Dose Adjustment of Allopurinol According to Creatinine Clearance Does Not Provide Adequate Control of Hyperuricemia in Patients with Gout

NICOLA DALBETH, SUNIL KUMAR, LISA STAMP, and PETER GOW

ABSTRACT. *Objective*. Published guidelines state that allopurinol doses should be adjusted according to creatinine clearance. We investigated whether such dosing provides adequate control of hyperuricemia.

Methods. We studied 250 patients with gout attending rheumatology clinics in South Auckland from 2001 to 2004. Allopurinol dose, creatinine clearance, and serum uric acid (SUA) level were recorded. We analyzed the relationship between recommended allopurinol dose and SUA lowering to ≤ 0.36 mmol/l.

Results. For patients taking allopurinol, 70.9% were taking recommended doses, based on published allopurinol dosing guidelines. There were 4 (1.6%) patients with cutaneous hypersensitivity reactions to allopurinol, but none of these patients were taking higher than recommended allopurinol doses. The proportion of patients achieving SUA ≤ 0.36 mmol/l was lower in those taking recommended doses, compared with those taking higher than recommended doses (19% vs 38.1%; p < 0.01).

Conclusion. Adherence to published allopurinol dosing guidelines led to suboptimal control of hyperuricemia in this population of patients with gout. Further work is required to clarify the safety and efficacy of allopurinol dose escalation, particularly in patients with renal impairment. (First Release June 15 2006; J Rheumatol 2006;33:1646–50)

Key Indexing Terms:
GOUT   ALLOPURINOL   URIC ACID

Effective longterm treatment of gout aims to prevent recurrent acute attacks of arthritis and development of tophaceous disease. These goals are achieved by lowering the serum uric acid (SUA) level to ≤ 0.36 mmol/l (6 mg/l)[1-3]. The current mainstay of urate-lowering therapy is allopurinol, which has the advantages of once-daily dosing and efficacy, irrespective of the cause of hyperuricemia.

Although allopurinol is generally well tolerated, this drug has been associated with rare but life-threatening hypersensitivity reactions[4,5]. The underlying mechanism of this reaction is uncertain, but has been attributed to cell mediated immunity to allopurinol and its metabolite, oxypurinol[6,7]. Renal impairment is associated with accumulation of oxypurinol[8-10] and has been identified as a risk factor for development of hypersensitivity[4,5]. These observations led to the development of clinical guidelines that advocate dosing of allopurinol according to creatinine clearance[5]. However, a recent study has reported that patients receiving higher than recommended doses of allopurinol do not have a greater risk of hypersensitivity reactions[11]. Further, dose reduction of allopurinol in patients with renal impairment may potentially lead to undertreatment of gout due to persistent hyperuricemia. Our aim was to determine whether allopurinol dosing according to current published guidelines provides adequate control of hyperuricemia.

A study from our unit in 1999 examined the dosing of allopurinol according to these guidelines. At that time, 29% of patients were taking recommended doses of allopurinol, and 55% were taking higher than recommended doses[9]. These results were in keeping with reports from other studies of both primary and secondary care[8,12,13]. These findings led to the development and introduction of an allopurinol dose calculator to our unit in 2000, to facilitate recommended dosing of allopurinol. Introduction of this calculator has allowed us to determine the effect of the published allopurinol dosing guidelines on control of hyperuricemia in patients with gout.

MATERIALS AND METHODS

Allopurinol dose calculator. This calculator was introduced in 2000 following our previous study of allopurinol dosing[9]. It is available in electronic form on our institution's intranet, via all ward and clinic computers (also available from authors on request). Following entry of sex, age, height, and serum creatinine data into the calculator, the ideal body mass is calculated (based on height) and creatinine clearance and recommended allopurinol dose are dis-

From the Department of Medicine, University of Auckland, Auckland; Counties Manukau District Health Board, Auckland; Department of Medicine, Christchurch School of Medicine, Christchurch; and the University of Otago, Dunedin, New Zealand.

N. Dalbeth, MD, FRACP, Rheumatologist, Senior Lecturer, Department of Medicine, University of Auckland; S. Kumar, FRACP, Rheumatologist, Counties Manukau District Health Board; L. Stamp, PhD, FRACP, Rheumatologist, Senior Lecturer, Department of Medicine, Christchurch School of Medicine, University of Otago; P. Gow, FRACP, Rheumatologist, Counties Manukau District Health Board.

Address reprint requests to Dr. N. Dalbeth, Department of Medicine, University of Auckland, Private Bag 92019, 85 Park Road, Grafton, Auckland, New Zealand. E-mail: n.dalbeth@auckland.ac.nz

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played (Figure 1). Guidelines within our institution state that allopurinol should be gradually increased to the dose recommended by the treatment guidelines, as displayed on the dose calculator. The calculator and these guidelines have been widely adopted by rheumatologists within our institution for use in patients with gout since 2000; a recent survey of rheumatologists indicated that the allopurinol dose calculator was used for 79% of all allopurinol prescriptions in our institution.

Patients. We studied the clinical notes of 258 patients attending rheumatology outpatient clinics for management of gout within our institution (Counties Manukau District Health Board) in South Auckland from July 2001 to December 2004. These patients were identified from a database of clinic attendees. All patients included in the study met the American College of Rheumatology diagnostic criteria for gout[14]. There were 8 patients with end-stage renal failure receiving renal replacement therapy. These patients were excluded from analysis, as the allopurinol dosing guidelines are not routinely applied to patients receiving renal replacement therapy within our institution. Therefore, a total of 250 patients were studied. This study was approved by the local ethics committee.

Data were collected from computerized patient notes. Information collected included age, sex, ethnicity, presence of tophi, weight, height, urate-lowering therapies, SUA level on urate-lowering therapy, and creatinine. Creatinine clearance was calculated based on the Cockcroft-Gault equation[15].

For those patients taking an increasing dose of allopurinol, the final dose achieved was recorded. If more than one SUA level was available following commencement of urate-lowering therapy, the last available result was recorded at the time when the patient was established on longterm therapy. The effect of treatment on SUA levels was only recorded if the patient had been taking urate-lowering therapy for at least 3 months.

Data analysis. Current allopurinol doses were compared with recommended allopurinol doses, based on published allopurinol dosing guidelines[5] (as included in Figure 1). Patients were allocated into 4 groups depending on their current allopurinol dose — no allopurinol, lower than recommended allopurinol dose, recommended allopurinol dose, and higher than recommended allopurinol dose.

Comparisons between groups were made using contingency tables and Student t tests on GraphPad Prism. p values are expressed as 2-tailed values. Unless otherwise specified, data are expressed as mean [standard deviation (SD)].

RESULTS

Patient characteristics. We studied allopurinol dosing in 250 patients attending rheumatology clinics for gout from 2001 to 2004. The clinical characteristics of these patients are summarized in Table 1. Compared with our institution's catchment population, Maori and Pacific people were overrepresented within the study group. There were 25.6% New Zealand Maori patients, compared with 17% of the catchment population[16] ($p < 0.001$), and 46.0% Pacific patients (Samoan, Tongan, Niuean, and Cook Island Maori), compared with 16% of the catchment population[16] ($p < 1 \times 10^{37}$).

Of the 250 patients studied, 227 (90.8%) were taking allopurinol. The use of other urate-lowering agents was limited in this population. There were 23 (9.2%) patients not taking

Allopurinol Dosage Calculator

| Gender | Male ▼ | Age | | years |
| Plasma Creatinine | | mmol/l | Height | | cm |

| | Recommended allopurinol dosage | | |

Estimation of creatinine clearance (CrCl): using an adaptation of the Cockcroft - Gault Equation.

$$CrCl_{(ml/s)} = \frac{F \times (140-Age) \times Weight^{**}}{50,000 \times Serum\ Creat_{(mmol/l)}}$$

* where F = **1.0** for **males** and **0.85** for **females**

** Use ideal body weight.

Males: 50 kg + 0.9 kg for every cm over 150 cm in height

Females: 45.5 kg + 0.9 kg for every cm over 150 cm in height

Recommended Maintenance Allopurinol Dosage

CrCl (ml/s)	Maintenance Dosage
0	100 mg every 3 days
0.17	100 mg every 2 days
0.33	100 mg daily
0.67	150 mg daily
1.0	200 mg daily
1.3	250 mg daily
1.7	300 mg daily
2.0	350 mg daily
2.3	400 mg daily

Figure 1. The electronic allopurinol dose calculator with dosing guidelines based on Hande, *et al*[5] and revised by Ross Boswell. Available from the authors upon request.

Table 1. Clinical characteristics of patients with gout.

Variable	Patients, n = 250
Age, yrs, median (range)	56 (26–86)
Ethnicity, n (%)	
Pacific	115 (46.0)
New Zealand Maori	64 (25.6)
New Zealand European	53 (21.2)
Other/not stated	18 (7.2)
Male, n (%)	205 (82.0)
Tophaceous disease, n (%)	134 (53.6)
Allopurinol therapy, n (%)	227 (90.8)
Uricosuric therapy, n (%)	19 (7.6)
Creatinine, μmol/l, median (range)	110 (60–410)
Creatinine clearance, ml/min, median (range)	66 (12–138)

allopurinol. The reasons for not taking allopurinol were: poor cooperation with therapy (n = 12), adverse drug reaction (n = 6), first episode of gout (n = 2), prescriber incongruity (n = 2), and normal SUA level with lifestyle modification (n = 1). Within the study population of 250 patients, there were 4 patients (1.6%) with hypersensitivity reactions to allopurinol, and no patient was taking higher than recommended doses of allopurinol (Table 2). No patient had reactions affecting the mucosal surfaces, exfoliating skin disease, or multiorgan involvement. Allopurinol was not reestablished in these 4 patients.

Prescription of allopurinol based on dosing guidelines. For those 227 patients taking allopurinol, the mean actual allopurinol dose was 214 (SD 95) mg/day. The actual allopurinol doses were compared with recommended allopurinol doses, based on the treatment guidelines. There were 22 (9.7%) patients taking lower than recommended doses of allopurinol, 161 (70.9%) patients taking recommended allopurinol doses, and 44 (19.4%) patients taking higher than recommended doses of allopurinol. The clinical characteristics did not differ between the 3 allopurinol-treated groups in our study. Patients treated with higher than recommended doses tended to have more frequent tophaceous disease (p = 0.06 vs recommended dose). There was no difference between the groups with respect to mean creatinine clearance or recommended allopurinol dose.

Effect of allopurinol dosing on SUA levels. SUA levels during allopurinol therapy were available for 214/227 patients (20 in the lower than recommended dose group, 152 in recommend-

ed dose group, and 42 in higher than recommended dose group). SUA results following commencement of allopurinol treatment were not available for 13/227 (5.7%) patients due to nonattendance at followup clinic (n = 8), or commencement of treatment at the last clinic attendance (n = 5). In addition, SUA levels were available for 23/23 patients in the group not taking allopurinol.

The mean SUA level for the entire allopurinol-treated group was 0.49 (SD 0.14) mmol/l. SUA levels remained high in the vast majority of these patients, and only 48/214 (22.4%) allopurinol-treated patients achieved a SUA level ≤ 0.36 mmol/l. For those 23 patients not taking allopurinol, the mean SUA level was 0.57 (SD 0.10) mmol/l (p < 0.05 vs entire allopurinol-treated group). One patient (4%) within this group achieved a SUA ≤ 0.36 mmol/l (p < 0.05 vs entire allopurinol-treated group).

SUA levels were analyzed based on allopurinol dosing guidelines (Figure 2). For those patients taking recommended allopurinol doses, mean SUA was 0.48 (SD 0.12) mmol/l, and 29/152 (19.1%) patients achieved a SUA ≤ 0.36 mmol/l. For those patients taking lower than recommended doses of allopurinol, the mean SUA level was 0.53 (SD 0.09) mmol/l (p = 0.4 vs recommended allopurinol dose group), and there were 3/20 (15%) patients achieving a SUA ≤ 0.36 mmol/l (p = 0.7 vs recommended allopurinol dose group). For those patients taking higher than recommended doses of allopurinol, the mean SUA was 0.48 (SD 0.13) mmol/l (p = 0.8 vs recommended allopurinol dose group), and 16/42 (38%) achieved a SUA ≤ 0.36 mmol/l (p < 0.01 vs recommended allopurinol dose group). Analysis of subgroups based on ethnicity showed that this effect of allopurinol dosing was found in Pacific patients and non-Polynesian patients, with similar trends in Maori patients (Table 3).

Comparison with previous study. The results of our current study were compared with data from a previous study in 1999, where the mean allopurinol dose was 251 (SD 139) mg/day (current study vs previous study, p < 0.05), and 55% of patients were taking higher than recommended doses (current study vs previous study, p < 0.00001)[9]. The patients studied in 1999 were recruited from the same clinics as the patients in our current study and did not differ in their baseline clinical characteristics (including age, sex, and renal function). For those patients in the previous study, 12/31 (39%) achieved SUA levels ≤ 0.36 mmol/l (p < 0.05 vs allopurinol-treated patients in the current study).

Table 2. Characteristics of the patients with allopurinol hypersensitivity reactions.

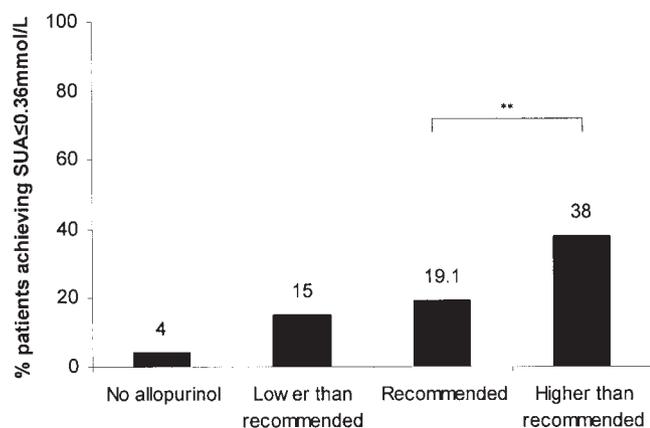| Patient	Age	Sex	Actual Allopurinol Dose, mg/day	Recommended Allopurinol Dose, mg/day	Reaction
1	45	M	300	300	Angioedema and rash
2	58	F	100	200	Pruritic rash
3	80	F	100	100	Generalized erythematous rash
4	42	M	100	250	Pruritic rash

Figure 2. SUA levels based on allopurinol dose guidelines. Percentage of patients achieving SUA ≤ 0.36 mmol/l. **p < 0.01.

DISCUSSION

Our study has demonstrated that dosing of allopurinol based on published guidelines does not achieve the major therapeutic goal of lowering SUA in our population of patients with gout. The electronic allopurinol dose calculator was introduced into our institution in an attempt to improve patient care and safety. The calculator and guidelines have been widely adopted and have led to significant changes in prescriber behavior. Indeed, the reported use of the calculator (for 79% of allopurinol prescriptions) was similar to the observed prescription of allopurinol (recommended doses in 70.9% patients prescribed allopurinol). Unfortunately, this intervention, with close adherence to treatment guidelines, may have led to undertreatment of patients with gout.

Severe allopurinol toxicity has been associated with other risk factors in addition to renal impairment, such as use of thiazide diuretics, treatment of asymptomatic hyperuricemia, and specific genetic risk factors[7,17,18]. Further, no study has systematically demonstrated that dose reduction in patients with renal impairment, as recommended by current guidelines, reduces the risk of severe hypersensitivity reactions. In our population, there was no clear relationship between allopurinol dosing and adverse drug reactions. Indeed, 2 of the 4 cutaneous reactions occurred in patients taking lower than recommended allopurinol doses, and none were found in those receiving higher than recommended doses. These findings are in accord with the report of Vazquez-Mellado and colleagues[11]. However, this group did not address whether target SUA levels were achieved in their patients taking recom-

mended doses of allopurinol. Our data extend these previous observations to raise further questions about the validity of the allopurinol dosing guidelines.

The majority of our patients taking allopurinol did not obtain SUA levels low enough to achieve tophus regression. Many of the patients in our study were of Maori or Pacific ethnic origin. This may limit the general applicability of this study, as these populations frequently have severe gout[19,20]; moreover, the guidelines were not devised for these populations. However, analysis based on ethnicity has indicated that titration to higher doses, above those recommended by current guidelines, was associated with greater levels of normouricemia in both Polynesian and non-Polynesian patients. Therefore, we believe that these results are of general relevance. Confirmation of these results in other populations would be of great interest.

We recognize that our study has limitations; in particular, a retrospective study cannot accurately assess important clinical outcomes such as flare frequency and tophus regression. It is difficult to assess patient compliance to medications in a retrospective manner, and it is possible that compliance may have varied between the groups or over time, leading to differences in SUA levels independent of allopurinol dose. SUA levels fluctuate, and a single measure may not accurately reflect overall control of hyperuricemia. The cross-sectional study design did not allow for analysis of changes in SUA level from baseline or the effect of initial allopurinol dosing on the frequency of adverse drug reactions. In addition, our study was limited to secondary rheumatology care, rather than primary care where many patients with gout are treated. However, despite these reservations, we believe that this study has highlighted the difficulties of achieving normouricemia in clinical practice using currently available treatment guidelines.

The original purpose of the dosing guidelines was to reduce the risk of serious adverse reactions related to overdosing with allopurinol while not reducing the efficacy significantly. These guidelines may be most suitable for the starting dose in an individual patient, as suggested in the recently published quality of care indicators for gout[21]. The SUA target would then be pursued by a range of approaches including further dose adjustment, with care and consideration if the dose exceeds the suggested guidelines. This would be particularly relevant for those patients with recurrent acute gout attacks or tophaceous disease. However, the safety of such an approach in patients with renal impairment remains uncertain.

Table 3. Number (%) of patients achieving SUA ≤ 0.36 mmol/l based on ethnicity.

	Recommended Allopurinol Dose	Higher Than Recommended Allopurinol Dose	p
Pacific	4/70 (6)	4/20 (20)	< 0.05
Maori	13/39 (33)	5/11 (46)	NS
European/other	9/32 (28)	6/10 (60)	< 0.05

In summary, longterm allopurinol dose reduction according to published clinical guidelines has not led to adequate control of hyperuricemia in our population of patients with gout. Given the very small risk of severe adverse drug reactions in patients taking allopurinol, the calculated risk of persistent hyperuricemia may be greater than the risk of allopurinol related adverse events, especially for patients with severe gout. These data highlight the need for further studies to clarify the safe dosing of allopurinol, particularly in patients with significant renal impairment.

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