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Clinical Pharmacokinetics of 5-Fluorouracil and Its Metabolites in Plasma, Urine, and Bile[1]

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ABSTRACT

Kinetics of 5-fluorouracil (FUra) and FUra metabolites in plasma and urine were investigated in 10 cancer patients following i.v. bolus administration of 500 mg/m² FUra with 600 μCi of [6-³H]FUra. Biliary excretion was examined in two patients with external biliary catheters. Quantitation of unchanged drug and metabolites was assessed by a highly specific high-performance liquid chromatographic method.

FUra plasma levels declined rapidly with an apparent elimination half-life of 12.9 ± 7.3 min. Dihydrofluorouracil was detected within 5 min in most patients, demonstrating rapid catabolism and reached maximum peak levels of 23.7 ± 9.9 μM at approximately 60 min. The apparent elimination half-life of dihydrofluorouracil (61.9 ± 39.0 min) was consistently greater than that of the unchanged drug. The apparent elimination half-lives of the subsequent metabolites α-fluoro-β-ureidopropionic acid and α-fluoro-β-alanine were prolonged with values of 238.9 ± 175.4 min and 1976 ± 358 min, respectively.

Approximately 60–90% of the administered dose was excreted in urine within 24 h, primarily as α-fluoro-β-alanine. Biliary excretion accounted for 2–3% of total administered radioactivity. The major fraction of this radioactivity eluted on high-performance liquid chromatography as a previously unrecognized FUra metabolite. Analysis of its structure is currently ongoing in our laboratory. In conclusion, this study provides the first comprehensive analysis of the formation and excretion of FUra metabolites in plasma, urine, and bile following i.v. bolus administration of FUra in humans.

INTRODUCTION

More than two decades after its synthesis (1), FUra[3] continues to be one of the major agents used in the treatment of breast, gastrointestinal, head and neck, and ovarian cancers (2). Recent investigations have focused on the role of biochemical modulators (3) and alternative dosing schedules (4) in improving the efficacy of FUra. Coincidentally, continuing basic research in the area of FUra anabolism has provided new insights into the "elusive" mechanisms of FUra cytotoxicity (5). In contrast, FUra catabolism, despite being an important component of FUra metabolism (6), has received less emphasis. Although the kinetics of unchanged FUra have been extensively studied (6), an understanding of the formation and elimination of metabolites in patients is fragmented, conflicting, and frequently based on chromatography methods which do not allow a simultaneous quantitation of FUra and its metabolites.

The purpose of the present study was to provide a comprehensive analysis of FUra metabolism in cancer patients following i.v. bolus administration of radiolabeled FUra. Emphasis was focused on plasma FUH_2 levels since recent studies have suggested that FUH_2 appears to be cytotoxic to human cancer cells *in vitro* (7). In addition, the recent demonstration of a FUra glucuronide in isolated rat hepatocytes (8) prompted a search for the presence of this conjugate and possibly other metabolites in human bile.

MATERIALS AND METHODS

Patient Selection. Ten patients participated in the study and had a variety of cancers for which FUra was judged the most appropriate therapy by their attending physicians. All patients had histological evidence of cancer. Pregnant females and children were excluded. All patients gave written informed consent according to institutional guidelines. None had received previous therapy with FUra or other antimetabolites. Baseline values for hepatic and renal function as well as other patient characteristics are listed in Table 1.

Drug Administration. FUra was administered over 1 min by i.v. bolus injection. All patients received an initial dose of 500 mg/m² of FUra. Five of the patients also received a second dose of 750 mg/m² of FUra. [6-³H]FUra (26 Ci/mmol) was obtained from Moravek Biochemicals (Brea, CA). Chemical and radiolabeled purity of [6-³H]FUra was greater than 99% as analyzed by HPLC. Radiolabeled FUra was passed through a 0.22-μm Nalgene filter (Rochester, NY) and 660-μCi aliquots were stored in sterile vials at −20°C until use. Sterility and pyrogen testing were performed either by South Mountains Labs (South Orange, NJ) or Leberco Testing Inc. (Roselle Park, NJ). On the day of treatment, 110% of the dose of "cold" FUra to be administered was mixed with an aliquot of radiolabeled FUra using sterile technique. The calculated dose of FUra (with 600 μCi of [6-³H]FUra) was administered by bolus injection over 1 min. The remaining 10% of the mixture was stored at −20°C, and analyzed periodically for evidence of degradation during storage of the labeled drug.

Sample Collection. A heparin lock was placed in each patient in the arm opposite from drug administration. Two-ml samples of blood were collected in heparinized tubes at 0, 2, 5, 8, 12, 20, 30, 45, 60, 180, and 360 min following injection. In order to deliniate more precisely the kinetics of FUH_2, the last four patients also had additional blood withdrawn at 1.5, 2, 4, 8, and 24 h postinjection. The tubes were immediately placed on ice and later centrifuged at 3–4000 × *g* for 10 min at 4°C. Plasma was separated and stored at −20°C until analysis. Urine was collected in 2-h fractions × 8 h and then 8-h fractions × 16 h. All urine was kept refrigerated during collection and 10-ml aliquots were frozen and stored at −20°C until analysis. Bile from two patients who had preexisting external biliary drainage catheters was collected in 15-min fractions × 1 h, 30-min fractions × 1 h, 2-h fractions × 4 h, 6-h fractions × 18 h, and in one patient additional 12-h fractions × 24 h. Aliquots (10 ml) of each bile sample were frozen and stored at −20°C until analysis.

Analysis of FUra and Metabolites. Unchanged FUra and its metabolites, FUH_2, FUPA, and FBAL were quantitated as previously described (9). Authentic standards of FUra, FUH_2, FUPA, and FBAL were kindly supplied by Hoffmann-LaRoche (Nutley, NJ). Briefly, samples of the biological fluids were passed through a 0.22-μm Acro filter (Gelman Sciences, Ann Arbor, MI) and aliquots of plasma (100 μl), bile (100 μl), or urine (10–200 μl) were analyzed with a model 1084B Hewlett-Packard high-performance liquid chromatograph (Avondale, PA). Two (25 x 0.4-cm) 5-μm RP-18 columns (IBM Instruments, Inc., Poughkeepsie, NY) in tandem were used. Elution was carried out isocratically at 1 ml/min with a mobile phase consisting of 5 mM tetrabutylammonium hydrogen sulfate and 1.5 mM potassium phosphate buffer (pH 8). Samples were collected into 7-ml plastic liquid

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[3] The abbreviations used are: FUra, 5-fluorouracil; FUH_2, dihydrofluorouracil; FUPA, α-fluoro-ureidopropionic acid; FBAL, α-fluoro-β-alanine; HPLC, high-performance liquid chromatography.

Table 1 *Patient Characteristics*

Patient	Age	Sex	Tumor	Body surface area (m^2)	Dose 1 (mg)	Dose 2 (mg)	Serum bilirubin (mg/dl)	Serum creatinine (mg/dl)
C. K.	57	M	Colon	1.98	990	1485	0.6	1.0
V. T.	27	M	Gastric	1.72	860	1290	0.8	1.0
W. M.	47	F	Pancreas	1.92	960	1440	3.4[a]	0.6
W. M., Jr.	58	M	Pancreas	1.96	980	1470	7.4[a]	1.0
L. H.	44	F	Colon	1.72	860	1290	0.8	0.6
R. H.	63	M	Adenocarcinoma of unknown primary	1.88	940		0.6	1.1
W. A.	52	M	Colon	1.72	860		0.7	0.9
J. C.	40	M	Gastric	1.72	860		0.2	0.7
S. B.	48	F	Colon	1.70	850		0.4	1.0
D. J.	63	M	Pancreas	1.72	860		2.4	1.0

[a] External biliary drainage catheter.

scintillation vials using a Redirac 2122 fraction collector (LKB Instruments, Rockville, MD) with radioactivity in each fraction being analyzed with an LS-5801 liquid scintillation counter (Beckman Instruments, Inc., Irvine, CA). Bile samples were analyzed for the presence of a possible FUra glucuronide and other FUra metabolites as well. Samples were analyzed by HPLC with one (25 x 0.4-cm) 5-μm RP-18 column (IBM Instruments Inc., Poughkeepsie, NY) as stationary phase and a water:methanol mixture as mobile phase with the following gradient (0–10 min, 0% methanol; 10–20 min, 0–25% methanol; 20–30 min, 25% methanol; 30–40 min, 25–75% methanol; 40–60 min, 75% methanol). Timed fractions were collected and radioactivity was analyzed as described above.

Pharmacokinetic Analysis. Pharmacokinetic parameters were calculated using a noncompartmental analysis based on statistical moment theory (10). The area under the curve was calculated from time zero to the last time point using the trapezoidal rule with extrapolation to affinity. Elimination half-lives of the unchanged drug and the catabolites (FUH_2, FUPA, and FBAL) were obtained by linear regression analysis of the kinetics terminal points (least-squares method). The apparent volume of distribution was calculated as the product of clearance and mean residence time. The total plasma clearance of FUra was calculated by dividing the dose by the area under the curve. The values for each parameter are reported as mean ± standard deviation.

RESULTS

Kinetics of Unchanged Drug and Metabolites in Plasma. The average plasma levels of FUra and its metabolites for each time point in 10 patients are listed in Table 2. It can be seen that FUra was no longer detectable after 2 h following drug injection. (It should be noted that the limit of detection of our HPLC assay is approximately 2 μM.) In most patients, FUH_2 levels were detectable within 5 min following drug administration. Peak FUH_2 levels were usually observed about 1 h following injection but average FUH_2 plasma levels were relatively constant and ranged between 19.8 ± 8.9 μM and 23.7 ± 9.2 μM from 30 to 90 min. There was a lag of approximately 10 min in most patients between the appearance of FUH_2 and detectable levels of FUPA and FBAL. FUPA gradually increased reaching a maximum peak level of 13.0 ± 6.3 μM at 90 min following FUra injection. Similarly, maximum plasma levels (59.7 ± 18.4 μM) of FBAL were also observed between 60 and 90 min and significant levels (24.3 ± 8.2 μM) persisted 24 h postinjection. The apparent elimination half-life of FUra and its metabolites (FUH_2, FUPA, and FBAL) for each patient are listed in Table 3, as well as the area under the curve, volume of distribution, and total plasma clearance of FUra. The average apparent elimination half-life of FUH_2 was approximately 61.9 ± 39.0 min, representing almost five times the half-life of the unchanged drug (12.9 ± 7.3 min). The apparent elimination half-lives of FUPA and FBAL were also significantly prolonged with values of 238.9 ± 175.4 min and 1976 ± 358 min, respectively. In addition, it should be noted that in order to obtain a more accurate estimate, the apparent elimination half-life of FBAL was calculated using values from the four patients who had plasma samples collected until 24 h postinjection. Plasma concentrations of FUra and its metabolites in an individual patient are shown in Fig. 1. Total radioactivity applied to the columns was recovered (range 90–110%) for both unchanged drug and metabolites except in three patients. In these three patients, later time points were associated with considerably lower recoveries ranging from 18 to 65%. The possibility that unrecovered radioactivity could represent a novel metabolite was then evaluated. A metabolite which did not coelute with any known FUra metabolites and with a similar chromatographic pattern to the metabolite found in bile (see below) was detected in plasma of all three patients. A maximum level of 26 μM for this metabolite was observed in patient L. H. 6 h after FUra administration. In general this metabolite was detected only between 1 and 6 h postinjection.

Table 2 *Plasma levels (μM) of FUra and its catabolites (±SD with range) in 10 patients*

Time	FUra	FUH_2	FUPA	FBAL
5 min	419.8 ± 102.3 (262, 624)[a]	4.0 ± 3.0 (0, 9)	1.0 ± 1.7 (0, 4)	1.1 ± 2.3 (0, 7)
8 min	309.3 ± 69.7 (185, 421)	6.3 ± 3.0 (0, 11)	2.1 ± 2.8 (0, 7)	1.5 ± 1.8 (0, 5)
12 min	216.8 ± 51.6 (150, 316)	9.4 ± 3.2 (3, 13)	3.3 ± 4.0 (0, 10)	4.5 ± 4.9 (0, 13)
20 min	113.9 ± 52.1 (11, 191)	16.5 ± 4.5 (7, 24)	8.5 ± 7.1 (4, 28)	15.6 ± 11.9 (0, 33)
30 min	65.8 ± 33.0 (20, 123)	21.3 ± 5.3 (12, 30)	7.7 ± 5.1 (0, 13)	29.3 ± 17.5 (0, 60)
45 min	22.9 ± 17.8 (2, 53)	21.2 ± 9.7 (3, 36)	9.7 ± 4.9 (3, 16)	51.1 ± 19.4 (29, 87)
60 min	10.4 ± 10.6 (0, 34)	23.7 ± 9.2 (12, 42)	11.5 ± 3.4 (5, 17)	59.7 ± 18.4 (38, 101)
90 min[b]	5.0 ± 9.3 (0, 19)	19.8 ± 8.9 (14, 33)	13.0 ± 6.3 (5, 18)	59.0 ± 21.5 (40, 89)
2 h[b]	ND[c]	13.0 ± 8.8 (4, 25)	10.3 ± 3.9 (5, 14)	53.3 ± 19.4 (25, 68)
3 h	ND	5.4 ± 8.8 (0, 28)	6.8 ± 3.5 (0, 11)	38.3 ± 20.0 (4, 76)
4 h[b]	ND	0.8 ± 1.5 (0, 3)	5.5 ± 4.5 (0, 11)	40.5 ± 18.1 (14, 54)
6 h	ND	0.9 ± 2.0 (0, 6)	1.9 ± 2.7 (0, 7)	20.5 ± 15.5 (5, 43)
8 h[d]	ND	ND	1.7 ± 2.9 (0, 5)	35.0 ± 7.0 (28, 42)
24 h[d]	ND	ND	0.5 ± 1.0 (0, 2)	24.3 ± 8.2 (13, 32)

[a] Numbers in parentheses, range of plasma levels.
[b] Measurements made in four patients.
[c] ND, not detectable.
[d] Measurements made in three patients.

Urinary Excretion. Fig. 2 depicts the cumulative urinary excretion of the unchanged drug, FUPA, and FBAL expressed as the percentage of the total dose. Of note, was the minimal amount of FUH_2 (less than 1%) recovered in urine (data not

Table 3 *Pharmacokinetic parameters of FUra and its catabolites*

Patient	FUra $t_{½}$ (min)[a]	FUra AUC (μM/min)	FUra V_d (liters/m²)	FUra Cl (ml/min/m²)	FUH_2 $t_{½}$ (min)	FUPA $t_{½}$ (min)	FBAL $t_{½}$ (min)
C. K.	16.5	10217	7.89	376	38.5	346.5	144.4
O. T.	8.9	5429	8.48	707	22.5	318.0	83.5
W. M.	7.6	6446	7.15	596	110.3	99.0	407.7
R. H.	11.4	8907	6.89	431	69.3	ND[b]	100.1
L. H.	26.7	11451	6.70	335	ND	64.0	43.3
W. M., Jr.	7.9	6068	6.33	633	46.6	162.9	154.0
S. B.	7.9	6883	6.14	558	43.9	184.3	1858.3
W. A.	5.3	3787	10.14	1014	141.5	597.5	1698.9
D. J.	23.9	6776	19.28	567	39.2	ND	2502.3
J. C.	12.6	5287	9.44	726	45.1	ND	1848.4
Mean ± SD	12.9 ± 7.3	7125 ± 2371	8.84 ± 3.90	594 ± 198	61.9 ± 39.0	238.9 ± 175.4	1976 ± 358[c]

[a] $t_{½}$, apparent elimination half-life; AUC, area under the curve; V_d, volume of distribution; Cl, total plasma clearance.
[b] ND, not determined.
[c] Mean ± SD based on the last four patients of the table whose kinetics were investigated over 24 h.

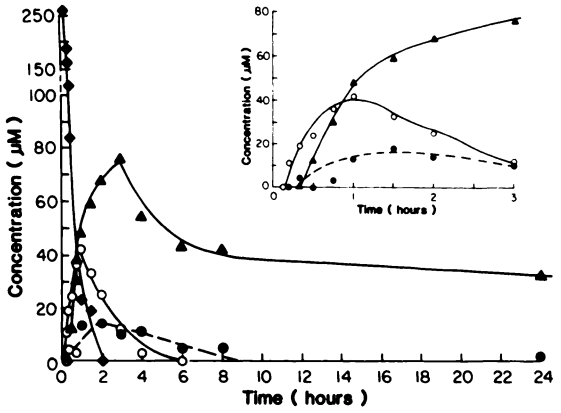

Fig. 1. Plasma concentration of FUra (♦), FUH_2 (○), FUPA (●), and FBAL (▲) in patient D. J. over 24 h following i.v. bolus of 500 mg/m² FUra. *Inset*, expanded time course of FUra catabolites over the initial 3 h.

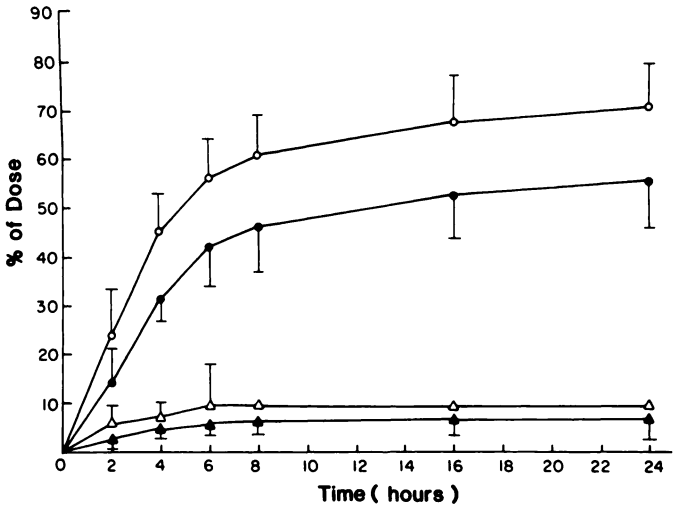

Fig. 2. Urinary excretion of total radioactivity (○), FUra (△), FUPA (▲), and FBAL (●) expressed as the cumulative percentage of administered radioactivity excreted over time. Mean ± SD based on eight patients with complete urine collections.

shown). The excretion of unchanged drug and FUPA was rapid with most occurring within the initial 6 h. FBAL represented the major metabolite in all urine fractions and accounted for as much as 50% of the administered dose of radioactivity. Urine was collected for an additional 24 h in two patients, and only 2% of the administered radioactivity was further excreted during this time period. There was no evidence of the novel metabolite in urine at any of the time periods.

HPLC Analysis of Radioactivity in Human Bile. Fig. 3 shows the concentration in bile of unchanged FUra, metabolite pool,

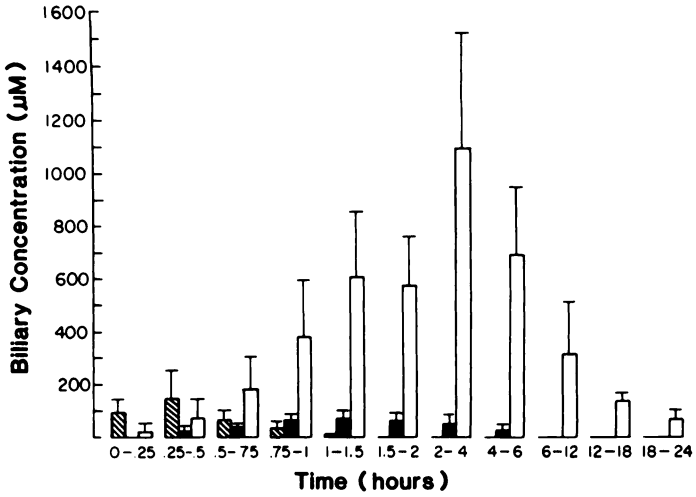

Fig. 3. Bile concentration of FUra (■), catabolite pool (▩), and novel derivative (□), in each timed collection over 24 h. Concentrations are expressed as mean ± SD based on values calculated from two patients with biliary drainage.

and novel FUra derivative for specified time periods following i.v. FUra administration. These data are based on two patients treated with both 500 and 750 mg/m² FUra. The bile levels of the novel metabolite appeared generally higher after 750 mg/m² dose but varied with the volume of bile collected during each time period. Significant concentrations of FUra ranging from 11 to 259 μM were present during the first hour. Bile concentrations of the novel derivative exceeded that of unchanged drug within 30 min postinjection and reached maximum levels of 1088 ± 430 μM between 2 and 4 h, and subsequently declined to approximately 50 μM after 18–24 h. Total biliary excretion of radioactivity represented 2–3% of the total dose over 24 h. In one patient, bile was collected for an additional 24 h and only 0.1% of total radioactivity was further excreted.

DISCUSSION

Our knowledge of FUra metabolism in humans has been limited by the unavailability of a methodology that would permit accurate quantitation of unchanged drug and its putative metabolites (FUH_2, FUPA, and FBAL). The present study utilizes a rapid, specific, and reproducible HPLC method which allows simultaneous resolution of FUra and its metabolites, clarifying for the first time the kinetics of FUra metabolite formation and excretion following i.v. bolus administration of FUra.

The pharmacokinetic data ($t_{½}$, V_d, and Cl) of unchanged FUra in the present study are in agreement with previous reports in the literature determined by different methodologies (11–15). In contrast, there has been a paucity of detailed information regarding kinetics of FUra metabolites. In particular, there has been conflict regarding the quantitative importance of FUH_2, the initial catabolite of FUra. In the original studies of Heidelberger and associates (12) FUH_2 was not detectable in either serum or urine, possibly reflecting chemical breakdown of FUH_2 due to prolonged alkaline exposure during analysis. More recently, utilizing a gas chromatography/mass spectrometry methodology, Aubert *et al.* (16) detected significant levels (5–15 μM) of FUH_2 after administration of FUra by either i.v. bolus or short i.v. infusion of drug over 8 h. However, only two patients were studied and no pharmacokinetic data for FUH_2 were reported. Subsequently, McDermott *et al.* (13) using a gas chromatography method with an electron capture detector, assessed the plasma levels of FUH_2 in nine patients after administration of FUra. Surprisingly, FUH_2 was present in only five of nine patients studied, again raising the question of the quantitative importance of this metabolite. In our study, we demonstrated that FUH_2 was present in plasma of each of the 10 patients at multiple time points with doses of FUra commonly used in clinical practice.

The importance of these elevated FUH_2 plasma levels is further emphasized by our recent report that FUH_2 may have cytotoxic properties itself (7). The mechanism of FUH_2 cytotoxicity remains unclear but in part may be explained by the reversibility of the enzyme, uracil reductase, that converts FUra to FUH_2 (17). When FUH_2 formation was analyzed with an increased dose of 750 mg/m^2 FUra, no significant difference in plasma levels could be ascertained, suggesting saturation of uracil reductase at this dose (data not shown).

In agreement with earlier studies (12, 18), FUPA and FBAL were detected in plasma. However, in contrast to these earlier findings which suggested that FUPA was the major plasma catabolite, we have demonstrated FUPA to be a transient and minor plasma metabolite. This is in agreement with our recent reported studies in rat hepatocytes (9). A possible explanation for the elevated levels of FUPA observed in earlier studies (12, 18) was the probable chemical degradation of FUH_2 to FUPA. In our study, FBAL was the major plasma metabolite particularly at late time points.

Urinary excretion represents the major pathway of elimination of polar derivatives of FUra in humans (6). Previous studies have demonstrated approximately 60–90% of total administered dose was recovered in urine (12, 13). However, limited information has been available regarding excretion of individual metabolites except in one patient described by Heidelberger and Mukherjee (12). Our results are in agreement with these studies demonstrating that 60–90% of total radioactivity is excreted in urine within 24 h. Of importance, is the clarification of the excretion pattern of individual metabolites during this interval. FBAL accounted for more than 70% of total radioactivity excreted in urine with FUra and FUPA being minor metabolites. In contrast, FUH_2 represented less than 1% of radioactivity in urine and was detected only in the first 2 h of collection.

The high concentration of a novel FUra metabolite in bile is a new observation regarding FUra metabolism in humans. Biliary excretion of FUra was previously examined by Douglas and Mittelman in two patients with surgically placed T-tubes (19). They demonstrated that unchanged FUra appeared rapidly in bile and was no longer detectable 3 h following injection. No other FUra metabolites were detected, which may reflect inadequate resolution by the thin layer chromatography method they utilized. Our motivation for searching for the presence of FUra metabolites in bile was based on a recent study from our laboratory in which the presence of a FUra-glucuronide was isolated from rat hepatocytes (8). Preliminary studies with HPLC suggest that this novel metabolite detected in bile of cancer patients treated with [6-^{3}H]FUra is not a FUra glucuronide. Studies to identify this biliary FUra metabolite are currently in progress.

In summary, the results of the present study provide the first comprehensive analysis of formation and excretion of FUra metabolites following i.v. bolus injection of FUra in cancer patients. Of particular note, the substantial plasma levels of FUH_2 detected suggest that FUH_2 may participate in the cytotoxicity of FUra. In addition, further evaluation of the structure of the novel metabolite of FUra observed in bile will be needed.

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