Allopurinol dosage selection: relationships between dose and plasma oxipurinol and urate concentrations and urinary urate excretion

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- 1 Allopurinol usage in 50 patients of a city teaching hospital was surveyed.
- 2 The plasma concentrations of oxipurinol and uric acid and the urinary production of uric acid were examined.
- 3 The daily doses of allopurinol ranged from 50 to 1200 mg but 83% of patients were taking 300 mg daily.
- 4 A wide range of plasma oxipurinol concentrations was observed from 2.8 to 55.8 mg l⁻¹ with a mean $\pm$ s.d. of 15.2 $\pm$ 11.7 mg l⁻¹.
- 5 The population studied included a high proportion of patients with renal impairment and creatinine clearance was a significant determinant of oxipurinol concentrations ($P < 0.005$).
- 6 There was no significant correlation between plasma urate and plasma oxipurinol concentrations and only a few plasma urates were above the upper limit of the reference range of the laboratory.
- 7 It was apparent that many patients were taking unnecessarily high daily doses of allopurinol and that renal status was not always considered when deciding dosage regimens of allopurinol.

Keywords allopurinol oxipurinol uric acid renal function dose-response

Introduction

Allopurinol is widely employed to control hyperuricaemia. Accepted indications include recurrent acute gout, tophaceous gout and urate-induced renal disease. Additionally, the drug is used to prevent the consequences of acute hyperuricaemia seen in association with various haematological and malignant diseases, particularly during the pharmacological treatment of these diseases (Emmerson, 1983).

Allopurinol and its active metabolite, oxipurinol, inhibit the enzyme xanthine oxidase, which is instrumental in the production of uric

acid from hypoxanthine and xanthine. Furthermore the accumulation of the purine nucleotides, adenylic acid, guanylic acid and inosinic acid, due to the combined effects of xanthine oxidase blockade and the hypoxanthine-guanine phosphoribosyl transferase salvage pathway, leads to suppression of the activity of the purine synthetic pathway (Elion, 1978).

Allopurinol is rapidly metabolized to oxipurinol which has a half-life of about 16 h in subjects with normal renal function (Hande *et al.*, 1978). Oxipurinol is a potent inhibitor of xanthine

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oxidase and the longer residence of oxipurinol in the body means that it accounts for the majority of the effect of allopurinol (Spector, 1977). Oxipurinol is cleared from the body through the kidneys and accordingly, the dosage of oxipurinol should be reduced in patients with renal impairment (Elion *et al.*, 1968; Hande *et al.*, 1984). Severe toxic reactions to allopurinol are observed uncommonly but can be fatal (Hande *et al.*, 1984; Singer & Wallace, 1986). Exfoliative dermatitis, hepatitis and progressive renal failure are features of the toxic reaction to this drug. These severe adverse effects of allopurinol are almost always observed in patients with renal impairment and, usually, when the dose of drug is excessive for the patient's renal status (Hande *et al.*, 1984). Despite this information, it was suspected that many patients continued to receive larger doses of allopurinol than necessary.

This paper surveys allopurinol usage in 50 patients of a university affiliated, city teaching hospital. The concentrations of oxipurinol observed and the effect of allopurinol treatment upon urate concentrations in plasma and urine are presented.

Methods

This study was approved by the Ethics and Research committee of St Vincent's Hospital, Sydney and all patients gave informed consent for their participation in the survey. During the period of the survey, all patients prescribed allopurinol were identified through the Hospital Pharmacy and approached to enter the study. Most were inpatients on the rheumatology, renal, oncology and general medical services. A small number were outpatients of the rheumatology service.

The following information about the patients was obtained: age, sex, weight, disease categories and daily dose of allopurinol. As often as possible the patients were asked to regularize their time of dosing with allopurinol in the days before the study was performed. Venous blood (10 ml) was collected into VacutainerTM tubes containing a small amount of sodium edetate (for allopurinol and oxipurinol assays) and sodium heparin (for plasma biochemistry) respectively, as close as possible to the 'trough' point of the daily dosing schedule, that is, just before a dose of allopurinol. In order to measure the output of urate and creatinine, a 24 h urine collection was made which encompassed the collection of blood samples. The creatinine clearance was calculated by dividing the urinary output of creatinine over

24 h by the plasma creatinine taken during the urinary collection period. Creatinine clearance also was estimated from the patient's age, weight and plasma creatinine concentration using the formula of Cockcroft & Gault (1976).

Plasma allopurinol and oxipurinol concentrations were measured by reversed phase high performance liquid chromatography according to the method of Kramer & Feldman, (1979) but with a minor modification, namely that 8-methylxanthine was used as the internal standard instead of paracetamol. As a result, total chromatography time was reduced from 30 to 15 min. The intra- and inter-assay coefficients of variation of the assay were < 6%. All assays were performed in duplicate. Plasma and urinary creatinine concentrations were measured using a standard auto-analyser (Beckman, Astra). The creatinine measurement in this system is dependent upon the development of a colour reaction with alkaline picrate. Plasma and urinary urate measurements were performed using a routine but specific, uricase/catalase linked method (Beckman Instruments, USA). This method is based upon the disappearance of uric acid from the sample and the reaction is followed by measuring the absorbance of the solution at 340 nm.

All results are expressed as mean $\pm$ s.d. unless otherwise stated. Statistical tests performed were least squares linear regression, stepwise linear regression and analysis of variance. The factor required for the conversion of plasma oxipurinol concentration $\mu\text{g ml}^{-1}$ to S.I. units ($\mu\text{mol l}^{-1}$) is 6.57.

Results

The average age of the patients admitted to the study was 60.8 ± 11.6 years, with a range of 35 to 90 years. There were 40 males and 10 females. The indications for allopurinol were: history consistent with gout, including urate nephrolithiasis (39 patients); hyperuricaemia in association with renal disease but without a history of gout (four patients); prevention of hyperuricaemia in association with the treatment of a malignant disease (three patients); others (four patients). The duration of allopurinol therapy was 6 ± 7.5 years with a range of 0.1 to 30 years. The daily doses of allopurinol ranged from 50 to 1200 mg daily but 82.8% of the patients were taking 300 mg daily (Figure 1).

Allopurinol concentrations were undetectable in the plasma samples, which were drawn more than 3.5 h after a dose of allopurinol, in keeping with the short half-life of elimination of allopurinol. The majority of plasma samples for

Figure 1 Frequency distribution of daily doses of allopurinol given to this study population of 50 patients.

Figure 2 The relationship between dose of allopurinol corrected for patient weight and steady-state plasma oxipurinol concentrations: $y = 5.02 + 2.47x$, where y = plasma oxipurinol in mg l^{-1} and x = allopurinol dose in $\text{mg kg}^{-1} \text{ day}^{-1}$ ($r = 0.32$; $P < 0.025$, analysis of variance F test; $n = 48$).

drug concentration measurement were drawn within $\pm 20\%$ of the estimated time of the true trough (pre-dose) concentration (75% of samples). Only three subjects were taking allopurinol doses more frequently than every 24 h.

A wide range of plasma oxipurinol concentrations was observed in this patient population: from 2.8 to 55.8 mg l^{-1} with a mean $\pm$ s.d. of $15.2 \pm 11.7 \text{ mg l}^{-1}$ (Figure 2). Linear regression analysis indicated that the dose of allopurinol corrected for the patient's weight was a significant, but weak, determinant of trough plasma oxipurinol concentrations ($r = 0.32$; $P < 0.025$, analysis of variance F test; $n = 48$). The slope of this relationship was $2.47 \text{ kg day l}^{-1}$ and the intercept was 5.02 mg l^{-1} . Data from two patients were excluded from this analysis as oxipurinol was not detectable in plasma despite allopurinol

Figure 3 Relationship between creatinine clearance and steady-state plasma oxipurinol concentration corrected for daily dose of allopurinol: $y = 7.14 - 0.05x$, where y = plasma oxipurinol in mg l^{-1} corrected for allopurinol dose in $\text{mg kg}^{-1} \text{ day}^{-1}$ and x = creatinine clearance in ml min^{-1} ($r = 0.57$; $P < 0.005$, analysis of variance F test; $n = 31$).

doses of approximately 12 and 16 $\text{mg kg}^{-1} \text{ day}^{-1}$, respectively. The population studied included a high percentage of patients with renal impairment (Figure 3) and creatinine clearance was a significant determinant of oxipurinol concentrations ($r = 0.57$; $P < 0.005$, F test; $n = 31$; Figure 3). In this analysis, the effect of dose was accounted for by dividing the plasma oxipurinol concentrations by the daily dose of allopurinol in mg kg^{-1} . Not all subjects could be included in this regression analysis as some creatinine clearances were unavailable, usually because of a problem in achieving a satisfactory urine collection. In the 31 subjects who had a formal creatinine clearance measurement from a 24 h urinary collection, there was a reasonable correlation with the estimate of creatinine clearance according to the method of Cockcroft & Gault (1976) ($r = 0.85$). Therefore, the analysis of the effect of creatinine clearance upon plasma oxipurinol concentrations was repeated using the creatinine clearances estimated for all subjects from their plasma creatinine concentrations according to the method of Cockcroft & Gault (1976). In this re-analysis, including all subjects bar the two who were clearly non-compliant, creatinine clearance was again a significant determinant of plasma oxipurinol concentrations ($r = 0.56$; $P < 0.0005$, F test; $n = 48$).

In order to determine the relative contributions of allopurinol dose, creatinine clearance (Cockcroft & Gault, 1976) and age to the plasma oxipurinol concentrations observed, stepwise linear regression was performed. Only allopurinol dose and the patient's creatinine clearance were found to contribute significantly to the regression.

Figure 4 The relationship between steady-state plasma oxipurinol concentrations and plasma urate concentrations. There was no significant relationship between these two variables.

Figure 5 The relationship between 24 h urinary excretion of uric acid and steady-state plasma oxipurinol concentrations: $y = 3.73 \cdot 10^{(-0.03x)}$ where y = uric acid excretion in $\text{mmol } 24 \text{ h}^{-1}$ and x = plasma oxipurinol in mg l^{-1} ($r = 0.086$; $n = 31$).

The relationship describing plasma oxipurinol concentrations, was: $y = 17.414 + 2.68 \cdot \text{allopurinol dose (mg kg}^{-1}) - 0.184 \cdot \text{creatinine clearance ml min}^{-1}$, where y = plasma oxipurinol in mg l^{-1} . The correlation coefficient, r , for this relationship was 0.63 and the analysis of variance F statistic was 15.06 with 48 degrees of freedom.

There was no significant correlation between plasma urate concentrations and the wide range of plasma oxipurinol concentrations observed in this study (Figure 4). Only a few plasma urate concentrations were above the upper limits of the laboratory's reference range (0.25–0.5 mmol l^{-1}). Twenty-four hour urinary urate excretions were available for 32 patients and showed an exponential relationship to plasma oxipurinol concentrations, $y = 3.73 \cdot 10^{(-0.03x)}$ where y = 24 h urinary urate excretion in $\text{mmol } 24 \text{ h}^{-1}$ and x = plasma oxipurinol concentrations in mg l^{-1} ($r = 0.86$; Figure 5).

Discussion

Data have been published recently indicating that dosages of allopurinol should be reduced in patients with renal impairment (Hande *et al.*, 1984; Cameron & Simmonds, 1987). Also, it has been known for some time that serious adverse effects of allopurinol are almost always observed in patients with renal impairment in whom the dose has not been reduced appropriately. Despite this knowledge, this survey indicates that a significant proportion of patients in a teaching hospital given allopurinol for a variety of indications are being exposed to excessive daily doses and thus the potential for serious adverse effect. Allopurinol formulation, as a single 300 mg tablet, may have contributed to the lack of appreciation that 300 mg may be too much for an individual patient. In particular, it is apparently commonly forgotten that the elderly may have significant reductions in creatinine clearance, despite relatively normal plasma creatinine concentrations. Although possible adverse effects to this medication were not specifically looked for, there were no reports of severe reactions to this drug in this population of patients.

The study also showed that there was great variability in steady-state plasma concentrations of oxipurinol for given doses of allopurinol. A significant proportion of the variability was explained by the patient's creatinine clearance and the dose expressed in mg kg^{-1} , but considerable variability remained unexplained. The linear regression of plasma oxipurinol against creatinine clearance presented here is similar, with respect to slope and intercept, to that published by Hande *et al.* (1984), once correction for different units has been made. Due to the nature of this survey, absolute steady-state conditions of allopurinol dosing cannot be assured. Additionally, all plasma oxipurinol samples were not drawn precisely at the trough point of the dosing interval, although the long half-life of oxipurinol, considerably longer than young normals in the majority of these patients as a result of age and renal impairment, would render this a relatively small source of variability. Also, defective compliance was likely to be a source of variability as suggested by two subjects on high doses of allopurinol who had no oxipurinol detectable in their plasma.

An optimal concentration range for steady-state plasma oxipurinol concentrations has not been established formally. This is partly because reliable and sensitive assays for allopurinol and oxipurinol have only recently become available. Another difficulty is that plasma urate concentrations are influenced not only by xanthine

oxidase activity but also by the dietary intake of urate precursors, release of urate from tophaceous deposits and by renal function. Thus, plasma urate is not always a reliable indicator of xanthine oxidase activity. The availability of a therapeutic range for plasma oxipurinol concentrations would be useful in certain clinical situations.

Generally, review of clinical status and plasma urate concentrations both before and during therapy will suffice from the point of view of monitoring the efficacy of this drug in patients. However, as suggested in this survey, this method of monitoring allopurinol therapy may not identify patients being given unnecessarily high doses of allopurinol and who are therefore at greater risk for toxicity. Thus, the relationship between plasma oxipurinol and plasma urate observed in this survey is remarkable because the majority of plasma urate values are in the normal range and there is little decrement in plasma urate concentrations with higher plasma oxipurinol concentrations. It should be noted that it has been suggested that 0.42 mmol l^{-1} is an appropriate ceiling for plasma urate in gout patients treated with allopurinol (Emmerson *et al.*, 1987; Scott, 1987). Nevertheless, our findings suggest that smaller doses of allopurinol might suffice in many patients. Alternatively, it could be argued that the dose of allopurinol could have been increased to bring the plasma urate into the normal range in the patients in this survey. This appears to be most unlikely as more than 80% of the subjects were taking a standard dose of 300 mg allopurinol daily.

In this cross-sectional survey, the 24 h urinary urate collections were strongly related to plasma oxipurinol concentrations. This parameter is probably a reasonable method of assessing the change in urate production in an individual patient, assuming that the intake of urate precursors in the diet is controlled, which was not the case in this survey.

An additional problem with simply monitoring clinical status and plasma urate concentrations is that a very small proportion of gout sufferers do not respond appropriately to allopurinol. This is manifest by failure of plasma urate to fall and continued deposition of urate as tophaceous deposits despite increasing doses of allopurinol (Gibson *et al.*, 1983). Availability of plasma oxipurinol concentrations and knowledge of the

range of plasma concentrations of oxipurinol associated with efficacy would be extremely useful in evaluating such patients.

One approach to establishing a concentration-response relationship for allopurinol has been to relate the concentrations of oxipurinol to the degree of inhibition of the enzyme xanthine oxidase using the conversion of 1-methylxanthine to 1-methylurate *in vivo* as an index of xanthine oxidase activity (Day *et al.*, 1988). This method is based upon the knowledge that 1-methylxanthine, a metabolite of caffeine, paraxanthine and theophylline is metabolized to 1-methyluric acid by the enzyme xanthine oxidase (Birkett *et al.*, 1983). This work, performed in normal volunteers, suggests that there is 90% inhibition of xanthine oxidase for the oxidation of 1-methylxanthine at concentrations of oxipurinol of about 3 mg l^{-1} (Day *et al.*, 1988). Thus, the normal volunteer data would also suggest that the population surveyed in the present study was excessively dosed with allopurinol.

Measurement of plasma xanthine concentrations which increase as a result of allopurinol-induced xanthine oxidase inhibition, may be another method of assessing xanthine oxidase enzyme activity *in vivo*. Emmerson *et al.* (1987) have suggested that plasma concentrations of xanthine between $6\text{--}9 \text{ }\mu\text{mol l}^{-1}$ indicate satisfactory inhibition of xanthine oxidase. These levels of xanthine were achieved at concentrations of oxipurinol, 6–9 h post-dose, of $30\text{--}100 \text{ }\mu\text{mol l}^{-1}$ ($5\text{--}15.2 \text{ mg l}^{-1}$) and Emmerson *et al.* (1987) have suggested that this concentration range of oxipurinol may be optimal for effective control of hyperuricaemia in patients with normal renal function. A considerable proportion of our patient population (32%) had oxipurinol concentrations in excess of 15 mg l^{-1} , again suggesting excessive doses of allopurinol. However, further work is required to define precisely the optimal concentration range for plasma oxipurinol concentrations for efficacy with a low risk of toxicity.

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