Cancer Chemother Pharmacol (1982) 8:93–98

Cancer Chemotherapy and Pharmacology

Allopurinol Kinetics and Bioavailability

Intravenous, Oral and Rectal Administration

Steven J. Appelbaum*, Michael Mayersohn, Robert T. Dorr, and Donald Perrier

Departments of Pharmacy Practice and Pharmaceutical Sciences
and the Ruth E. Golding Clinical Pharmacokinetics Laboratory, College of Pharmacy,
The University of Arizona, Tucson, AZ 85721, USA

Summary. *Six normal, healthy adult males received a single dose of allopurinol intravenously, orally in the form of a commercial tablet, and rectally in the form of an extemperaneously prepared suppository (either in a cocoa butter or in polyethylene glycol base). Plasma allopurinol and oxipurinol concentrations were measured over a period of at least 60 h. The following mean (± SD) values were obtained from the intravenous allopurinol experiment: clearance, 9.62 ± 3.49 ml · kg^{-1} · min^{-1}; Vd, 1.61 ± 0.74 l/kg; $t^{l}/_{2}$, 1.62 h. Oxipurinol had a mean $t^{l}/_{2}$ of 16.90 h. The absolute systemic bioavailability of the oral tablet was 67% ± 23%, while the allopurinol rectal suppositories produced no measurable plasma concentrations of allopurinol or oxipurinol in any of the subjects. Current use of rectal dosage forms as an adjunct in cancer chemotherapy should therefore be re-examined.*

Introduction

Allopurinol is an effective anti-hyperuricemic agent for the treatment of gout. In addition to its use in the treatment of hyperuricemia, initial clinical studies [14] demonstrated that allopurinol was effective in reducing serum and urine uric acid concentrations in normals and in leukemic patients. As a result, it has become common practice to administer allopurinol prophylactically to patients who are going to receive cytotoxic drugs to prevent the development of hyperuricemia and consequent uric acid nephropathy [5, 10, 12, 15].

Allopurinol is conventionally administered orally in the form of commercial tablets; nonetheless, the development of nausea and vomiting among patients undergoing cancer chemotherapy frequently precludes the use of oral tablets. Although an injectable form of sodium allopurinol is available on an investigational basis this is not a common mode of therapy. The use of rectal suppositories may provide an alternative means of therapy and this approach has been used by several cancer centers in the United States. Allopurinol suppositories are usually prepared extemporaneously by incorporating ground tablets into an appropriate base (e.g., cocoa butter). Although the clinical impression is that the suppository dosage form appears effective, there is an absence of data concerned with absorption efficiency and allopurinol blood concentrations achieved following this route of administration. A recent report by Chang et al. [4], however, indicates virtually no allopurinol absorption from rectal suppositories. Furthermore, to our knowledge, the absolute absorption of allopurinol from commercial tablets has not been reported.

The purpose of this study was to examine the disposition kinetics of allopurinol and oxipurinol, the major metabolite of allopurinol, after IV dosing and to determine the absolute systemic bioavailability of allopurinol from commercial tablets and extemporaneously prepared rectal suppositories. A brief report of the results of the suppository study has been published [1].

Materials and Methods

Protocol. Six normal, healthy male subjects (23–38 years; 74–95 kg) participated in the study after providing written informed consent. Subjects were not taking any medication during the study. Each subject received single doses of three different allopurinol dosage forms: 500 mg IV (as sodium allopurinol, lot no. 932713, kindly supplied by the Burroughs Wellcome Co.); two 300-mg tablets (Zyloprim, lot no. 902247) and two 300-mg suppositories. The suppositories were prepared by grinding tablets into a fine

Reprint requests should be addressed to Michael Mayersohn PhD at the College of Pharmacy

* *Present address:* Assistant Director for Clinical Services, Sarasota Memorial Hospital, Sarasota, FL 33579, USA

0344-5704/82/0008/0093/$ 01.20

powder and adding 2% carboxymethylcellulose to form a paste. This paste was incorporated into melted cocoa butter and poured into a suppository mold. Three subjects received the above suppository formulation. Three other subjects received suppositories formulated into a mixture of 96% polyethylene glycol 1,000 and 4% polyethylene glycol 4,000. The finely ground powder was incorporated directly into the melted base without the prior formation of a paste. Suppositories were stored in a refrigerator prior to use. Subjects were randomized by factorial design so that no two subjects completed the three experiments in the same sequence. Experiments were separated by at least 1 week.

The IV preparation was diluted with 50 ml 5% dextrose in water and infused over 15 min. The oral tablets were ingested with 200 ml water after an overnight fast, and food was withheld for 4 h following administration. The rectal suppositories were inserted with a careful check to make sure that penetration was past the anal sphincter. Subjects were asked to retain the suppositories for at least 6 h if possible. The time of expulsion of the suppository and the time of the first bowel movement were recorded. Fasting was required as for the oral tablets. Blood samples were obtained over a period of 72 h after dosing. All samples were centrifuged immediately after collection to obtain plasma and stored frozen prior to assay. Samples were assayed within 4 days of collection.

Analytical. A gas-liquid chromatographic procedure was used to quantitate allopurinol and oxipurinol (unpublished data). A volume of 0.3 ml 20% trichloracetic acid was added to 1 ml plasma and centrifuged. An aliquot of the supernatant (0.5 ml) was taken and added to 0.035 ml 2.5 N NaOH to raise the pH to approximately 6. The aqueous phase was extracted with 2 ml l-butanol which contained 2.0 μg/ml β-hydroxypropyl theophylline as the internal standard. The tube was vortexed for 15 s and centrifuged. The l-butanol phase was transferred to a Reactivial and evaporated to dryness at 60° C under nitrogen. The di-and triethyl derivatives of allopurinol and oxipurinol, respectively, were formed by adding 0.075 ml 1 M tetramethyl ammonium hydroxide, and 0.05 ml iodoethane, and heating at 60° C for 20 min. The samples were extracted with 2 ml hexane and evaporated to dryness under nitrogen. Samples were reconstituted with 15 μl ethyl acetate and 3 μl injected in a gas chromatograph equipped with a nitrogen-specific detector (Hewlett Packard model 5711A). The column used was SE-30 on 100/120 mesh chromasorb Q. The injection port and detector temperatures were held at 250° and 300° C, respectively. The oven temperature was programmed to increase from 170° C to 230° C at a rate of 8 deg.C/min and to hold the final temperature for 2 min. The hydrogen, nitrogen, and air flow rates were 4, 30, and 80 ml/min, respectively. Standard curves for allopurinol and oxipurinol were prepared each day plasma samples were assayed.

Data Analysis. Allopurinol plasma concentration (C) versus time (t) data were fit by nonlinear regression analysis [13]. The IV data were analyzed with reference to the equations for one- and two-compartment models and the most appropriate model determined by the F-test [3]. The coefficients of the appropriate model equation were corrected for infusion time [8]. Based upon those corrected values and the rate constants, the total area under the C vs t curve (AUC) was calculated by the equation

$$AUC = \sum_{i=1}^{n} \frac{A_i}{\lambda_i} \qquad \text{(Eq. 1)}$$

where A_i is a coefficient and λ_i is a rate constant which best describe the C vs t curve. Systemic clearance (Cls) and apparent volume of distribution (Vd) were calculated from the following equations

$$Cls = \frac{\text{IV dose}}{AUC} \qquad \text{(Eq. 2)}$$

$$V_d - \frac{\text{Cls}}{\beta} \qquad \text{(Eq. 3)}$$

where β is the terminal elimination rate constant.

Allopurinol C vs t data after oral administration were fit to an equation appropriate for a one-compartment model assuming drug absorption to follow either first-order or zero-order kinetics. The equation which describes the entire C-t curve for zero-order absorption is

$$C = \frac{K_0 \cdot F}{\beta \cdot V_d}(e^{\beta T} - 1)\, e^{-\beta t} \qquad \text{(Eq. 4)}$$

where Ko is the rate of drug absorption, F is the fraction of the dose absorbed, and T is the time during which absorption takes place. The parameters estimated by the program were the coefficient, $Ko \cdot F/\beta \cdot V_d$, β, and T. AUC was calculated from the trapezoidal rule. The absolute bioavailability of allopurinol was determined by

$$F = \frac{(AUC)\ \text{oral}}{(AUC)\ \text{IV}} \times \frac{\text{IV dose}}{\text{oral dose}}. \qquad \text{(Eq. 5)}$$

Results

The IV solution and rectal suppositories were tolerated well by the subjects. Two subjects reported

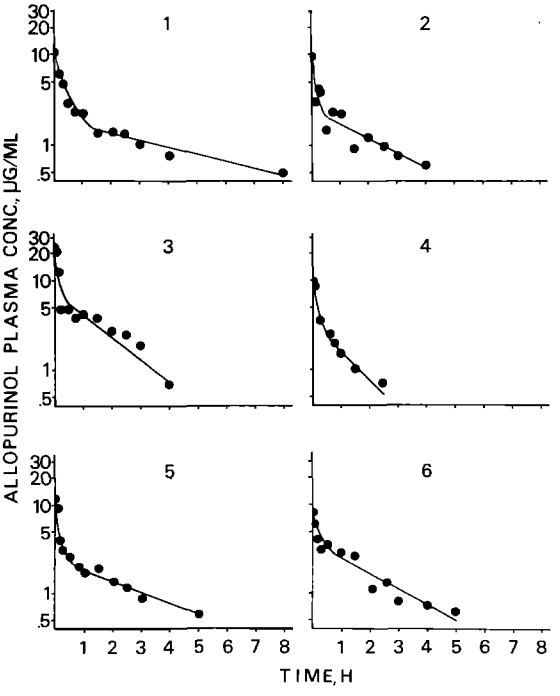

Fig. 1. Allopurinol plasma concentration as a function of time after IV administration. The *solid line* represents the nonlinear regression fit of the data

Table 1. Pharmacokinetic parameters of allopurinol and oxipurinol following IV and oral allopurinol administration

Subject	Allopurinol					Oxipurinol[a]
	Cls (ml/min/kg)	Vd (l/kg)	β (h^{-1})	$t_{1/2}$ (h)	F	$t_{1/2}$ (h)
1	7.40	2.46	0.18	3.85	0.56	11.99
2	12.83	2.08	0.37	1.87	1.07	21.65
3	4.42	0.46	0.58	1.19	0.75	13.59
4	13.93	1.12	0.75	0.93	0.67	21.06
5	9.45	2.09	0.29	2.39	0.41	16.78
6	9.67	1.44	0.40	1.72	0.58	22.35
Mean	9.62	1.61	0.43	1.62[b]	0.67	16.90[b]
± SD	3.49	0.74	0.21		0.23	

[a] Based on IV data
[b] Harmonic mean

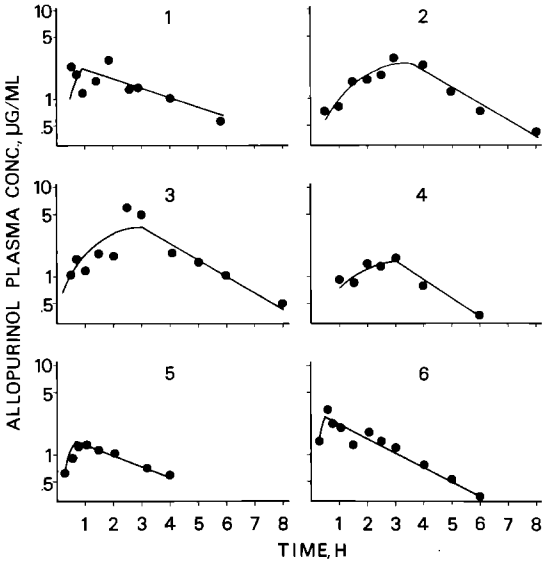

Fig. 2. Allopurinol plasma concentration as a function of time after ingestion of an oral tablet. The *solid line* represents the nonlinear regression fit of the data

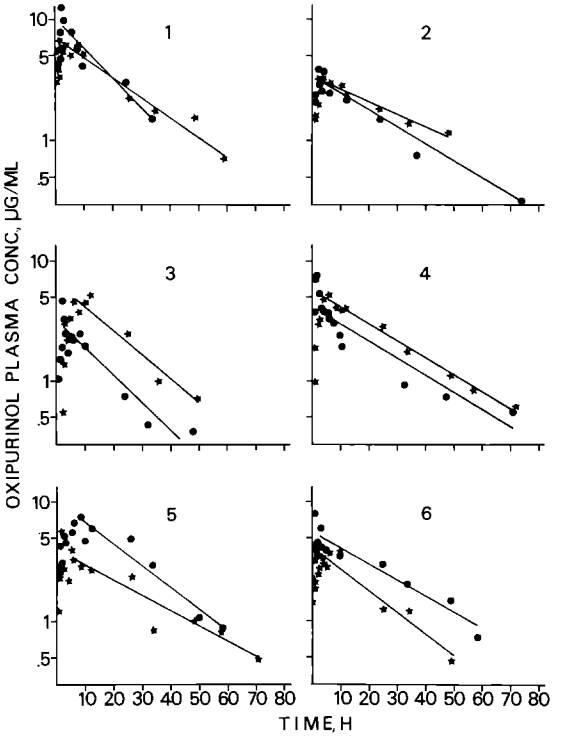

Fig. 3. Oxipurinol plasma concentration as a function of time after IV (●) and oral (★) administration of allopurinol. The *solid line* represents a linear regression fit of the terminal data

a burning sensation following rectal administration but this subsided within 10 min.

Figure 1 presents the allopurinol plasma concentration-time curves for each subject after IV dosing. All of these curves were best described by a biexponential equation. Table 1 summarizes the pharmacokinetic parameters associated with the IV experiments. There is considerable inter-subject variation in each of the parameters reported. Allopurinol is rapidly eliminated from the body, having an average $t_{1/2}$ of 1.62 h.

Figure 2 illustrates the allopurinol plasma concentration-time profiles after oral ingestion. The data were better fit assuming zero-order rather than first-order absorption. The time at which maximum plasma concentrations were achieved (T in Eq. 4)

varied from 0.5 to 3.6 h (average 1.95 h), indicating variable rates of drug absorption among the subjects. The oral product has an average absolute systemic bioavailability of 67% (range 41%–107%).

Neither suppository formulation gave any measurable plasma concentrations of allopurinol or oxipurinol. The suppositories were retained for a minimum of 6 h in all but one subject (3-h retention). These data indicate that the drug is not absorbed rectally from the suppositories examined.

Figure 3 illustrates the oxipurinol plasma concentration-time profiles after IV and oral allopurinol administration. The average elimination rate constant for oxipurinol (after IV allopurinol) is $0.041 \pm 0.011\ h^{-1}$ (range; $0.031-0.058\ h^{-1}$), which corresponds to a $t_{1/2}$ of 16.9 h. This value is similar to the average $t_{1/2}$ of 19.8 h following oral allopurinol administration. Oxipurinol plasma concentrations fluctuated considerably during times soon after administration and, as a result, the entire curve was not fit to an equation. The elimination rate constant was determined from linear regression of the data after the maximum concentration was achieved.

Discussion

Elion et al. [6] examined allopurinol disposition after IV administration of ^{14}C-allopurinol to one subject and oral ingestion by two other subjects. Six hours after the IV dose all radioactivity in the plasma was associated with the oxipurinol fraction, suggesting that allopurinol is rapidly cleared from the body. The elimination $t_{1/2}$ of oxipurinol was approximately 28 h. In addition, only 10% of the administered dose was recovered in the urine as allopurinol, while oxipurinol accounted for 45% of the dose. The latter value is probably an underestimate of the true value, since urine was collected for a relatively short period, 24 h. Oxipurinol was reported to have a renal clearance of about 20 ml/min, which may be due to renal tubular reabsorption, as the renal clearance increased in the presence of probenacid [7].

More recently Hande et al. [9] examined allopurinol and oxipurinol disposition in eight subjects after IV allopurinol administration. The average $t_{1/2}$ values for allopurinol and oxipurinol were 39 min and 13.6 h, respectively, and the renal clearance for both compounds was less than 30 ml/min. The low renal clearance of allopurinol in conjunction with its rapid loss from the body and the small fraction of the dose recovered in the urine as unchanged drug suggest that clearance is primarily via metabolism.

The results of the IV study reported here are in general agreement with the few studies that have been reported to date. Allopurinol is rapidly cleared from the body (Fig. 1) and, as reported by Elion et al. [7] concentrations are small 6 h after injection. The average $t_{1/2}$ of 1.62 h substantially longer than that reported by Hande et al. (0.65 h) [9]. Although it is difficult to explain this disparity, it should be noted that larger doses were employed in this study (500 mg vs 100–300 mg). In addition, Hande et al. collected blood samples for only 3 h after a dose, which may have resulted in inclusion of part of the distributive phase (see Fig. 1) in the calculation of $t_{1/2}$. This would tend to underestimate the $t_{1/2}$. The $t_{1/2}$ for oxipurinol found here, 16.9 h, agrees well with the value of 13.6 h reported by Hande et al. [9].

The Vd of allopurinol is relatively large, 1.61 l/kg (Table 1), suggesting substantial extravascular distribution. The large values for allopurinol clearance (Table 1) are consistent with its rapid disappearance from the body. Assuming allopurinol elimination is primarily hepatic and an average hepatic blood flow is 1500 ml/70 kg, allopurinol would be predicted to have a relatively large extraction ratio (approx. 0.50). This conclusion however, is based upon plasma rather than blood clearance. If one estimates clearance based upon the data reported by Hande et al. [9] a value about 2.5 times that reported here (approx. $23.6\ ml \cdot min^{-1} \cdot kg^{-1}$) would be obtained. This value may represent an overestimate of the true clearance as a result of an underestimate in AUCs. The ratio of the $t_{1/2}$ reported here and that reported by Hande et al. [9] is 2.5, a value identical to the ratio of clearances.

Allopurinol plasma concentration-time data (Fig. 2) were better described by an infusion-input model (Eq. 4) than by assuming first-order absorption. This absorption pattern may reflect the low aqueous solubility of the drug (0.48 mg/ml) [2] and a resulting slow rate of dissolution. Allopurinol $t_{1/2}$ after oral administration was 1.86 h (harmonic mean), which agrees well with the $t_{1/2}$ after IV dosing (1.62 h). The rate of absorption varied among the subjects, with peak plasma concentration achieved at an average of about 2 h after dosing (range, 0.5–3.6 h).

Based upon a comparison of AUCs from the oral and IV experiments, the tablets have an absolute systemic availability of 67%. Thus, either allopurinol is incompletely absorbed or is subject to pre-systemic metabolism. Based upon the previous discussion and an estimated hepatic extraction ratio of 0.50, one would predict that 50% of an oral dose would be absorbed intact into the systemic circulation if the drug is completely absorbed. This prediction is in reasonable agreement with our observed average value of 67%. The possibility remains, however, that

allopurinol may undergo metabolism to oxipurinol via xanthine oxidase enzymes present in the gut. Consistent with the above data is the fact that in four of the six subjects the AUCs for oxipurinol after oral dosing were greater than the AUCs after IV dosing.

The most striking result of this study is the observation that allopurinol is not absorbed rectally after suppository administration from either of the two formulations used. In addition, measurable concentrations of oxipurinol were not seen. While there may be several reasons for this observation we can offer no definitive explanation. The release of allopurinol from the formulations used may be poor, and thereby provide little drug in a form available for absorption. Alternatively, because of the low aqueous solubility of the drug and the relatively small fluid volume in the rectal area, dissolution, and therefore absorption, may be incomplete. The small surface area of the absorbing membrane in the rectal area would further contribute to poor absorption. An additional possibility is that the drug is metabolized to oxipurinol within the lumen of the lower intestine and this metabolite may have a small membrane permeability, thereby preventing its absorption.

Our results are in excellent agreement with the recent published findings of Chang et al. [4], who examined allopurinol absorption from oral tablets and rectal suppositories. These investigators found that allopurinol suppositories (cocoa butter base) had an average 6% availability relative to the oral tablets, while a polyethylene glycol base suppository produced no measurable concentrations of allopurinol or oxipurinol. The elimination half-lives of allopurinol and oxipurinol also agree well with those reported by Chang et al. [4].

Although this study was conducted in normal healthy subjects the results reported here should also apply to patients requiring allopurinol therapy. Our findings indicate that rectal suppository administration would not be a recommended mode of therapy. Further study is required to ascertain why rectal absorption is so poor.

It is of interest to note that the early clinical studies which investigated the use of allopurinol in lowering serum uric acid both in normal and gouty patients and in cancer patients being treated for hyperuricemia indicate a time delay in the therapeutic effect of allopurinol [5, 11, 16]. Although a serum urate-lowering effect was noted within 24 h, a maximal response was generally not seen for 3–5 days. Kjellstrand et al. [10] found that if allopurinol therapy was started concomitantly with chemotherapy, uric acid nephropathy still developed. The data from the present investigation may suggest a basis for this time delay. The time needed to reach steady-state concentrations in the plasma is primarily dependent on a drug's $t\frac{1}{2}$, with steady-state concentrations for a given dose achieved after four to five times $t\frac{1}{2}$. With a $t\frac{1}{2}$ of approximately 17 h for oxipurinol, 3 days would be required before oxipurinol would reach steady-state concentrations. This would suggest that the maximal serum urate-lowering effect may be due to oxipurinol rather than allopurinol. Therefore, in patients receiving allopurinol prophylactically for the prevention of hyperuricemia, secondary to cancer chemotherapy, it would be advisable to either start these patients on allopurinol therapy approximately 3 days prior to chemotherapy or use a loading dose of allopurinol to immediately attain steady-state concentrations of oxipurinol. The use of loading doses of allopurinol has not been clinically evaluated. It is also important to remember that too high a dose might, by itself, precipitate renal deposition of urate. Future studies should examine the clinical efficacy, as well as the magnitude, of the loading dose approach.

Acknowledgements. One of the authors (SJA) is supported by a Roche Grant in Hospital Pharmacy.

References

1. Appelbaum SJ, Mayersohn M, Perrier D, Dorr RT (1980) Allopurinol absorption from rectal suppositories. Drug Intell Clin Pharmacy 14: 789
2. Benezra SA, Bennett TR (1978) Allopurinol. In: Florey K (ed) Analytical profiles of drug substances, vol 7. Academic Press, New York, pp 1–17
3. Boxenbaum HG, Riegelman RM, Elashoff M (1974) Statistical estimations in pharmacokinetics. J Pharmacokin Biopharm 2: 123
4. Chang S-L, Kramer WG, Feldman S, Ballentine R, Frankel LS (1981) Bioavailability of allopurinol oral and rectal dosage forms. Am J Hosp Pharm 38: 365
5. DeConti RC, Calabresi P (1966) Use of allopurinol for prevention and control of hyperuricemia in patients with neoplastic disease. N Engl J Med 274: 481
6. Elion GB, Kovensky A, Hitchings GH, Metz E, Rundles RW (1966) Metabolic studies of allopurinol, an inhibitor of xanthine oxidase. Biochem Pharmacol 15: 863
7. Elion GB, Yu T-F, Gutman AB, Hitchings GH (1968) Renal clearance of oxipurinol, the chief metabolite of allopurinol. Am J Med 45: 69
8. Gibaldi M, Perrier D (1975) Pharmacokinetics. Marcel Dekker, New York, pp 73–75
9. Hande K, Reed E, Chabner B (1978) Allopurinol kinetics. Clin Pharmacol Ther 23: 598
10. Kjellstrand CM, Campbell DC, von Hartitzsch B, Buselmeier TJ (1974) Hyperuricemic acute renal failure. Arch Intern Med 133: 349
11. Klinenberg JR, Goldfinger SE, Seegmiller JE (1965) The effectiveness of the xanthine oxidase inhibitor allopurinol in the treatment of gout. Ann Intern Med 62: 639

12. Krakoff CW, Meyer RL (1965) Prevention of hyperuricemia in leukemia and lymphoma. JAMA 193: 89
13. Metzler CM (1969) A Users Manual for NONLIN. Upjohn Co., Kalamazoo
14. Rundles RW, Wyngaarden JB, Hitchings GH, Elion GB, Silberman HR (1963) Effects of xanthine oxidase inhibitor on thiopurine metabolism, hyperuricemia and gout. Trans Assoc Am Physicians 76: 126
15. Vogler WR, Bain JA, Huguley CM, Palmer HG, Lowrey ME (1966) Metabolic and therapeutic effects of allopurinol in patients with leukemia and gout. Am J Med 40: 548
16. Yu TF, Gutman AB (1964) Effects of allopurinol (4-hydroxypyrazolo-(3,4-*d*) pyrimidine) on serum and urinary uric acid in primary and secondary gout. Am J Med 37: 885

Received September 9/Accepted November 6, 1981