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Pharmacodynamics of oxypurinol after administration of allopurinol to healthy subjects

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1 Eight healthy subjects received 50, 100, 300, 600 and 900 mg allopurinol daily for 1 week each, in random order with 1 week separating each treatment period. The pre-dose plasma concentration of oxypurinol, the extent of inhibition of xanthine oxidase, plasma urate concentration and urine urate excretion rate were assessed on the last 2 days of each treatment week.

2 The ratio of 1-methyluric acid (1MU) over 1-methylxanthine (1MX) in the urine, following a dose of 50 mg 1MX infused intravenously over 20 min, was used to measure the inhibition of xanthine oxidase.

3 The steady-state plasma concentration of oxypurinol increased linearly with increasing dose of allopurinol between 50 mg to 600 mg day^{-1}, with a weak indication of saturation at the higher 900 mg day^{-1} dose rate.

4 The relationships between plasma oxypurinol concentration and xanthine oxidase inhibition (1MU/1MX ratio), plasma urate concentration and urine urate excretion rate were fitted to an inhibition sigmoid E_{max} model and the C_{50} values for oxypurinol were 26.38 ± 4.87, (mean $\pm$ s.d.) 36.58 ± 8.36 and 24.61 ± 9.08 μM, respectively.

5 1MU/1MX ratio appeared to be a reliable index of xanthine oxidase activity *in vivo* as the C_{50} for oxypurinol observed for 1MU/1MX ratio, plasma urate concentration and urine urate excretion rate were similar.

6 The concentration of oxypurinol required for inhibition of xanthine oxidase, as indicated by C_{50}, was lower than those often observed in clinical practice.

Keywords allopurinol oxypurinol xanthine oxidase urate pharmacodynamics

Introduction

Allopurinol was first synthesized in the 1950s [1] for the purpose of increasing the efficiency of antineoplastic drugs such as mercaptopurine. It was discovered that allopurinol was not only a substrate, but also a potent inhibitor, of xanthine oxidase. Xanthine oxidase is involved in purine metabolism and it mediates the conversion of hypoxanthine to xanthine and xanthine to uric acid. Xanthine oxidase inhibition leads to a decrease in uric acid production and allopurinol has been an effective drug for the treatment of hyperuricaemia associated with gout [2] and haematological malignancies [3]. Additionally, the drug has other applications in the areas of ischaemia-reperfusion injury, treatment of protozoal diseases and prevention of the development of urinary tract stone [4].

After an oral dose, allopurinol is well absorbed from the intestinal tract [5]. The maximum allopurinol concentration is achieved after 1 h and 60% to 70% of allopurinol is converted rapidly to oxypurinol by xanthine oxidase [6]. Oxypurinol has a half-life of approximately 16 h compared with the parent drug, allopurinol, which has a half-life of 1 to 2 h [6]. Oxypurinol undergoes net renal reabsorption which has been shown to be influenced by changes in urine pH, glomerular filtration and uric acid concentrations [7].

The hypouricaemic action of allopurinol and its

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metabolite, oxypurinol, is due to the inhibition of xanthine oxidase, thus reducing the production of uric acid directly as a result of enzyme inhibition and indirectly due to negative feedback of the rate limiting enzyme for purine synthetic pathway, PRPP synthetase, by adenosine and guanosine nucleotides. Since oxypurinol has a longer half-life than allopurinol, it is thus relevant to relate the therapeutic effect of allopurinol with the plasma concentration of oxypurinol. The plasma concentration of oxypurinol is found to correlate with allopurinol dosage [8] and it is also found to correlate with renal glomerular function. The reduction of plasma urate concentrations has been used as an indication of efficiency of allopurinol therapy. However, the concentration of urate in plasma depends on many factors such as endogenous and exogenous production of urate and renal function. A better measure of efficiency of allopurinol therapy would be to measure the level of inhibition of the target enzyme, xanthine oxidase. 1-Methylxanthine (1MX) is a good substrate of xanthine oxidase and is metabolized exclusively to 1-methyluric acid (1MU) [9, 10]. Previously, Birkett *et al.* [10] have shown that allopurinol was found to markedly decrease the conversion of 1MX to 1MU. More recently, Day *et al.* [11] used the ratio of 1MU to 1MX as an index of xanthine oxidase activity in relation to plasma concentration of oxypurinol in healthy volunteers after the administration of allopurinol. These workers found the concentration of oxypurinol needed for almost complete inhibition to be substantially less than that often observed in clinical practice.

The present study aims to investigate further the pharmacodynamics of allopurinol by extending the allopurinol dosage from a maximum of 600 mg day^{-1} to 900 mg day^{-1} and investigating the relationship between plasma concentration of oxypurinol and xanthine oxidase activity over this wider dosage range. The plasma urate concentrations and urine excretion of urate in relation to plasma oxypurinol concentration and xanthine oxidase inhibition were also examined for the first time.

Methods

Subjects and study design

Informed consent was obtained from eight healthy volunteers, aged between 21 and 26 years, seven of whom were male. All subjects were non smokers, not receiving other medications and abstained from alcohol during the period of the study. The doses of allopurinol studied were 50, 100, 300, 600 and 900 mg day^{-1}. Daily allopurinol doses were administered orally using a standard formulation as either half of a 100 mg tablet, one 100 mg tablet, one 300 mg tablet, two 300 mg tablets or three 300 mg tablets, respectively. Each treatment was administered as a single daily dose for 1 week with at least 1 week in between different allopurinol dose treatment phases. The treatment order was randomized according to a Latin Square design with five possible treatment orders and two subjects following each of these orders. Compliance was promoted by the use of compliance boxes. This study had the approval of the Research and Ethics Committee of St Vincent's Hospital and the Committee on Experimental Procedures of the University of New South Wales.

Assessment of xanthine oxidase activity

Prior to the administration of allopurinol, each subject had their baseline xanthine oxidase activity assessed on 2 consecutive days after 3 days on a methylxanthine free diet (as described previously by Day *et al.* [11]). The activity of xanthine oxidase *in vivo* was determined using the concentration ratio of 1MU to 1MX in urine 4 h after infusing 20 ml of a sterile solution containing 50 mg of 1MX intravenously via an antecubital vein over 20 min using a constant volume infusion rate pump (Terumo STC-521). The 1MX infusion was prepared under aseptic conditions as previously described [11].

Sample collection protocol

Blood and urine samples were taken after the administration of allopurinol on days 6 and 7 of each treatment phase. A 20 h urine collection began after administration of allopurinol on these days. The last 4 h of the 24 h dosing interval were used to study the xanthine oxidase activity and the infusion of 1MX was given at this time. The subjects had pulse and blood pressure monitored at 5 min intervals throughout infusion and ECG monitoring for at least their first 1MX infusion. Complete 4 h urine collection commenced with the 1MX infusion and the urine samples were preserved with an equal volume of 0.1 M acetic acid. Blood (10 ml) was drawn just before the doses of allopurinol to coincide with the trough concentration of oxypurinol. Samples were collected in Vacutainer™ glass tubes containing sodium edetate.

Analysis of urine and plasma samples methods

The plasma concentrations of oxypurinol were determined using the h.p.l.c. method of Kramer & Feldman [12], except that 8-methylxanthine was used as the internal standard instead of paracetamol. This modification reduced the chromatography time from 30 min to 15 min. All assays were performed in duplicate. The inter- and intra-assay coefficient of variation was less than 6% [11]. The concentrations of 1MX and 1MU from the 4 h urine samples were measured according to the procedure of Birkett *et al.* [10]. The results were expressed as the ratio of 1MU/1MX in mg equivalents of 1MX. The concentration of urate in plasma and 20 h urine samples were determined by 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.

Data analysis

A preliminary data analysis found that a sigmoid E_{max} model, rather than a linear or log-linear model, most appropriately described that relationship between steady state oxypurinol plasma concentration and the ratio of 1MU/1MX in urine, the urine urate excretion rate (mol min^{-1}) or the plasma urate concentration (mM), as judged by a comparison of Akaike Information Criterion and the pattern of the weighted residuals [13].

An inhibition sigmoid E_{max} model that examines the decrease of a response measure from a pretreatment baseline (Ro) was used, as shown in Equation 1

$$R = Ro - \frac{E_{max} \cdot C^{\gamma}}{C_{50}{}^{\gamma} + C^{\gamma}} \quad (1)$$

where R is one of three response measures that were investigated in this study, being either the ratio of 1MU/1MX in urine, the urine urate excretion rate (mol min^{-1}) or the plasma urate concentration (mM). E_{max} is the maximum decrease in the baseline effect that can be achieved by oxypurinol, C is the steady state plasma concentration of oxypurinol, C_{50} is the steady state plasma concentration of oxypurinol required to produce an effect that is 50% of the E_{max} and γ is the Hill exponent that is a measure of steepness of the dose response curve. The conversion factor for oxypurinol concentrations is 1 mg l^{-1} is equivalent to 6.58 μM.

A population approach which considers both random and fixed effects was employed to fit Equation 1 to the concentration-effect data. The population pharmacokinetic-pharmacodynamic software package, P-PHARM Ver 1.3a, which uses an EM-like algorithm was employed in the non-linear mixed effects modelling [16]. The random effects were considered to be made up of both intersubject variability and residual error (comprising of intrasubject variability and measurement error). Pharmacodynamic parameters (Ro, E_{max}, C_{50} or γ) were assumed to be normally distributed with a population mean (p_{pop}) and variance (ω). The variance of the residual error (σ) was described by a heteroscedastic (proportional to the squared valued of the predicted value) model.

The starting estimates for the population analysis were obtained from a standard two-stage analysis, using concentration-effect data from six subjects and further refined using a simplex search option in the P-PHARM software to minimize the difference between predicted and observed data. Individual posterior Bayesian estimates of pharmacodynamic parameters were generated using P-PHARM.

Results

The mean (±s.d.) steady-state oxypurinol concentration at 50, 100, 300, 600 and 900 mg day^{-1} of allopurinol was 1.77±1.59, 2.67±1.59, 5.59±1.50, 9.56±1.92 and 12.21±2.13 mg l^{-1}. The oxypurinol concentration at steady-state was found to increase in a linear fashion over the dosage range of 50 to 600 mg day^{-1} of allopurinol, which is in agreement with our previous study [11]. There was a less than proportional increase in the steady-state concentration of oxypurinol at the highest dose level. There was considerable variation between individuals in steady-state plasma oxypurinol concentrations for given doses of allopurinol as indicated in Figure 1 which shows mean steady-state concentration data for each of the eight subjects.

Xanthine oxidase activity decreased with increasing steady-state plasma oxypurinol concentrations (Figure 2). The inhibition of xanthine oxidase activity, expressed as the 1MU/1MX ratio in the 4 h urine samples, over the oxypurinol concentration measured was fitted to Equation 1. The C_{50} of plasma oxypurinol concentration for inhibition of the formation of 1MU

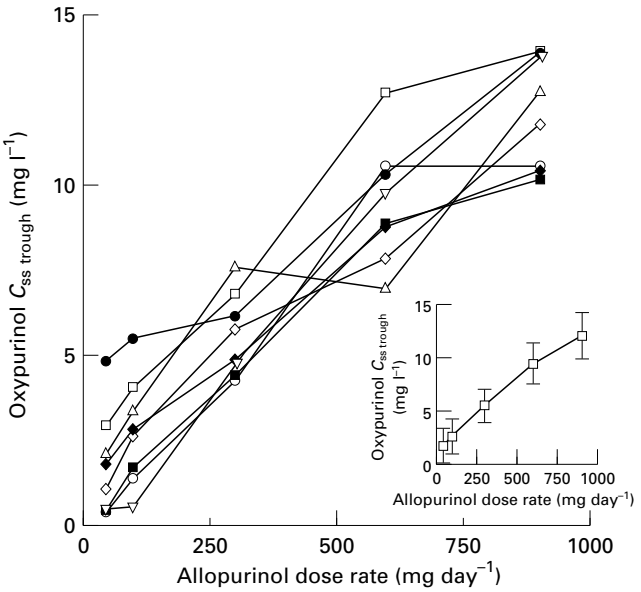

Figure 1 The relationship between the oxypurinol steady-state trough plasma concentration ($C_{ss,trough}$) and the allopurinol dose rate (mg day^{-1}) for eight subjects. Inset: overall mean relationship between $C_{ss,trough}$ and allopurinol dose rate. Error bars represent standard deviation. 1 mg l^{-1} of oxypurinol is equivalent to 6.58 μM.

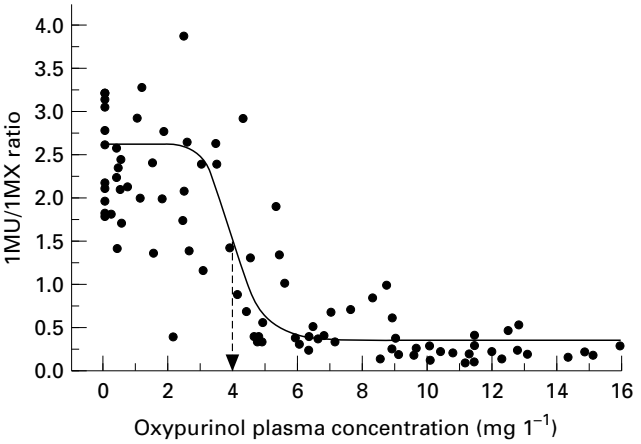

Figure 2 Ratio of 1-methyluric acid and 1-methylxanthine *vs* oxypurinol plasma concentration. Observed data (filled circles) and population fit (solid line) are shown. The dotted line indicates the C_{50} (Table 1). 1 mg l^{-1} of oxypurinol is equivalent to 6.58 μM.

from 1MX *in vivo* was 4.01 mg l^{-1} (26.38 μM) with an intersubject CV of 18.5% (Table 1). The Ro and E_{max} ratios were predicted to be 2.63 and 2.27, respectively and γ was 8.92 (range of Bayesian posterior estimates was 4.59 to 10.95). Using these data it is possible to calculate the oxypurinol concentration when xanthine oxidase is maximally inhibited (90% inhibition; C_{90}) which was 5.13 mg l^{-1} (33.75 μM).

A decrease of plasma urate concentration was observed over the increasing steady-state plasma oxypurinol concentration (Figure 3). The data for one subject with the allopurinol dose of 900 mg day^{-1} was not included in the model fitting as plasma urate concentrations were about six times higher than the average data (plasma urate concentration of 0.5 mM and 0.7 mM as compared with the average of 0.2 mM). The C_{50} of plasma oxypurinol concentration for the decrease of plasma urate concentration was 5.56 mg l^{-1} (36.58 μM) with an intersubject CV of 22.8%. The Ro and E_{max} were predicted to be 0.35 mM and 0.29 mM, respectively (Table 1), while γ was 1.22.

The urine urate excretion rate decreased over the steady-state plasma oxypurinol concentration measured (Figure 4). The population mean C_{50} of plasma oxypurinol concentration for the decrease of urine urate excretion rate was 3.74 mg l^{-1} (24.61 μM) with an intersubject CV of 36.8%. The Ro and E_{max} were predicted to be 3.53 mol min^{-1} and 3.26 mol min^{-1}, respectively (Table 1), and γ was 1.08.

Table 1 Population mean pharmacodynamic parameters for oxypurinol after the administration of allopurinol in healthy subjects ($n=8$)

	Mean	*s.d.*	*CV**
1MU/1MX ratio			
C_{50} (mg l^{-1})	4.01 (26.38 μM)	0.74	19%
γ	8.92	3.91	44%
E_{max}	2.27	0.12	5%
Ro	2.63	0.12	5%
σ#			0.06
Plasma urate concentration			
C_{50} (mg l^{-1})	5.56 (36.58 μM)	1.27	23%
γ	1.22	0.51	42%
E_{max} (mM)	0.29	0.04	15%
Ro (mM)	0.35	0.03	8%
σ (mM)			0.05
Urine urate excretion rate			
C_{50} (mg l^{-1})	3.74 (24.61 μM)	1.38	37%
γ	1.08	0.14	13%
E_{max} (mol min^{-1})	3.26	0.16	5%
Ro (mol min^{-1})	3.53	0.12	4%
σ (mol min^{-1})			0.05

* coefficient of variation of intersubject variability (ω) of mean estimate

residual error (σ) expressed in response units

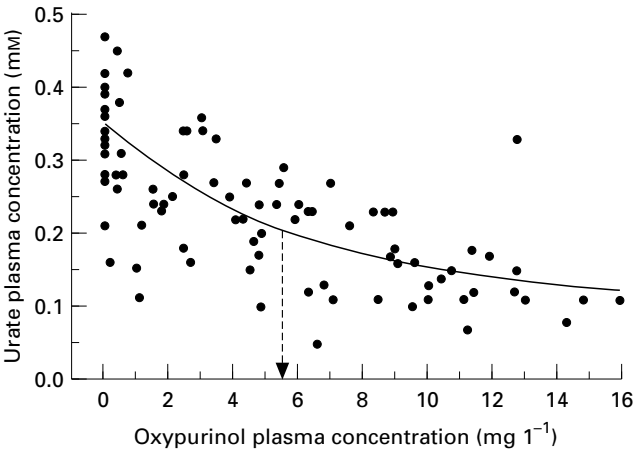

Figure 3 Plasma urate concentration (mM) versus oxypurinol plasma concentration. Observed data (filled circles) and population fit (solid line) are shown. The dotted line indicates the C_{50} (Table 1). 1 mg l^{-1} of oxypurinol is equivalent to 6.58 μM.

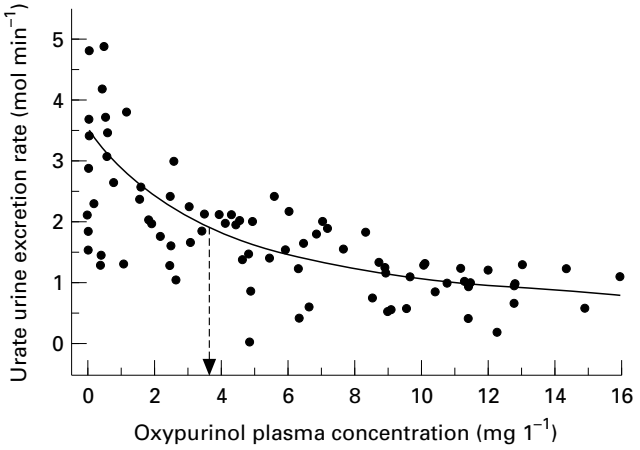

Figure 4 Urinary excretion rate of urate (mol min^{-1}) versus oxypurinol plasma concentration. Observed data (closed circles) and population fit (solid line) are shown. The dotted line indicates the C_{50} (Table 1). 1 mg l^{-1} of oxypurinol is equivalent to 6.58 μM.

Discussion

The steady-state concentration of oxypurinol increased over the dosage range of allopurinol (Figure 1) with considerable variation being observed between the individuals studied at the given doses of allopurinol. There appeared to be a linear relationship between the steady-state plasma oxypurinol concentration and allopurinol dose though the oxypurinol concentration did not appear to increase proportionally at higher allopurinol dose range (600 to 900 mg day^{-1}), suggesting saturation of xanthine oxidase or the saturation of the tubular reabsorption of oxypurinol. However, the intersubject variability made it difficult to verify the saturable relationship at the higher allopurinol dosage range. Oxypurinol, having a longer half-life than the parent allopurinol, is probably responsible for most of the urate-lowering effect observed after allopurinol administration. Therefore, the knowledge of the relationship between allopurinol dose and steady-state plasma oxypurinol concentration and the range of oxypurinol

concentration associated with efficacy would be useful to ensure effective treatment of patients with allopurinol.

The ratio of 1MU/1MX in the 4 h urine samples decreased with increasing concentration of oxypurinol in the plasma (Figure 2). 1MX is converted to 1MU and this reaction is catalysed by xanthine oxidase [10]. The ratio of 1MU to 1MX has been used as an index of xanthine oxidase activity [11, 14] and the decrease in 1MU/1MX indicated decreased xanthine oxidase activity over the increasing concentration of oxypurinol. In this study the C_{50} for the relationship between oxypurinol concentrations and the 1MU/1MX ratio was 4.01 mg l^{-1} (26.38 μM) which is slightly higher, but in agreement with, C_{50} estimates obtained in previous studies (1.40 ± 0.46 mg l^{-1} (9.21 μM) [11] and 3.0 ± 1.1 mg l^{-1} (19.74 μM) [14]).

The C_{90} in this study (5.13 mg l^{-1}) confirms the finding that the mean oxypurinol concentrations found during routine therapy with standard doses of allopurinol (15.2 mg l^{-1}; 100 μM) [15], is far in excess of that required to inhibit the activity of xanthine oxidase, suggesting that patients in general are given excessive doses of allopurinol.

The effect of increasing plasma oxypurinol concentration on the concentration of plasma urate was investigated and the concentration of plasma urate decreased over the range of oxypurinol concentration (Figure 3). In a previous cross-sectional study conducted in patients receiving allopurinol therapy there was no significant correlation between plasma urate and plasma oxypurinol concentrations [15]. Plasma urate concentration is not only influenced by xanthine oxidase activity but also by the dietary intake of urate precursors and urate renal clearance. In the present study, healthy volunteers were required to follow a diet free from methyl xanthine. Patients in the previous study were not, and dietary methyl xanthine may have masked the inhibitory effect of oxypurinol on xanthine oxidase. The renal clearance of urate may have been a contributing factor in the patient study [15] as many patients in the study group had decreased renal function. Also, starting plasma urate concentrations would be more variable than those observed in healthy volunteers making it more difficult to detect a pharmacodynamic relationship. The C_{50} predicted in this study was 5.56 mg l^{-1} (36.58 μM) and this is again lower than the mean oxypurinol observed in patients given standard doses of allopurinol for clinical indications.

The effect of increasing oxypurinol concentration on urine urate excretion was investigated and the excretion of urine urate decreased over the concentration range of oxypurinol measured (Figure 4). The decreased excretion of urate in urine was a probable consequence of a decrease in plasma urate concentration as a result of the inhibitory effect of oxypurinol on xanthine oxidase. The C_{50} predicted using the urine urate excretion rate was 3.74 mg l^{-1} (24.61 μM). Urine urate excretion was suggested to be a reasonable parameter to assess the change in urate production and thus, xanthine oxidase activity [15]. In this study, the C_{50} predicted for oxypurinol concentrations needed to inhibit the excretion of urine urate by 50% was similar to that observed for the 50% inhibition of uric acid production as reflected in the plasma urate and the 1MU/1MX ratios, respectively. This would suggest that urine urate excretion may be used to assess the effect of allopurinol on xanthine oxidase activity. However, one should bear in mind that urine urate excretion is influenced by renal function. Therefore, it is important to determine the renal function of patients in order to correctly assess xanthine oxidase activity using urine urate excretion.

The results from the decrease of plasma urate concentration and urine urate excretion appeared to support that 1MU/1MX ratio provides a reasonable index for xanthine oxidase activity as the oxypurinol C_{50}s predicted for the three parameters were similar (4.01, 5.56, 3.74 mg l^{-1}, respectively, Table 1). This further suggests that patients are being treated with excessively high doses of allopurinol as it was found that the mean oxypurinol concentration of patients treated with standard doses of allopurinol (usually 300 mg day^{-1}) is 15.2 mg l^{-1} while 32% of the patient population had oxypurinol concentrations higher than 15 mg l^{-1} [15]. However, the current study was carried out in healthy volunteers with normal plasma concentrations of urate *in vivo* and normal renal function. In patients with hyperuricaemia, there is a high plasma concentration of urate and a higher dose of allopurinol may be required than that predicted in this study. As a result, the standard dose of allopurinol of 300 mg day^{-1} may be a reasonable therapeutic dose for treatment in many individuals. However, plasma concentrations of oxypurinol will be substantially higher in individuals with reduced renal function and the dose of allopurinol should be reduced to lessen the risk of serious allopurinol-induced toxicity.

The value of the Hill exponent (γ) for the urate excretion rate and plasma concentration data was close to unity, indicating that the Emax model would be appropriate for these data. This result is in contrast to the estimated value of γ for the 1MU/1MX response data (8.92 ± 3.91) which is large in comparison. In each case the value of E_{max} is close to the value of Ro, the response at baseline (see Table 1) suggesting essentially complete inhibition of xanthine oxidase and a complete block in urate production. It is difficult to reconcile these differences in the value of the Hill exponent but one suggestion is that the relationship between oxypurinol concentration and urate plasma concentration and excretion rate is more complex than that for 1MU/1MX. This is supported by the fact that once urate production is inhibited the decline in plasma concentrations and urine excretion rate may be slow due to depletion of tissue stores, the long plasma half-life and subject specific factors such as renal function.

In conclusion, this study shows that the administration of allopurinol effectively inhibits the conversion of 1MX to 1MU and decreases the plasma urate concentration and urine urate excretion. The ratio of 1MU/1MX observed following administration of 1MX provides a reasonable index for xanthine oxidase activity and the C_{50} for oxypurinol is similar to that derived from plasma urate concentration and urine urate excretion. This

technique may be useful in determining the therapeutic dose of allopurinol required for an individual before the commencement of allopurinol therapy. This would decrease the risk of allopurinol adverse effects due to excessive doses of allopurinol. An effective dose of allopurinol may also be determined using this technique for patients who are 'non-responders' to allopurinol. However, further studies of this technique involving patients with various levels of renal impairment are required to evaluate its usefulness in a patient population.

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