

Acute adverse reactions attributed to allopurinol in hospitalised patients

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SUMMARY Of 29 524 hospitalised medical patients monitored in a drug surveillance programme 1835 (6.2%) received the xanthine oxidase inhibitor allopurinol. After the exclusion of skin reactions adverse effects were attributed to this drug in 33 (1.8%) patients, the most frequent being haematological abnormalities (11 patients, 0.6%) and diarrhoea and drug fever (5 each, 0.3%). Adverse effects were dose-related. Reactions were unrelated to age, weight, reason for therapy, admission blood urea, or albumin concentrations. Acute exacerbation of gout was troublesome in 3 patients (1 in 600 exposed).

Allopurinol achieves its major pharmacological effect through inhibition of the enzyme xanthine oxidase. The resultant alterations in purine metabolism explain its effectiveness in the treatment both of idiopathic gout and of hyperuricaemia secondary to blood dyscrasias, antineoplastic chemotherapy, and diuretic therapy.¹⁻⁵ It is generally well tolerated, the most frequently noted side effects being reactions involving the skin, gastrointestinal system, and blood. The present study describes the adverse effects attributed to allopurinol in 1835 consecutive medical patients treated with the drug in wards participating in the Boston Collaborative Drug Surveillance Program.

Materials and methods

The aims and methods of the Boston Collaborative Drug Surveillance Program have been described in detail elsewhere.⁶ Trained nurse monitors use standardised self-coding sheets to record information on consecutive patients admitted to participating medical wards. The information collected includes patients' characteristics, diagnosis, drug administration, and outcome of hospitalisation. When a drug is prescribed, details ascertained include indications, dosage, frequency, reason for discontinuation, and any adverse effects attributed to the drug by the

attending physician. When an adverse effect is reported, details of the effect are recorded on a separate form and the reaction is evaluated by a trained clinical pharmacologist.

This report is derived from data gathered since 1966 on 29 524 patients in 22 hospitals, of whom 1835 (6.2%) received allopurinol.

Allopurinol is frequently administered with other potent drugs (for example, antitumour agents and antibiotics) which cause many adverse effects. It is therefore often difficult to ascribe a particular reaction to this drug with complete confidence. This problem is particularly troublesome with skin rashes. Several publications from this programme have reviewed different aspects of allergic skin reactions in allopurinol recipients.^{7,8} In the light of these reviews it appears that in almost all cases skin rashes in recipients of allopurinol could have been caused by other, more allergenic drugs. For this reason, although there were 32 recipients of allopurinol who developed allergic skin reactions which were attributed to this drug by attending physicians, these reports have been excluded from further analysis.

Results

The mean age of the 1835 recipients of allopurinol was 60 years; 64% were male, and 209 (11%) died during admission to hospital. The primary discharge diagnosis was of cancer in 36%, cardiovascular disease in 30%, respiratory disease in 8%, genitourinary disease in 6%, endocrine disease in 5%, and other conditions in the remaining 15%.

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Allopurinol was given to treat patients with gout in 19% of instances and prophylactically in the remainder. The usual daily dose was 300 mg (66%), some 23% receiving lower doses and 11% higher daily doses.

With the exception of skin lesions, adverse reactions attributed to allopurinol by the attending physician were reported in 33 patients (1.8%).

Table 1 *Adverse reactions attributed to allopurinol*

Drug fever	5 (0.3%)
Diarrhoea	5 (0.3%)
Nausea ± vomiting	3 (0.2%)
Acute gout	3 (0.2%)
Hepatotoxicity	3 (0.2%)
Leucopenia ± thrombocytopenia	3 (0.2%)
Thrombocytopenia	3 (0.2%)
Clotting abnormalities	2 (0.1%)
Haemolytic anaemia	1 (0.05%)
Malaena	1 (0.05%)
Pulmonary haemorrhage	1 (0.05%)
Periorbital oedema	1 (0.05%)
Acute tubular necrosis	1 (0.05%)
Generalised vasodilation and mental confusion	1 (0.05%)

Details of the types of reaction reported are given in Table 1. No patient developed neurological or visual symptoms attributable to allopurinol. In 7 patients (0.4%) reactions were deemed to be life-threatening. Details of these patients are given in Table 2. In the 2 patients with a primary diagnosis of cancer allopurinol was thought to have exacerbated toxicity primarily attributable to other drugs given with it.

There was a strong positive correlation between adverse effects attributed to allopurinol and the total dose received; 0.8% of patients receiving less than 2 g during admission to hospital developing a reaction (6/693) as compared with 2% of those receiving between 2 and 5 g (15/726) and 3.1% of those receiving over 5 g (11/356)— χ^2 for linear trend = 6.95, $P < 0.01$. Allopurinol toxicity was not related to hospital, age, weight, discharge diagnosis, survival, admission blood urea nitrogen concentration, admission albumin concentration, or previous allopurinol use.

Table 2 *Life-threatening adverse effects attributed to allopurinol by attending physicians*

Case	Age/sex	Diagnosis	Allopurinol therapy		Physician rating*	
			Daily dose (mg)	Duration (day)		
1	74 F	Chronic renal failure	400	1	Agitation and confusion with erythematous (toxic) rash and peripheral vasodilation developed shortly after commencing allopurinol 400 mg daily; gradually resolved over one week after allopurinol stopped. Admission blood urea nitrogen 40mg/100 ml (6.6 mmol/l)	P
2	61 M	Congestive heart failure	300	5	Developed weakness, hepatomegaly, stomatitis, and lymphadenopathy with thrombocytopenia and raised blood urea nitrogen concentrations which returned to normal on discontinuing therapy. Jaundice and hepatomegaly accompanied by acute hepatocellular destruction, thought definitely due to allopurinol. Patient also received 8 g erythromycin in preceding week. No other drug likely to be involved.	D
3	78 F	Congestive heart failure	200	22	Morbilliform rash with leucopenia (10 900 → 1700/mm ³ (10.9 → 1.7 × 10 ⁹ /l) in 11 days): patient subsequently developed bronchopneumonia and died. Allopurinol thought to have caused leucopenia; rash attributed equally to co-administered amoxicillin and cloxacillin	D
4	38 M	Disseminated carcinoma	200	9	Leucopenia (900/mm ³ (0.9 × 10 ⁹ /l)) and thrombocytopenia (67 000/mm ³ (67 × 10 ⁹ /l)) noted during treatment of cancer with azathioprine, cyclophosphamide, and allopurinol. Cytopenia felt to be due to interaction between allopurinol and azathioprine	D
5	73 M	Acute myeloid leukaemia	300	8	Severe thrombocytopenia (3000/mm ³ (3 × 10 ⁹ /l)) developed during treatment with azathioprine, amphotericin, and allopurinol; latter thought to have increased cytotoxic effect of former. Patient recovered without sequelae.	P
6	59 F	Pulmonary thromboembolism	600	4	Developed proteinuria with elevated urea and creatinine concentrations and oliguria with 10% eosinophilia, creatinine clearance reduced to 13 ml/min. Gradually resolved 2 weeks after allopurinol discontinued. Drug-disease relationship unclear, though possibly causal.	DK
7	80 M	Congestive heart failure Renal failure	300	2	Developed extensive intrapulmonary haemorrhage (haemoglobin fell to 10 g/dl) while taking warfarin and allopurinol. Prothrombin time prolonged to 71 s in presence of renal failure (at the time of admission blood urea nitrogen 41 mg/100 ml (6.8 mmol/l)). Allopurinol consumed regularly for month prior to admission and continued in hospital	P

*D = definitely allopurinol induced. P = probably allopurinol induced. DK = unsure of relationship between allopurinol and event.

Of the 11 patients with haematological reactions attributed to allopurinol 6 developed leucopenia and/or thrombocytopenia. Brief details of 3 of these patients are given in Table 2 (cases 3, 4 and 5). The remaining patients with leucopenia (1) and thrombocytopenia (2) had reductions of peripheral cell counts which were not severe and did not result in any clinical complications. All 3 recovered on withdrawing therapy.

Three patients developed excessive anticoagulation when taking warfarin and allopurinol, the time relationships being such as to render a drug interaction possible. In 1 (case 7, Table 2) extensive intrapulmonary haemorrhage developed while he was anticoagulated excessively (prothrombin time 71 s).

Hepatotoxicity was reported in 3 patients. A 61 year-old-male with cardiac failure (case 2, Table 2) developed jaundice and hepatocellular necrosis after 5 days' treatment with allopurinol (300 mg daily). Coincidental therapy for chest infection included erythromycin 8 g in the preceding week. The attending physician attributed hepatitis to allopurinol and not to erythromycin. No biopsy was taken, and the patient recovered on stopping both drugs. A 19-year-old male with histiocytosis X developed jaundice and hepatocellular necrosis (bilirubin 14.5 mg/100 ml (248 μ mol/l), alanine transferase 355 U/l), after receiving allopurinol 200 mg daily for 19 days. The patient gradually improved despite continuing allopurinol, which was doubtfully incriminated as a cause of the liver disorder by the attending physician. Finally, a 75-year-old male with pancytopenia developed jaundice (bilirubin 4.0 mg/100 ml (68 μ mol/l)) of hepatocellular type (alanine transferase 413 U/l) after 16 days of 300 mg allopurinol daily. Jaundice regressed after cessation of allopurinol therapy. No other potential hepatotoxin was given. The cause of underlying pancytopenia was not fully established. Although allopurinol was incriminated in all 3 cases with varying degrees of conviction, and although jaundice regressed on stopping the drug, no objective evidence proving the association can be provided, and the link between drug and disorder must be regarded as tenuous.

Overall allopurinol toxicity was unrelated to coadministration of digoxin, thiazide diuretics, and cytotoxic drugs other than mercaptopurine. Only 21 patients received both allopurinol and mercaptopurine during their admission to hospital, and of these 2 (9.6%) developed reactions attributed to allopurinol as compared to 31 of 1814 patients who received allopurinol alone (1.8%) ($\chi^2 = 7.18$, $P < 0.01$). In none of these cases was the reaction of major severity.

Acute flare-up of gout was reported in 3 patients. All were males suffering from primary or drug-induced gout, and were asymptomatic when treatment with allopurinol 300 mg daily was started. Within 2-4 days of starting therapy each developed acute symptoms of gout, which responded to colchicine (2 patients) or phenylbutazone (1 patient). Thereafter all 3 continued allopurinol treatment without difficulty.

Discussion

Clinical experience with allopurinol suggests that most patients tolerate this drug well⁵⁻⁹—a finding strongly supported by our data. Undesired or unintended effects of therapy were reported in only 1.8% of 1835 consecutive recipients.

Severe hypersensitivity reactions have been attributed to allopurinol. The range of lesions includes widespread skin lesions varying from single erythematous eruptions to vasculitic lesions, toxic epidermal necrolysis, fever, eosinophilia, nephritis, and hepatitis.¹⁰⁻¹⁴ The mechanism whereby allopurinol may cause such effects is not understood. Symptoms may arise within days of beginning allopurinol but in some cases are delayed by 1 or more months.¹⁰ In the present series 2 patients developed possible hypersensitivity reactions to allopurinol (both of life-threatening severity; cases 2 and 6). In both the reaction developed rapidly after starting allopurinol. Both had diuretic-related hyperuricaemia, a condition thought to predispose to allopurinol hypersensitivity.¹³

Allopurinol is metabolised to oxipurinol, which is excreted slowly by the kidney.^{15,16} This metabolite is retained in renal impairment and it has been suggested that adverse effects of allopurinol are more frequent when there is renal insufficiency. This was not the case in the present series, which indicates either that the toxicity of oxipurinol is minimal or that the reduction in dosage normally made in patients with renal failure is effective in minimising toxicity.

Leucopenia and/or thrombocytopenia were infrequently attributed to allopurinol therapy in this series. Although they were not confined to patients taking cytotoxic drugs, in general, severe bone marrow depression was reported only in those recipients of allopurinol with underlying tumours who also received cytotoxic therapy. Under those circumstances it is impossible to isolate the effect of allopurinol from that of the cytotoxic drugs or the underlying disease. However, the mode of action of allopurinol indicates that it will reduce the metabolic clearance of both mercaptopurine and azathioprine and hence lead to a prolongation of the

effect of unit doses of either.¹⁷ While this may account for some of the cases of bone marrow depression reported here, it does not explain them all. In particular it does not explain the reported interaction between allopurinol and cyclophosphamide resulting in bone marrow damage,¹⁸ nor does it account for the occasional instances of mild leucopenia or thrombocytopenia occurring in patients with no malignancy. It appears likely that allopurinol itself may rarely cause mild transient leucopenia or thrombocytopenia, which is reported only if the patients develop a serious consequence of the reaction such as major infection (case 3, Table 2).

Reversible hepatotoxicity has been reported in recipients of allopurinol, usually as part of a generalised hypersensitivity reaction.¹⁰ This appears to be infrequent and has been observed in 3 of 1835 consecutive recipients in the present study (i.e., 1 per 600 exposed). Recently Medline *et al.*¹⁹ reported a case of granulomatous hepatitis in a male who received allopurinol daily for 6 years for asymptomatic hyperuricaemia. This condition improved on stopping allopurinol and returned on rechallenge. A similar case was reported by Swank *et al.*²⁰ Thus it seems possible that allopurinol may occasionally be associated with granulomatous hepatitis. No such case was observed in the current series.

Drug interactions with allopurinol have been reported by several workers. The most relevant are those with mercaptopurine and azathioprine referred to above. In addition it has been reported that thiazide diuretics inhibit elimination of oxipurinol by the renal tubules in the same way as they inhibit uric acid elimination.¹⁵ Therefore theoretically these drugs could exacerbate dose-related allopurinol toxicity. The present study provides no support for this interaction being of clinical significance.

Vesell *et al.*²¹ reported that long-term use of allopurinol prolonged the half-life of bishydroxycoumarin. However Rawlins and Smith²² did not observe significant changes in the steady-state plasma concentrations of warfarin in patients receiving allopurinol, though there were considerable variations between individual patients. In the present series 3 patients developed an increased anticoagulant effect while taking both warfarin and allopurinol. The significance of this observation requires more detailed evaluation once a larger number of recipients of both drugs have been studied. By contrast, allopurinol-attributed toxicity appeared to be independent of coadministered warfarin.

Allopurinol has been associated with the development of acute gout or its exacerbation in patients with asymptomatic hyperuricaemia or mild gout.^{2 23}

In the current series this occurred in only 3 patients (1 in 600). However, it should be emphasised that hospitalised medical patients represent a selected population. Cancer sufferers figured prominently among the recipients of allopurinol, which was usually prescribed prophylactically. Only 19% of those studied received the drug for the treatment of gout, the major indication for its use in the general community. All 3 patients who developed acute gout were in the latter category, suggesting a prevalence of this reaction in gouty subjects of 1 in 120 exposures.

The present study of a large series of recipients of allopurinol indicates that therapy with this drug is seldom associated with toxicity, though when it does arise it may be of serious consequence, particularly in patients with underlying malignancy. Apart from skin reactions the principal adverse effects are haematological reactions, diarrhoea, and fever.

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