University Medical Center: Excess of ampicillin rashes associated with allopurinol or hyperuricemia. *N Engl J Med* 286: 505, 1972

8. Kantor GL: Toxic epidermal necrolysis, azotemia, and death after allopurinol therapy. *JAMA* 212: 478, 1970

9. Briney WG, Ogden D, Bartholomew B, et al: The influence of allopurinol on renal function in gout. *Arthritis Rheum* 18 (suppl): 877, 1975

10. Meyrier A: Desensitization in a patient with chronic renal failure and severe allergy to allopurinol. *Br Med J* 2: 458, 1976