Singapore Med J 2000 Vol 41(4) : 156-160

A Review of Inpatients with Adverse Drug Reactions to Allopurinol

B P Khoo,Y H Leow

ABSTRACT

Allopurinol is still an effective uric-acid lowering drug since its introduction in 1963. However it has been frequently incriminated for severe adverse drug reactions. From our retrospective review of 13 inpatients with allopurinol adverse reactions seen over 3 years, fever and rash were the commonest presenting symptoms, occurring several weeks after initiation of the drug. Other associated abnormalities included leukocytosis (62% of patients), eosinophilia (54%), renal impairment (54%) and liver dysfunction (69%). Although 12 patients (92%) met the criteria for allopurinol hypersensitivity syndrome, there was no mortality recorded. The indications for initiating allopurinol therapy were frequently unclear. In view of the severe adverse reactions experienced with allopurinol, we propose that it should only be prescribed when truly indicated.

Keywords: allopurinol, adverse drug reactions, gout and hyperuricemia, multi-organ involvement

Singapore Med J 2000 Vol 41(4):156-160

INTRODUCTION

Allopurinol was developed in 1956 for use as an adjuvant in chemotherapy for leukemia[1]. Incidentally, it was found to possess the ability to lower serum uric acid level by inhibiting the conversion of hypoxanthine to xanthine and xanthine to uric acid respectively. It was thus subsequently marketed as a uric acid-lowering agent in 1963.

It had become the most widely prescribed medication for the management of gout, but at the same time, the problem of adverse drug reaction to allopurinol also began to surface. In 1981, allopurinol was incriminated in 6.2% of hospitalised patients with adverse drug reactions[2]. 0.4% of these patients who received allopurinol had life-threatening reactions.

The objective of this 3-year retrospective study is to document the clinical characteristics, degree of severity of allopurinol adverse reactions in our patients who were admitted to a local tertiary referral dermatological institution and review the indications for allopurinol therapy.

Raffles Surgicentre
182 Clemenceau Avenue
Singapore 239923

B P Khoo, MBBS, MRCP (UK), FAMS
Consultant

National Skin Centre
1 Mandalay Road
Singapore 308205

Y H Leow, MBBS, M Med (Int Med), FAMS
Consultant

Corespondence to:
Dr B P Khoo

MATERIALS AND METHODS

Medical records were reviewed to study the clinical features of patients admitted to the National Skin Centre dermatology ward between July 1995 and June 1998 for

Table I. Inpatients with allopurinol allergy.

Patient no.	Age/sex/race	Indication for Allopurinol use	Onset of rash (days)
1.	41/M/Ch	asymptomatic hyperuricemia	14
2.	43/M/Ch	asymptomatic hyperuricemia	17
3.	32/M/Ch	hyperuricemia with gout	45
4.	42/M/Ma	gout	11
5.	29/M/Ch	hyperuricemia	9
6.	86/F/Ch	gout	30
7.	57/F/Ch	gout	14
8.	62/M/Ch	gout	22
9.	37/M/Ch	hyperuricemia	16
10.	58/M/Ch	gout	54
11.	66/F/Ch	asymptomatic hyperuricemia	23
12.	62/F/Ch	foot pain with hyperuricemia	4
13.	63/M/Ch	gout	11

adverse reactions to allopurinol. Patients included in the study had definite history of exposure to allopurinol and whose clinical conditions warranted admission to the hospital wards. Excluded from the study were patients in whom drug reactions could not be definitely attributed to allopurinol alone or had mild cutaneous drug reactions that could be managed as outpatients.

RESULTS

A total of 13 patients were admitted during this 3-year period of which 4 were females and 9 were males. The age ranged from 29 to 86 years, with a mean of 52 years. All were Chinese except for 1 Malay.

Six patients were previously labeled as having "gout", 3 had asymptomatic elevated uric acid levels while 4 had joint symptoms that might be associated with increased uric acid levels. The skin eruptions started within 4 to 54 days (mean of 21 days) after the initiation of the drug. The presenting symptoms included itchy rash in 9 patients, rash and fever in 3, and an asymptomatic rash in 1 patient (Table I).

Ten out of 13 patients had documented fever (oral temperature more than 37°C). Eight patients had exanthematous rash (Fig. 1), 1 had generalized exfoliative dermatitis and 4 had erythema multiforme/ Steven Johnsons syndrome (EM/SJS). All the patients had symmetrical and extensive involvement of the skin; in addition, there were mucosal involvement in 2 of the patients with EM/SJS (Patients 6 and 7). None of the patients had jaundice, enlarged spleen or liver except

Morphology	Fever	ECG/CXR	Leukocytes/ eosinophil (x 10^9/L)	Serum creatinine (umol/L)	Liver function test (U/L)	Serum uric acid (umol/L)	Complications	Hospital stay (days)
EM/SJS	present	not done/normal	13.7/0.14	92	ALT - 87 AST - 39 GGTP - 114	224	nil	5
exanthematous	present	normal/normal	26.9/2.15	105	ALT - 289 AST - 136 GGTP - 548	345	nil	4
exanthematous	present	not done/not done	16.8/4.37	95	ALT - 127 AST - 66 GGTP - 119	475	nil	6
exanthematous	present	not done/not done	8.7/0.44	172	ALT - 35 AST - 28 GGTP - 90	678	nil	3
exanthematous	present	not done/normal	13.2/1.72	165	ALT - 216 AST - 93 GGTP - 62	455	nil	10
EM/SJS	absent	normal/normal	11.5/0.35	129	ALT - 11 AST - 25 GGTP - 18	not done	nil	8
EM/SJS	present	not done/normal	4.6/0.10	84	ALT - 67 AST - 35 GGTP - 84	275	nil	14
exanthematous	present	normal/normal	16.1/4.51	112	ALT - 53 AST - 29 GGTP - 29	349	nil	4
exanthematous	present	not done/normal	27.4/1.10	128	ALT - 285 AST - 108 GGTP - 652	not done	nil	defaulted
EM/SJS	present	not done/normal	7.0/1.40	212	ALT - 25 AST - 18 GGTP - 56	573	nil	10
exanthematous	present	normal/normal	11.1/0.22	85	ALT - 21 AST - 18 GGTP - 18	375	nil	6
exanthematous	absent	normal/normal	7.2/1.10	125	ALT - 74 AST - 49	376	nil	6
exfoliative dermatitis	absent	not done/normal	7.0/0.39	125	ALT - 183 AST - 114 GGTP - 286	278	nil	3

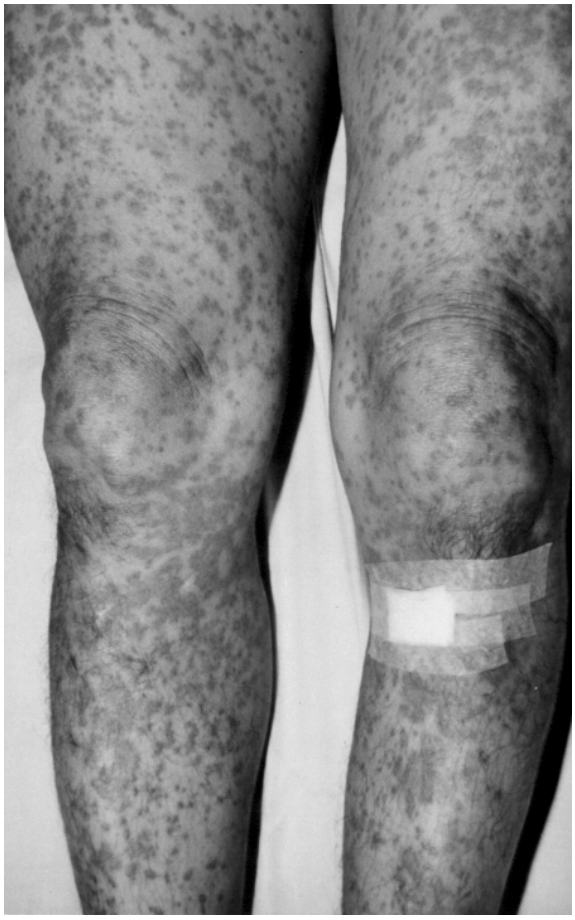

Fig. 1 An exanthematous rash in a patient with allopurinol hypersensitivity syndrome

Patient 10 who had an enlarged liver.

Electrocardiograms of 7 patients and chest X-rays of 9 patients were normal. Eight patients (62%) had leukocytosis (more than 10 x 10^9/L) but none of them had low platelet or low haemoglobin count. Eosinophilia (more than 5 x 10^9/L) was found in 7 (54%) patients. Six patients had mild renal impairment (creatinine 120 - 200 umol/L) and 1 had moderate renal impairment (creatinine 200 - 350 umol/L), giving a total of 7 patients (54%) with renal impairment. None of the patients had hyperbilirubinemia, but 3 had raised alkaline phosphatase levels. Seven had raised (more than two times the normal) alanine amino-transferase (ALT) levels, 5 had raised (more than two times the normal) aspartate-amino transferase (AST) levels and 7 out of 12 patients had raised (more than two times the normal) gamma-glutamyl transpeptidase (GGTP) levels. There were thus 9 patients (69%) who had abnormal liver function tests as defined by having one or more raised liver enzymes. Only 2 out of 11 patients had raised uric acid levels.

None of the patients had any further complications. All of them were started on systemic steroids on admission, either with prednisolone ranging from 30 mg to 60 mg daily, or intravenous hydrocortisone at 400 mg daily. The length of stay in the hospital ranged from 3 to 14 days (excluding Patient 9 who discharged against advice), with an average of 7 days.

Table II. Recommended indications for allopurinol therapy[8].

1.	Tophaceous gout
2.	Major uric acid overproduction (proven by urinary excretion of >53 mmol/24 hours (or 900 mg/dl) on a restricted purine diet)
3.	Frequent gouty attacks unresponsive to prophylactic colchicine, when uricosuric agents cannot be used due to intolerance, lack of efficacy, renal insufficiency, or poor patient compliance
4.	Recurrent uric acid renal calculi
5.	Recurrent calcium oxalate renal calculi when associated with hyperuricosuria
6.	Prevention of acute urate nepropathy in patients receiving cytotoxic therapy for malignancies

DISCUSSION

In Singapore, allopurinol is the most frequently prescribed uric acid-lowering drug. Exanthematous eruptions occur in about 5% of patients on allopurinol with the majority just experiencing a transient rash[3]. However allopurinol had previously been implicated in 3 (20%) out of 15 patients with toxic epidermal necrolysis (TEN) in one local series[4] and 3 (13%) out of 23 patients with TEN in another[5].

There are age and gender differences in the renal clearance of urate, probably due to the influence of estrogens and androgens. Hyperuricemia and gout are primarily diseases of adult men, and this accounted for the higher number of male patients seen in our study. Asymptomatic hyperuricemia is very common, affecting an estimate of 5-8% of the general population[6]. Most authorities in the literature would not recommend allopurinol therapy for mild-to-moderate hyperuricemia except in marked hyperuricemia (uric acid more than 780 umol/L or 13 mg/dl)[7]. However none of our 13 patients had clear clinical indications for allopurinol therapy. Although allopurinol is efficacious in lowering uric acid level, the potential risk of treatment must not outweigh its benefit. A good criteria for initiating allopurinol therapy was recommended by Singer and Wallace[8] who documented one of the largest series of drug reactions to allopurinol, and we proposed that this be adopted by our local medical community (Table II). Singer also suggested that allopurinol should not be considered in asymptomatic hyperuricemia, uncomplicated gout, acute gouty attacks and hyperuricemia associated with renal impairment. A local series of 5 patients reported by Chan et al also noted that patients with renal impairment appeared particularly prone to severe and potentially fatal reactions with

allopurinol, therefore a dose reduction is required in such patients[9].

The onset of rash, which was defined as the time interval between initiation of allopurinol and appearance of skin rash, was at a mean of 21 days, comparable to a mean of 25 days reported in a series of 72 patients by Singer[8]. There were 9 (69%) out of 13 patients with diffuse exanthematous or exfoliative rash and 4 (31%) with EM/SJS eruption, once again the figures were also comparable with 65% and 35% respectively in Singer's series[8].

The normal electrocardiograms and chest X-rays in our patients, coupled with clinical examinations, showed that there were no evidence of myocarditis or pneumonitis. Singer's series however did not document these 2 aspects. Our proportion of patients with eosinophilia (54%) and renal impairment (54%) were comparable to Singer's series, however we saw more patients with leukocytosis (62%) and abnormal liver function (69%).

More importantly, the various clinical and biochemical abnormalities should be seen as a constellation of features and not in isolation. The term allopurinol hypersensitivity syndrome (AHS) has been coined to encompass the plethora of features caused by hypersensitivity to allopurinol. Diagnostic criteria had been proposed for the definition of AHS by Singer[8] (Table III). Using the same criteria, all our patients showed features of AHS except Patient 6. Allopurinol hypersensitivity syndrome, in contrast to other purely cutaneous drug eruptions, deserves special attention because of its multiorgan involvement, the liver and kidneys being the most commonly affected. Systemic corticosteroids are usually prescribed in such instances although its benefit has never been proven in any controlled trials. It may take several months to taper off the steroid therapy in order to avoid a rebound phenomenon. Drug rash with eosinophilia and systemic symptoms (DRESS syndrome) is a new term proposed by recent authors[10] to replace drug hypersensitivity syndromes but its usage has yet to gain wider acceptability among clinicians.

Only 2 patients had elevated uric acid levels on admission. One explanation for the normal serum uric acid in the rest of the 11 patients might have been the therapeutic efficacy of the allopurinol used. Another possibility could be that the initial pretreatment uric acid levels of the 11 patients were only marginally elevated which rapidly normalised when treated with allopurinol, thus raising the question as to whether allopurinol should be initiated solely on a single, marginally elevated uric acid level that may or may not be associated with joint pain. It is generally believed that the combination of hyperuricemia with monoarticular arthralgia does not equate gout. The problem of hyperuricemia should be evaluated *per se* and likewise with monoarticular joint pain. If a patient is diagnosed with gouty arthritis after sufficient evaluation, the first-line management would consist of bed rest and an adequate dose of anti-inflammatory agents such as indomethacin or colchicine, followed by weight reduction advice and appropriate dietary advice[11].

There was no mortality from AHS in our patients as opposed to the high mortality rate of 26% noted by Singer[8]. The cases reported by Singer most likely had more overt liver dysfunction and renal impairment although these entities were not clearly defined in his report. The pathophysiology of drug reactions to allopurinol remains unknown and it is unclear why certain patients experience only cutaneous eruptions while others develop AHS. We suspect that full-blown, severe cases of AHS in our local population might have been admitted to the acute medical wards in the hospitals where there were emergency medical facilities available. In fact most of our patients could be discharged from the ward in less than a week.

Table III. Criteria for allopurinol hypersensitivity syndrome[8].

1. A clear history of exposure to allopurinol
2. A clinical picture including:
   a) at least 2 of the following major criteria:
      i) worsening renal function
      ii) acute hepatocellular injury
      iii) a rash including either TEN, EM, or a diffuse exanthematous or exfoliative dermatitis

   or b) 1 of the major criteria plus at least 1 of the following minor criteria:
      i) fever
      ii) eosinophilia
      iii) leukocytosis
3. Lack of exposure to another drug which may have caused a similar clinical picture.

CONCLUSION

Allopurinol is a time-honoured uric acid lowering drug. However taking into consideration its side effects, morbidity and mortality, it should be prescribed only when it is truly indicated (Table II). Isolated asymptomatic hyperuricemia does not warrant the use of this drug. Special precaution has to be taken in prescribing for patients with renal impairment. Physicians should have a high index of suspicion for possible allopurinol allergy in patients presenting with a rash and fever as late as 1 to 2 months after initiating therapy.

REFERENCES

1. Robin RK. Potential purine antagonists: synthesis of some 4,6 substituted pyrazolo (3,4-d) pyrimidines. J Am Chem Soc 1956; 78:784-90.
2. McInnes GT, Lawson DH, Jick H. Acute adverse reactions attributed to allopurinol in hospitalized patients. Ann Rheum Dis 1981; 40:245-9.
3. Wybo Bruinsma. A guide to drug eruption. 6th ed. File of Medicines publication. Chap 5:15-9.
4. Chan HL. Observations on drug-induced toxic epidermal necrolysis in Singapore. J Am Acad Dermatol 1984; 10:973-8.
5. Khoo AKM, Foo CL. Toxic epidermal necrolysis in a burns centre: a 6-year review. Burns 1996; 22:275-8.
6. Kelley WN. Current therapy of gout and hyperuricemia. Hosp Pract 1976; 11:69-76.
7. Kelley WN. Approach to the patient with hyperuricemia. Textbook of Rheumatology. First edition. Edited by WN Kelley, ED Harris Jr, S Ruddy, CB Sledge. Philadelphia, WB Saunders, 1981:494-500.
8. Singer JZ, Wallace SL. The allopurinol hypersensitivity syndrome: unnecessary morbidity and mortality. Arthritis and Rheum 1986; 29:82-7.
9. Chan HL, Ku G, Khoo OT. Allopurinol associated hypersensitivity reactions: cutaneous and renal manifestations. Aust. N.Z. J Med 1977; 7:518-22.
10. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (Drug Rash With Eosinophilia and Systemic Symptoms: DRESS) Bocquet H, Bagot M, Roujeau JC. Semin Cutan Med Surg 1996; 15:250-7.
11. Kelley WN, Palella TD. Gout and other disorders of purine metabolism. In: Braunwald E. Isselbacher KJ, Petersdorf RG, et al eds. Harrison's principles of internal medicine, 11th ed. McGraw-Hill 1987; 1623-32.