

Enhancing Effect of Allopurinol on the Induction of Bladder Cancer in Rats by *N*-[4-(5-Nitro-2-furyl)-2-thiazolyl]formamide¹

Ching Yung Wang, Shigeaki Hayashida, A. Mahir Pamukcu, and George T. Bryan

Division of Clinical Oncology, University of Wisconsin Center for Health Sciences, Madison, Wisconsin 53706

SUMMARY

The effects of allopurinol on the induction of bladder cancer by *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide (FANFT), excretion of urinary tryptophan metabolites, hepatic nitroreductase activity, and the acid-soluble thiol content of liver and blood in weanling female Fischer rats were investigated. Four groups of rats were given normal diet or normal diet supplemented with 0.005% allopurinol, 0.188% FANFT, or 0.005% allopurinol-0.188% FANFT. Transitional cell carcinomas appeared in 3 of 30 rats (10%) at 15 weeks and in 7 of 44 rats (16%) at 20 weeks in the FANFT-treated group; the carcinomas appeared in 14 of 35 rats (40%) at 15 weeks and in 27 of 50 rats (54%) at 20 weeks in the FANFT-allopurinol-treated group. Growth rate was not affected by allopurinol and FANFT. Allopurinol alone caused no morphological change in the epithelial cells of the urinary bladder but decreased hepatic cytosol nitroreductase activity. FANFT alone had no effect on hepatic cytosol or microsomal nitroreductase activity but increased hepatic and blood acid-soluble thiol content. FANFT increased the urinary excretion of anthranilic acid glucuronide, kynurenine, acetylkynurenine, and 3-hydroxykynurenine and decreased indican and *o*-aminohippurate excretion. Allopurinol did not alter the effects of FANFT on the acid-soluble thiol content of liver and blood or the excretion of urinary tryptophan metabolites.

INTRODUCTION

FANFT² administered p.o. induced high incidences of urinary bladder cancer in dogs (12), hamsters (10), mice (13), and rats (14, 26). Nitroreduction has been suggested as the initial activation of carcinogenic (8) and mutagenic (24) nitroheterocycles. FANFT and other carcinogenic nitrothiophenes (31) and nitrofurans (28) were reduced by NADPH-cytochrome *c* reductase and xanthine oxidase. Like other nitrofurans (25, 30), reduced metabolites of FANFT may interact with macromolecules and thiol.

Allopurinol, widely used in the treatment of gout, hyperuricemia, and neoplasia in humans (11, 20, 21, 27), has complicated effects on purine and pyrimidine biosynthesis (19, 22). It is a strong inhibitor of xanthine oxidase (7, 15) and

nitroreductase (28). It also inhibits tryptophan oxygenase (2, 4) and may alter the pattern of urinary tryptophan metabolites. Certain tryptophan metabolites have been implicated in the genesis of human bladder cancer (6). Thus, allopurinol may alter the activity of FANFT in inducing bladder cancer. The present study investigates the effects of allopurinol on FANFT carcinogenic activity, excretion of urinary tryptophan metabolites, nitroreductase activity of liver, and acid-soluble thiol content of liver and blood.

MATERIALS AND METHODS

Chemicals. FANFT was obtained from Saber Laboratories, Inc., Morton Grove, Ill.; 5,5'-dithiobis-(2-nitrobenzoic acid) was from Aldrich Chemical Co., Milwaukee, Wis.; and allopurinol, NADPH, and hypoxanthine were from Sigma Chemical Co., St. Louis, Mo. ANFT was synthesized as described (9).

Animal Experiment. Female Fischer rats, 45 to 60 g, were obtained from A. R. Schmidt Co., Madison, Wis. The animals were randomly divided into 4 groups and housed in screen-bottomed metal cages with 4 animals in each cage. Powdered Wayne-Lab-Blox, Allied Mills Inc., Chicago, Ill., was the basal diet fed the rats in Group 1. Animals in Groups 2 through 4 were fed basal diet supplemented with 0.005% allopurinol, 0.188% FANFT, or 0.005% allopurinol-0.188% FANFT, respectively. Fresh diets were provided twice weekly *ad libitum*, but the quantity introduced into each feeder was adjusted to ensure that the animals in a cage consumed approximately the same amount of diet in the same period of time; diet consumption of 4 rats in each cage was recorded. Animal weights were recorded at 0, 2, 4, 6, 9, 14, and 19 weeks. Drinking water was provided *ad libitum*.

Rats were selected at random from each group and were sacrificed under ether anesthesia at the end of weeks 10, 15, and 20 (Table 1). The urinary bladders were properly inflated and fixed (14). Histological sections were stained with hematoxylin and eosin and were evaluated microscopically.

Determination of Acid-soluble Thiol. Acid-soluble thiol content in blood and liver of rats that were fed the diets for 20 weeks was determined. The rats were placed under light ether anesthesia and blood was collected from the brachial artery into a heparinized tube. The blood was then diluted with 4 volumes of distilled water. One ml of the blood sample was mixed with 1 ml of 6% sulfosalicylic acid solution, placed at 4° for 20 min, and centrifuged at 15,000 rpm for 10 min in a Beckman J-21 refrigerated centrifuge. The

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² The abbreviations used are: FANFT, *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide; ANFT, 2-amino-4-(5-nitro-2-furyl)thiazole.

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clear supernatant fraction was used for thiol determination.

The livers from these rats were homogenized with 4 volumes of ice-cold 1.15% KCl solution in a Teflon-glass homogenizer. The liver homogenate was mixed with an equal volume of 6% sulfosalicylic acid solution, placed at 4° for 20 min, and centrifuged. The clear supernatant fraction was used for thiol determination using the colorimetric method with reduced glutathione as standard (18). One-half ml of an acid-soluble fraction of blood or liver was added to 2.0 ml of 5,5'-dithiobis(2-nitrobenzoic acid) reagent (18) and the absorption at 410 nm was measured immediately with a Beckman model 25 spectrophotometer.

Liver Nitroreductase Activity. Livers from rats fed the diets for 20 weeks were fractionated into supernatant and microsome fractions (28). Since rat liver deforms FANFT (29), interfering with the assay for nitroreductase, ANFT was used as the substrate. When cytosol was used as enzyme, the incubation mixture (2.5 ml) contained cytosol equivalent to 50 mg of fresh liver, 125 μ moles Tris-HCl (pH 7.4), 0.1 ml dimethylformamide containing 0.5 μ mole ANFT, and 1 μ mole of hypoxanthine. When microsomes were used as enzyme, hypoxanthine was replaced by NADPH. After incubation at 37° for 30 min under nitrogen atmosphere, the reaction was terminated with 1.25 ml of 20% trichloroacetic acid and 1.25 ml of dimethylformamide and the mixture was cooled at 4° for 20 min and centrifuged. Light absorption of the clear supernatant fraction at 400 nm was measured. The extinction coefficient for ANFT at 400 nm was 10.8 $\text{mm}^{-1} \text{cm}^{-1}$. Enzyme activity was expressed as μ moles ANFT disappearance per g per hr.

Determination of Urinary Tryptophan Metabolites. Rats fed the diets for 20 weeks were housed separately in a metal metabolic cage and were given water and prescribed diet *ad libitum*. Urine excreted in 24 hr was collected in a flask containing 1 ml glacial acetic acid. The cage was rinsed with distilled water, and urine and washings were combined and filtered through filter paper. The tryptophan metabolites were determined by the method described (23).

RESULTS

Bladder Carcinogenesis. All animals consumed approximately equal quantities of diet during the same period of time. The approximate total consumption of allopurinol and FANFT in Groups 2 through 4 is shown in Table 1. The animals in all 4 groups had similar growth rates during the 20 weeks of feeding, suggesting that allopurinol and FANFT were not toxic at these doses.

Bladders of allopurinol-fed animals (Group 2) were similar histologically to control animals (Group 1), indicating that allopurinol had no morphological effects on the bladders. Ten weeks or longer of feeding FANFT or FANFT and allopurinol induced severe hyperplasia of the bladder; "hyperplasia" used here includes not only micropapillae but also nodular and papillary hyperplasia, reported as tumors by Tiltman and Friedell (26). Fifteen weeks of feeding induced transitional cell carcinomas. Carcinomas were classified as follows: Stage I, invasion of a papillary carcinoma into supporting stroma or a sessile carcinoma into the lamina propria; Stage II, invasion into muscle; and Stage III, invasion into serosa. Carcinomas with slight anaplasia were designated Grade I; intermediate anaplasia, Grade II; and severe anaplasia, Grade III. Stage I, Grade I and, occasionally, Stage II, Grade II transitional cell carcinomas were found at 20 weeks. The incidence of transitional cell carcinoma was significantly higher in the FANFT-allopurinol group than in the FANFT group at 15 and 20 weeks (Table 1), demonstrating the enhancing effect of allopurinol on the carcinogenicity of FANFT. No urinary calculi were found in the bladders of these rats.

Acid-soluble Thiol. The acid-soluble thiol content of liver and blood was determined in rats fed the diets for 20 weeks. Thiol level was higher in Group 3 than in Group 1 and higher in Group 4 than in Group 2. However, there was no difference between Groups 1 and 2 and Groups 3 and 4 (Table 2). FANFT increased thiol levels in blood and liver. This effect was not altered by allopurinol.

Table 1
Incidence of transitional cell carcinoma of the urinary bladder

Wk	Group ^a	Approximate total FANFT consumed (g/rat)	Approximate total allopurinol consumed (g/rat)	No. of rats	Hyperplasia	Transitional cell carcinoma				p ^b	
						Stage		Grade			Incidence (%)
						I	II	I	II		
10	1	0	0	5	0	0	0	0	0	0	
	2	0	0.041	5	0	0	0	0	0	0	
	3	1.55	0	5	3	0	0	0	0	0	
	4	1.55	0.041	5	4	0	0	0	0	0	
15	1	0	0	30	0	0	0	0	0	0	
	2	0	0.069	29	0	0	0	0	0	0	
	3	2.56	0	30	29	2	1	2	1	10	
	4	2.56	0.069	35	35	14	0	14	0	40	<0.01
20	1	0	0	22	0	0	0	0	0	0	
	2	0	0.099	21	0	0	0	0	0	0	
	3	3.50	0	44	44	7	0	7	0	16	
	4	3.50	0.099	50	50	25	2	25	2	54	<0.001

^a Group 1, control; Group 2, allopurinol treated; Group 3, FANFT treated; Group 4, FANFT-allopurinol treated.

^b Comparison between Groups 3 and 4.

Table 2

Acid-soluble thiol content of liver and blood of rats fed the diets for 20 weeks

Organ	Group ^a	No. of rats ^b	Thiol content (μmoles/g or ml) ^c
Liver	1	7	2.85 ± 0.13 ^d
	2	8	2.93 ± 0.20
	3	10	3.18 ± 0.09
	4	10	3.20 ± 0.08
Blood	1	3	0.83 ± 0.02
	2	4	0.84 ± 0.02
	3	6	1.16 ± 0.05
	4	6	1.13 ± 0.03

^a Group 1, control; Group 2, allopurinol treated; Group 3, FANFT treated; Group 4, FANFT-allopurinol treated.

^b Urinary bladders were not examined histologically.

^c $p < 0.001$ for Group 1 versus Group 3 and Group 2 versus Group 4.

^d Mean ± S.D.

Nitroreductase Activity. Nitroreductase activity was measured in the liver of rats fed the diets for 20 weeks. Microsomal nitroreductase activity was not altered by FANFT or allopurinol (Table 3). The cytosol nitroreductase activity was not altered by FANFT but was decreased significantly by allopurinol (Groups 2 and 4) (Table 3).

Tryptophan Metabolites. Tryptophan metabolites excreted in the urine during a 24-hr period were assayed at 20 weeks. Among the 9 metabolites assayed, anthranilic acid glucuronide, kynurenine, and acetylkynurenine were significantly increased by treatment with FANFT or allopurinol-FANFT, whereas indican and *o*-aminohippurate were significantly decreased (comparing Groups 1 and 3 and Groups 2 and 4) (Table 4). 3-Hydroxykynurenine was increased but was not significant statistically. Allopurinol had no effect on the excretion of tryptophan metabolites at the present dose level (comparing Groups 1 and 2 and Groups 3 and 4) (Table 4).

DISCUSSION

An enhancing effect of allopurinol on bladder carcinogenicity by FANFT is clearly demonstrated by these data. At 2 different time periods, 15 and 20 weeks, the incidence of

bladder neoplasia in the allopurinol-FANFT treated animals was significantly greater than that observed in rats receiving only FANFT. High incidences of bladder tumors have been reported (14) for rats receiving FANFT, but the period of experimental observation has been about 1 year. Thus it appears that allopurinol may accelerate the appearance of FANFT-induced bladder tumors. This effect is indeed perplexing, as previous studies have suggested that nitroreduction of nitrofurans carcinogens may be central to their carcinogenicity. Allopurinol partially inhibits this nitroreduction, and it could be hypothesized that a reduction of tumor incidence would result from the concomitant administration of FANFT and allopurinol.

Other factors may be involved in abrogating the effects of allopurinol on nitroreduction. Elevated thiol levels in liver and blood were found in FANFT-treated rats. Additionally, elevated levels of anthranilic acid glucuronide, kynurenine, acetylkynurenine, and 3-hydroxykynurenine were present in urine. None of these biochemical parameters were altered by allopurinol.

The effect of thiol on nitrofurans-tissue interaction has been documented (25, 30). Thiols inhibited the covalent binding of nitrofurans with tissue macromolecules *in vitro* (25, 30). Depletion of thiol with diethyl maleate increased the binding of nitrofurans to macromolecules *in vivo* (25). Nitrofurazone, another carcinogenic nitrofurans, decreased hepatic acid-soluble thiol 2 hr after treatment (25), whereas, in the present long-term study, FANFT increased acid-solu-

Table 3

Hepatic nitroreductase activity of rats fed the diets for 20 weeks

Group ^a	No. of rats	Nitroreductase activity (μmoles/g/hr)	
		Cytosol ^b	Microsomes
1	6	11.24 ± 1.22	4.70 ± 0.74 ^c
2	6	6.74 ± 1.16	4.38 ± 1.38
3	6 ^d	12.14 ± 1.36	5.72 ± 1.02
4	6 ^e	6.44 ± 1.38	4.78 ± 1.20

^a Group 1, control; Group 2, allopurinol treated; Group 3, FANFT treated; Group 4, FANFT-allopurinol treated.

^b $p < 0.01$ for the cytosol nitroreductase activity of Group 1 versus Group 2 and Group 3 versus Group 4.

^c Mean ± S.D.

^d One of 6 rats had bladder cancer.

^e Three of 6 rats had bladder cancer.

Table 4

Tryptophan metabolites in the urine of rats fed the diets for 20 weeks

Group ^a	No. of rats	Urinary metabolites (μmoles/24 hr)								
		Kynurenic acid	Xanthurenic acid	Indican ^b	Anthranilic acid glucuronide ^b	<i>o</i> -Amino-hippurate ^b	Acetyl kynurenine ^b	Kynurenine ^b	3-Hydroxykynurenine	3-Hydroxyanthranilic acid
1	8	0.79 ± 0.18 ^c	0.39 ± 0.07	10.3 ± 1.4	0.19 ± 0.03	0.46 ± 0.08	0.17 ± 0.02	0.18 ± 0.03	0.13 ± 0.13	0.44 ± 0.19
2	8	0.78 ± 0.19	0.37 ± 0.09	9.8 ± 1.4	0.16 ± 0.04	0.43 ± 0.05	0.16 ± 0.01	0.20 ± 0.03	0.14 ± 0.11	0.35 ± 0.18
3	10 ^d	0.83 ± 0.12	0.33 ± 0.09	7.1 ± 0.9	0.28 ± 0.05	0.27 ± 0.04	0.34 ± 0.05	0.49 ± 0.05	0.23 ± 0.23	0.44 ± 0.23
4	9 ^e	0.86 ± 0.19	0.38 ± 0.10	5.6 ± 2.2	0.27 ± 0.04	0.26 ± 0.03	0.39 ± 0.04	0.52 ± 0.07	0.21 ± 0.14	0.35 ± 0.62

^a Group 1, control; Group 2, allopurinol treated; Group 3, FANFT treated; Group 4, FANFT-allopurinol treated.

^b Significant difference ($p < 0.001$) for Group 1 versus Group 3 and Group 2 versus Group 4.

^c Mean ± S.D.

^d None of these rats had bladder cancer.

^e Six of 9 rats had bladder cancer.

ble thiol in liver and blood. The increase in hepatic and blood thiol levels may be due to increased hepatic glutathione reductase activity (C. W. Chiu, S. Hayashida, and C. Y. Wang, unpublished data).

FANFT was associated with increases of anthranilic acid glucuronide, kynurenine, acetylkynurenine, and 3-hydroxykynurenine in urine. A good correlation between urinary kynurenine levels and liver tryptophan oxygenase activity in humans has been reported (1). An increase in kynurenine in the urine may reflect an increase in hepatic tryptophan oxygenase activity. The hepatic enzyme can be induced by cortisol. Abnormal tryptophan metabolism reported in a variety of diseases may be due to adrenal response to stress of the disease, resulting in increased steroid levels causing an adaptation of tryptophan oxygenase (1). This increased oxygenase activity would facilitate the entrance of tryptophan into the kynurenine pathway at such a rate as to overload the subsequent enzymes, causing spillage of the intermediate metabolites into the urine (1, 5). Vitamin B₆ deficiency can also produce an elevation of urinary tryptophan metabolites (3, 32). Whether greater activity in the kynurenine pathway in FANFT-treated rats is due to an elevated steroid level or vitamin B₆ deficiency remains unknown. Since allopurinol does not alter the abnormal excretion of tryptophan metabolites related to FANFT, apparently its effect on bladder cancer induction is unrelated to tryptophan metabolism.

Allopurinol has complex effects on purine and pyrimidine metabolism (19, 22). Excessive excretion of xanthine and orotidine in the urine is observed in human subjects taking allopurinol (17, 22). Allantoin is the main end-product of purine catabolism in the urine of rats (19), whereas the end product in humans is uric acid (7, 19). Allopurinol decreases the excretion of allantoin and increases the excretion of xanthine in the urine of rats (19). Xanthine is almost as insoluble as uric acid in water. Xanthine crystals have been found in rats treated with allopurinol (19). Urinary stones may be a contributing factor in the experimental induction of bladder cancer (16). Xanthine crystals may serve a function similar to urinary stones in enhancing bladder cancer. Allopurinol- and allopurinol-FANFT-treated rats excreted very turbid urine, although no urinary calculi were found. Whether this turbidity was caused by xanthinuria is not known because the xanthine content in the urine was not determined. More information is needed to determine the mechanism of the enhancing effect of allopurinol on bladder cancer induction.

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