CASE REPORT

Allopurinol Hypersensitivity Syndrome: A Case Report and Review

Donna Buna

INTRODUCTION

Allopurinol, an analogue of hypoxanthine, is widely used in the treatment of primary and secondary hyperuricemia. The drug is generally well tolerated, with a low prevalence of adverse effects. Allopurinol hypersensitivity syndrome is a rare but life-threatening adverse effect of allopurinol therapy. Although the prevalence of this syndrome is thought to be low, more than 100 cases have been reported since 1970.[1,2] Patients in hospital are at greater risk for allopurinol hypersensitivity syndrome because they often have poor renal function. The Boston Collaborative Drug Surveillance Program reported that 3.5% of a sample of hospital patients experienced an adverse effect attributed to allopurinol.[3] Early recognition of this syndrome can result in significant reduction of morbidity and mortality associated with allopurinol use.

CASE REPORT

A 77-year-old woman was admitted to acute care with bilateral basal crepitations, peripheral edema, orthopnea, and a pruritic rash. She was diagnosed with congestive heart failure in a setting of progressive renal failure. Her medical history included insulin-dependent diabetes mellitus with labile control, nephropathy (creatinine clearance 10 mL/min), retinopathy with blindness, gastroparesis with severe gastroesophageal reflux and recurrent aspiration, asthma, and anemia of chronic disease. The patient declined dialysis and subsequently signed a do-not-resuscitate order. The patient's husband reported that the rash had been "troublesome" for at least 2 months. Once stable, she was transferred to a transitional unit for assessment of care needs and activation.

Throughout her stay in the acute care ward and subsequently in transitional care, the patient continued to report an itchy rash and recurrent nausea, vomiting, and retching, which were not relieved by dimenhydrinate. The pharmacist was consulted regarding alternative treatment for the nausea and rash, initially thought to be secondary to uremia. The patient exhibited a diffuse, maculopapular rash, which became progressively worse despite high-dose hydroxyzine, Nutriderm® lotion, and hydrocortisone 1% cream. Her constant scratching caused her skin to bleed. Her medications included metolazone 5 mg po qam, furosemide 80 mg po bid, hydroxyzine 50 mg po qid, nitroglycerin patch 0.4 mg/h, hydralazine 50 mg po tid, allopurinol 100 mg po qd, thyroxine 50 µg po qd, quinidine bisulfite 250 mg po bid, oxazepam 15 to 30 mg po qhs prn, clonazepam 1 mg po q6h prn for anxiety, dimenhydrinate 50 mg po/IM q4-6h prn for nausea, acetaminophen 650 mg po q4h prn for pain, Humulin® 30/70 (human insulin) 30 units sc before breakfast and 10 units sc before supper, and Humulin® R sliding scale qid. The results of laboratory tests performed 6 days previously showed random glucose of 6.2 mmol/L (normal range 3.8 to 11.0 mmol/L), urea of 41 mmol/L (normal range 2.5 to 7.0 mmol/L), serum creatinine of 793 µmol/L (normal range 50 to 130 µmol/L), urate of 527 µmol/L (normal range 150 to 330 µmol/L), phosphorus of 2.57 mmol/L (normal range 0.8 to 1.50 mmol/L), and 11.6% eosinophils (normal range 0% to 7.0%), with absolute eosinophil count of 1.07 x 10^9/L (normal range 0 to 0.8 x 10^9/L). The patient

exhibited a low-grade fever (temperature 38.4°C).

The pharmacist suspected an allopurinol hypersensitivity reaction because of the fever and rash in the setting of declining renal function. The renal function had declined from a creatinine clearance of 18 mL/min 1 year before admission to less than 10 mL/min during the present admission. The patient reported that she had been on allopurinol "for years" but could not remember when she had had her most recent gouty attack. Allopurinol was discontinued, and prochlorperazine 5 mg po tid was ordered for the nausea and retching.

Within 4 days, the rash had significantly diminished, and the nausea and retching were controlled. Over the next 7 days, the rash and fever completely resolved, and the patient was comfortable. Palliative care ensued, and the patient died of renal failure 2 weeks later.

DISCUSSION

In 1986, Singer and Wallace[4] developed diagnostic criteria for allopurinol hypersensitivity syndrome after retrospectively examining the records of 14 patients who had been diagnosed with the syndrome:

1. a clear history of exposure to allopurinol
2. a clinical picture consisting of either A or B, as follows:

A. at least 2 of the following major criteria:
   (i) worsening renal function
   (ii) acute hepatocellular injury
   (iii) a rash, including either toxic epidermal necrolysis, erythema multiforme, or a diffuse maculopapular or exfoliative dermatitis

B. one of the above major criteria plus at least one of the following minor criteria:
   (i) fever
   (ii) eosinophilia
   (iii) leukocytosis

3. lack of exposure to another drug that might cause a similar clinical picture.

In 1993, Arellano and Sacristán modified these criteria after examining 101 cases that had been reported up to that point.[1] Because rash had developed in all but one case, they felt that the appearance of a rash should be a definite criterion. They also eliminated fever and leukocytosis, as they felt that these were not specific enough to be used as definite criteria. Therefore, they modified criterion 2 to state that the clinical picture should include a rash and at least one of the following criteria:

(i) worsening of renal function
(ii) acute hepatocellular injury
(iii) marked eosinophilia.

Although laboratory data were limited because of the palliative nature of this case, our patient did fit the profile of allopurinol hypersensitivity syndrome as previously reported.[5] She presented with a persistent maculopapular rash, fever, worsening of renal function, and mild eosinophilia, symptoms that meet both sets of criteria. She also had many of the chronic illnesses associated with this syndrome, including hypertension, diabetes, and congestive heart failure.[1,5] Allopurinol hypersensitivity syndrome is also associated with concomitant diuretic therapy, and this patient was receiving both metolazone and furosemide.

The severity of allopurinol hypersensitivity syndrome ranges from a mild rash to severe vasculitis. Death has been reported in 21% to 27% of cases.[1,4-6] The onset of the syndrome is extremely variable, ranging from 1 to 728 days (mean 47 days) after the initiation of allopurinol therapy.[1]

The pathogenesis of allopurinol hypersensitivity syndrome is thought to be the result of drug accumulation and immunologic processes.[1,4,5,7,8] Absorbed allopurinol is rapidly converted by xanthine oxidase to oxipurinol, which is then excreted by the kidneys.[6] The clearance of oxipurinol exhibits a direct linear relationship with creatinine clearance.[5] Oxipurinol elimination half-life ranges from 14 to 30 h with normal renal function to as high as 250 h in patients with severe renal impairment.[1,5,6,8,9] Accumulated oxipurinol is thought to cross-react with purine ribonucleotides or nucleic acids (or both) to form immunogenic antigenic complexes. These immune complexes can precipitate in vascular endothelium to cause diffuse vasculitis, activate complement, stimulate antibody formation, and induce serum sickness reactions.[1] Elevated circulating immune complexes and consumption of complement support a type III hypersensitivity reaction.[1] The result of skin testing against allopurinol and oxipurinol is usually negative, which disclaims the hypothesis that cell-mediated or type IV blastogenic transformation of lymphocytes is involved. Our patient had previously tolerated allopurinol for an undetermined number of years. It is likely that during the last few months of her life, when renal function declined, oxipurinol accumulated and the hypersensitivity reaction resulted.

Rechallenge has resulted in the reappearance of the syndrome in some patients and can be life-threatening.[5] Rechallenge was not an option in this case, since the goals of treatment were palliative at the time.

Successful desensitization regimens involving gradual dose escalation have been described.[10-12] A case of desensitization failure was reported in a 54-year-old woman in whom the original reaction (stridor, neck swelling, and itchy rash) recurred 2 weeks after she reached the target

Table 1. Indications for Allopurinol[4]

Tophaceous gout
Major uric acid overproduction (urinary excretion of > 900 mg uric acid per 24 h while on a rigid purine-restricted diet)
Frequent gouty attacks unresponsive to prophylactic colchicine and when uricosuric agents cannot be used because of intolerance, lack of efficacy, renal insufficiency, or poor patient compliance
Recurrent uric acid renal calculi
Recurrent calcium oxalate renal calculi in association with hyperuricosuria
For prevention of acute urate nephropathy in patients receiving cytotoxic therapy for malignant disease

dosage of 300 mg/day of allopurinol.[12] The authors concluded that the nature and severity of the original adverse event should be taken into consideration before desensitization is attempted.[12]

Allopurinol hypersensitivity syndrome can be prevented by avoiding allopurinol therapy unless it is truly indicated (Table 1). Allopurinol is not indicated in asymptomatic hyperuricemia (including thiazide-induced hyperuricemia), uncomplicated gout, acute gouty attacks, or vague symptomatology assumed to be gout. Numerous reviews have reported that many patients who experienced the hypersensitivity syndrome were receiving allopurinol for asymptomatic hyperuricemia, an indication that is not considered to carry a favourable benefit-risk ratio.[1,4,5]

Dose adjustment in renal insufficiency is critical in avoiding allopurinol hypersensitivity syndrome (Table 2).[1,4-7,9,13] Most patients with the syndrome exhibit renal insufficiency and are receiving dosages of 300 mg/day or greater, which exceed recommendations.[10] Allopurinol dose is correlated with oxipurinol concentrations, yet there is no correlation between plasma urate and oxipurinol concentrations.[5,6,9] The optimal range of oxipurinol to control hyperuricemia is 30 to 100 µmol/L; there appears to be no advantage to increasing oxipurinol concentration beyond that range in terms of lowering plasma urate or controlling gout symptoms. Measurement of oxipurinol concentrations, rather than plasma urate, has been suggested as a more accurate assessment of the effectiveness and potential toxicity of allopurinol.[9] However, oxipurinol measurement is not readily available in most laboratories. Concurrent use of thiazide diuretics might be expected to cause further accumulation of oxipurinol, given that the kidneys eliminate oxipurinol and uric acid in a similar fashion.[8] Alternative diuretics should be considered in patients with renal insufficiency and a predisposition to gout, because of the potential for hyperuricemia and oxipurinol accumulation when allopurinol and thiazide diuretics are taken together.

Table 2. Adjustment of Allopurinol Dosage in Renal Insufficiency*

Creatinine Clearance (mL/min)	Maintenance Dosage of Allopurinol (mg)
0	100 every 3 days
10	100 every 2 days
20	100 daily
30	150 daily
40	200 daily
60	250 daily
80	300 daily

* Adapted from *American Journal of Medicine*, volume 76, Hande KR, Noone RM, Stone WJ, "Severe allopurinol toxicity: description and guidelines for prevention in patients with renal insufficiency", pages 47-56, copyright 1984, with permission from Excerpta Medica Inc.

Management of toxicity consists of awareness and early recognition of the syndrome, withdrawal of the drug, and appropriate supportive therapy.[1,5] Patients starting allopurinol, particularly those with renal insufficiency, should be educated about the early signs of allopurinol hypersensitivity syndrome. In patients with near-normal renal function, a uricosuric drug such as probenecid may increase renal clearance of oxipurinol. In severe renal impairment, a 4-h hemodialysis can reduce serum oxipurinol concentrations by 39%.[5] The use of steroids is controversial and has not been shown to improve outcome.[1,2]

In this patient's case, failure to adjust the allopurinol dose as her renal function declined probably led to accumulation of oxipurinol and development of allopurinol hypersensitivity syndrome. Dosage adjustment might have reduced the occurrence or severity of the rash. Discontinuation of allopurinol did achieve the ultimate goal of palliative care, which was to make the patient as comfortable as possible.

References

1. Arellano F, Sacristán JA. Allopurinol hypersensitivity syndrome: a review. *Ann Pharmacother* 1993;27:337-43.
2. Elasy T, Kaminsky D, Tracy M, Mehler PS. Allopurinol hypersensitivity syndrome revisited. *West J Med* 1995;162:360-1.
3. McInnes GT, Lawson DH, Jick H. Acute adverse reactions attributed to allopurinol in hospitalized patients. *Ann Rheum Dis* 1981;40:245-9.
4. Singer JZ, Wallace SL. The allopurinol hypersensitivity syndrome: unnecessary morbidity and mortality. *Arthritis Rheum* 1986;29:82-7.
5. Hande KR, Noone RM, Stone WJ. Severe allopurinol toxicity: description and guidelines for prevention in patients with renal insufficiency. *Am J Med* 1984;76:47-56.
6. Peterson GM, Boyle RR, Francis HW, Oliver NWJ, Paterson J, vonWitt RJ, et al. Dosage prescribing and plasma oxipurinol levels in patients receiving allopurinol therapy. *Eur J Clin Pharmacol* 1990;39:419-21.
7. Hanger HC, Pillans PI. Death following allopurinol hypersensitivity syndrome [letter]. *N Z Med J* 1994;107:229.

8. Young JL, Boswell RB, Nies AS. Severe allopurinol hypersensitivity. *Arch Intern Med* 1974;134:553-8.
9. Day RO, Miners JO, Birkett DJ, Whitehead A, Naidoo D, Hayes J, et al. Allopurinol dosage selection and relationship between dose and plasma oxipurinol and urate concentrations and urinary urate excretion. *Br J Clin Pharmacol* 1988;26:423-8.
10. Meyrier A. Desensitisation in a patient with chronic renal disease and severe allergy to allopurinol. *BMJ* 1976;2:458.
11. Fam AG, Paton TW, Chaiton A. Reinstitution of allopurinol therapy for gouty arthritis after cutaneous reactions. *CMAJ* 1980;123:128-9.
12. Unsworth J, Blake DR, D'assis Fonseca AE, Beswick DT. Desensitisation to allopurinol: a cautionary tale [letter]. *Ann Rheum Dis* 1987;46:646.
13. McCLintock AD, Egan AJ, Woods DJ, Phillans PI. A survey of allopurinol dosage prescribing. *N Z Med J* 1995;108:346-7.

Donna Buna, PharmD, is the Supervisor, Long Term Care Pharmacy, Cottonwoods Extended Care Unit, Brookhaven Care Centre, Kelowna General Hospital, Kelowna, British Columbia.

Address correspondence to:
Dr Donna Buna
Supervisor, Long Term Care Pharmacy
Cottonwoods Extended Care Unit
Brookhaven Care Centre
Kelowna General Hospital
2255 Ethel Street
Kelowna BC
V1Y 2Z9
e-mail: bund@oshr.hnet.bc.ca