International Journal of Pharmaceutics, 30 (1986) 221–224
Elsevier

IJP 01014

Allopurinol rectal absorption in the rabbit

Vikram S. Patel [1,2] and William G. Kramer [1]

[1] *Department of Pharmaceutics, University of Houston, Houston, TX 77030 and*
[2] *Norwich Eaton Pharmaceuticals, Inc., Norwich, NY 13815 (U.S.A.)*

(Received November 18th, 1985)
(Modified version received and accepted January 6th, 1986)

Key words: allopurinol—oxipurinol—suppository—rectal absorption

Summary

Allopurinol is used clinically, with apparent success, as a rectal suppository for patients unable to take the medication by mouth. However, plasma levels of the drug or its active metabolite, oxipurinol, following administration of such dosage forms in man are either very low or undetectable. The absorption of allopurinol from rectal dosage forms was evaluated using the rabbit as a model. Following administration of the drug in suppositories formulated with cocoa butter, cocoa butter with 2% Tween 80 or polyethylene glycol, no measurable levels of either allopurinol or oxipurinol were seen, consistent with results reported in man. Administration of a rectal solution produced erratic absorption at a level less than 10% of that seen orally. The results indicate that allopurinol is not absorbed rectally and that there is no rationale for administering the drug by the rectal route. Continued clinical use of allopurinol suppositories should be documented by controlled efficacy studies.

Introduction

Allopurinol, a structural isomer of hypoxanthine, is used in the treatment of both the primary hyperuricemia of gout and that secondary to hematological disorders or antineoplastic therapy. Clinically, cocoa butter base allopurinol suppositories have been used effectively in adult and pediatric oncology patients with hyperuricemia due to the disease, chemotherapy or both (Chang et al., 1981). In contrast, studies done in human volunteers (Chang et al., 1981) examining the levels of allopurinol following administration of rectal dosage forms as compared to tablets showed only about 6% relative availability for a cocoa butter suppository (Chang et al., 1981), based upon oxipurinol levels. Following administration of polyethylene glycol suppositories, neither allopurinol nor oxipurinol were detectable in the plasma (Chang et al., 1981; Appelbaum et al., 1982).

The purpose of the studies reported here was to examine the rectal absorption of allopurinol, in a suitable animal model, to attempt to clarify this discrepancy between clinical effectiveness and apparent lack of absorption.

Materials and Methods

Dosage forms

Pure allopurinol (Burroughs Wellcome Co., gift) was used for the preparation of suppository and oral and rectal liquid dosage forms. Suppositories

Correspondence: W.G. Kramer, Department of Pharmaceutics, University of Houston, 1441 Moursund St., Houston, TX 77030, U.S.A.

were prepared by the fusion method (Carter, 1975) using standard rubber pediatric molds. The following suppository dosage forms were prepared: (1) cocoa butter; (2) cocoa butter with 2% Tween 80; and (3) polyethylene glycol (50% PEG 6000, 30% PEG 1500, 20% PEG 400). Cocoa butter suppositories incorporating Tween 80 were used because prior experiments had shown that the surfactant increased the dissolution rate of allopurinol from cocoa butter by a factor of two, allowing for the examination of dissolution as a factor in absorption. Suppositories from each batch were subjected to content uniformity and weight variation testing. The oral and rectal solutions were prepared by dissolving the required amount of pure allopurinol in very dilute sodium hydroxide (pH 8.5) followed by storage in a waterbath at 37°C to ensure complete dissolution of allopurinol until administration.

Drug administration and sample collection

Two male, New Zealand white rabbits, weighing about 4 kg, were used. Each animal received the following allopurinol treatments: oral aqueous solution, aqueous rectal solution, cocoa butter suppository, cocoa butter with Tween 80 suppository and PEG suppository. All drug administrations followed a 24 h fast and a minimum of 2 weeks separated treatments. Allopurinol was given at a dose of 6.25 mg/kg, reasonably equivalent to the usual human dose of 300–600 mg per day. The oral dose consisted of 5 ml of solution and was introduced directly into the stomach via a catheter followed by flushing with 15 ml of water. The suppositories were administered using a disposable vaginal suppository applicator (V-Applicator, Parke-Davis) premarked to place the suppository 2 cm into the rectum. The rectal solution (5 ml) was injected using a catheter. To prevent expulsion of the suppository or solution, a bulldog clamp was used to hold the anus closed for 4 h after dosing.

For all treatments, 1–2 ml blood samples were collected before and 0.17, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12 h after drug administration. Blood samples were collected from the marginal ear vein using a vacuum device (Patel, 1984). Samples were centrifuged at 8000 × *g* (MicroFuge, Beckman) immediately after collection to prevent possible metabolism of allopurinol by red blood cells (Thomas et al., 1982) and the plasma was removed and frozen until assay.

TABLE 1

WEIGHT VARIATION AND CONTENT UNIFORMITY OF THE SUPPOSITORIES *

Suppository	Weight (gm) (n = 24)	Content (mg) (n = 6)
Cocoa butter	1.05 ± 0.021	24.4 ± 0.92
PEG	1.39 ± 0.026	24.7 ± 0.50
Cocoa butter with 2% Tween 80	1.06 ± 0.018	25.6 ± 0.98

* Values reported at mean ± standard deviation.

Analytical

Allopurinol and oxipurinol concentrations in plasma were measured using a high-pressure liquid chromatographic method (Kramer and Feldman, 1979). This method has a lower detection limit of 0.1 mg/l.

Data analysis

For each rabbit and for each treatment, where appropriate, the elimination half-life ($t_{1/2}$) was

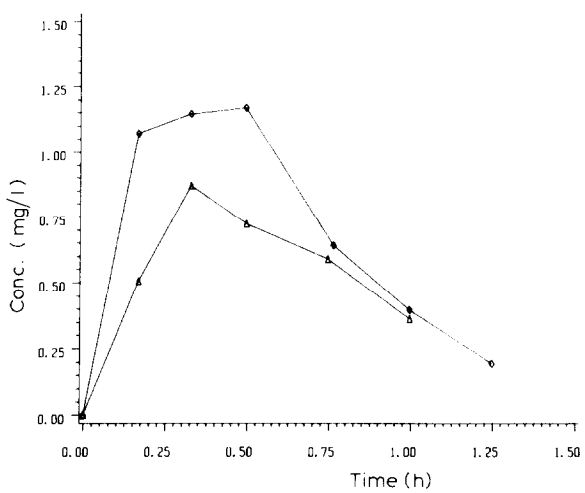

Fig. 1. Serum concentrations of allopurinol in rabbits A (◇) and B (△) following administration of an oral aqueous solution.

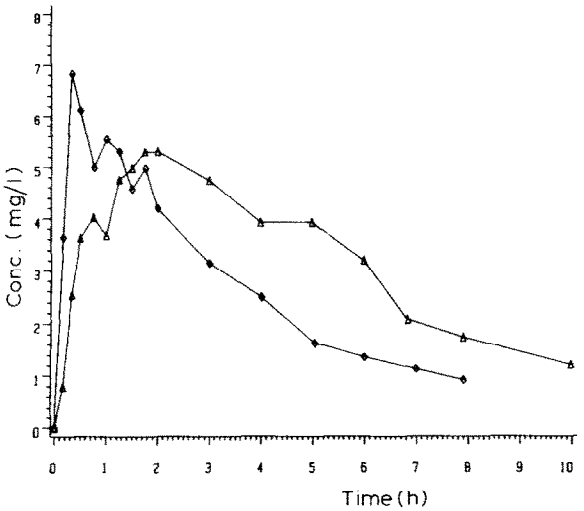

Fig. 2. Serum concentrations of oxipurinol in rabbits A (◇) and B (△) following administration of an oral aqueous solution.

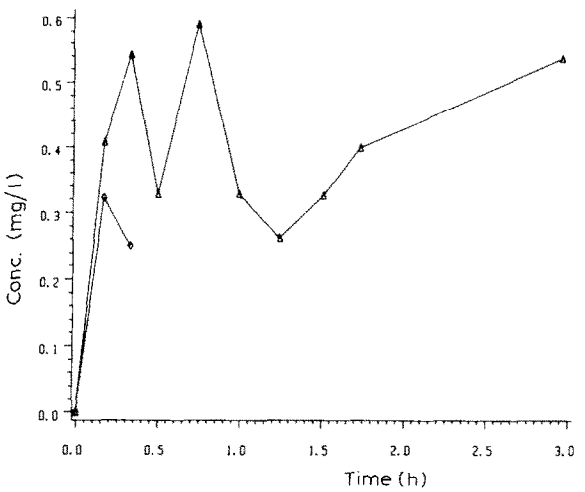

Fig. 3. Serum concentrations of allopurinol (◇) and oxipurinol (△) in rabbit A following administration of a rectal solution.

calculated from the slope of the terminal log-linear portion of the plasma concentration–time curve. Slopes were calculated using linear regression. The area under the concentration–time curve (AUC) was calculated using the linear trapezoidal method from time zero to the final sampling time and extrapolated to infinity using the slope. Maximum concentrations (C_{max}) and time to peak (t_p) were taken directly from the data.

Results

Weight variation and content uniformity of the prepared suppositories are shown in Table 1, and met the standards of the USP XIV (±10%).

The plasma concentration–time profiles of allopurinol and oxipurinol in both rabbits following administration of the oral solution are shown in Figs. 1 and 2, respectively, and the parameters of those curves are summarized in Table 2. Allopurinol was absorbed rapidly, reaching its peak concentration at about 0.4 h. Oxipurinol, as expected, peaked later, its appearance being a function of both absorption and metabolism, and reached levels from 5 to 7 times higher than the parent compound. Although differing in time scale, the relation between the two curves was similar to that seen in man (Patel, 1984; Appelbaum et al., 1982; Breithaupt and Tittel, 1982).

TABLE 2

ALLOPURINOL AND OXIPURINOL ABSORPTION PARAMETERS FOLLOWING ORAL ADMINISTRATION OF AN AQUEOUS SOLUTION

Rabbit	AUC (mg·h/l)	$t_{1/2}$ (h)	C_{max} (mg/l)	t_p (h)
Allopurinol				
A	0.98	0.3	1.17	0.5
B	0.81	0.5	0.87	0.3
Oxipurinol				
A	25.2	2.6	6.81	0.5
B	37.8	3.6	5.28	1.8

TABLE 3

ALLOPURINOL AND OXIPURINOL ABSORPTION PARAMETERS FOLLOWING RECTAL ADMINISTRATION OF AN AQUEOUS SOLUTION *

	AUC (mg·h/l)		C_{max} (mg/l)	
	Oral	Rectal	Oral	Rectal
Allopurinol	0.98	0.07 **	1.17	0.31
Oxipurinol	25.2	1.23 ***	6.81	0.59

* Data from rabbit A.

** Area to 0.33 h (end of detectable levels).

*** Area to 3 h (end of detectable levels).

Following administration of either the cocoa butter, cocoa butter with 2% Tween 80 or PEG suppositories, there was no apparent absorption, as evidenced by no measurable levels of either allopurinol or oxipurinol. These results are consistent with those seen in man (Chang et al., 1981; Appelbaum et al., 1982).

Rectal administration of allopurinol in its most readily absorbed form, the aqueous solution, did result in absorption, as shown in Fig. 3. However, absorption was erratic, was observed only in one rabbit, the concentrations were very low, as compared to the oral, and were undetectable after 3 h. Comparison of the maximum levels of oxipurinol with those seen following oral administration (Table 3) implies that absorption was less than 10%, consistent with that seen from cocoa butter suppositories in man by Chang et al. (1981).

Discussion

Allopurinol is a polar compound with strong intermolecular hydrogen bonding and poor solubility in both polar and nonpolar media (Hussain and Rytting, 1974). Consequently, it is most likely suspended, rather than dissolved, in any of the suppository bases tested. Further, the rectum generally contains only a small volume of fluid, which may not be sufficient to dissolve the amount of allopurinol contained in the suppository. If an aqueous solubility of 0.8 mg/ml is assumed (Chang et al., 1981), then a volume of 30 ml would be required to dissolve the 25 mg dose given to the rabbit or 375 ml for the 300 mg dose given to human subjects (Chang et al., 1981). Volumes that large are not present in the rectum. The lack of absorption following suppository administration may be due, in part, to poor release of drug from any of the dosage forms due to poor solubility, a problem not overcome either by the addition of a surfactant or the use of a base (PEG) previously shown to increase the solubility of allopurinol (Chang et al., 1981). However, as evidenced by the poor absorption when given as a rectal solution, the lack of absorption may also be due to poor absorbability of allopurinol from the rectum.

The results of this study indicate that, for all practical purposes, allopurinol is not absorbed from the rectum and that there is no rationale for administering the drug by that route. Continued clinical use of allopurinol suppositories must be documented by controlled efficacy studies.

References

Appelbaum, S.J., Mayersohn, M., Dorr, R.T. and Perrier, D., Allopurinol kinetics and bioavailability: intravenous, oral and rectal administration. Cancer Chemother. Pharmacol., 8 (1982) 93–98.

Breithaupt, H. and Tittel, M., Kinetics of allopurinol after single intravenous and oral doses: noninteraction with benzbromarone and hydrochlorothiazide. Eur. J. Clin. Pharmacol., 22 (1982) 77–84.

Carter, S.J., Cooper and Gunn's Dispensing for Pharmaceutical Students, Pitman Medical, London, 1975, p. 232.

Chang, S.-L., Kramer, W.G., Feldman, S., Ballentine, R. and Frankel, L.S., Bioavailability of allopurinol from oral and rectal dosage forms. Am. J. Hosp. Pharm., 38 (1981) 365–368.

Hussain, A. and Rytting, J.G., Prodrug approach to enhancement of rate of dissolution of allopurinol. J. Pharm. Sci., 63 (1974) 798–799.

Patel, V., Allopurinol Absorption and Disposition Studies and Pharmacokinetic Modeling, Dissertation, University of Houston, 1984.

Thomas, G., Feldman, S. and Kramer, W.G., Interaction of allopurinol with human blood. Biochem. Pharmacol., 31 (1982) 1937–1940.