Cancer Chemother Pharmacol (1988) 22: 5–10

Cancer Chemotherapy and Pharmacology

Effect of uridine coadministration on 5'-deoxy-5-fluorouridine disposition in rats*

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Summary. Uridine (UR) inhibits the metabolic activation of 5'-deoxy-5-fluorouridine (dFUR) to 5-fluorouracil (FU) by the intestinal pyrimidine nucleoside phosphorylases and could potentially reduce its intestinal toxicity. This study examined the effect of UR coadministration on the absorption and disposition of an oral dose of dFUR. Rats were given dFUR alone (500 mg kg^{-1}) and dFUR (300 mg kg^{-1}) plus UR (4.5 g kg^{-1}) in a random crossover experiment. Simultaneous injection of a tracer dose of [6-^{3}H]dFUR was used to asses the total body clearance (Cl) of dFUR. The absorption of UR was rapid and variable. The UR dose produced a maximal blood concentration of 80 μg/ml for UR and 100 μg/ml for its metabolite uracil (U). The absorption of dFUR was slower than UR, as indicated by its later time of maximal concentration. UR did not alter the Cl of dFUR, but reduced the absorption rate of dFUR from the gastrointestinal tract and significantly reduced the absolute oral bioavailability of dFUR from 55.2% to 33.4%. The effects of UR coadministration on the dFUR metabolite FU were opposite to those on dFUR; the FU availability was increased sixfold, and the elimination of FU was reduced. Based on the known competition between pyrimidine bases for their saturable metabolic enzymes, the increase in FU availability by UR coadministration was likely due to a competitive inhibition of FU metabolism by U. This study established the complex pharmacokinetic interactions between dFUR and UR and between their metabolites, which may be important in the modulation of dFUR activity by UR.

Introduction

5'-Deoxy-5-fluorouridine (dFUR) is a metabolic prodrug of 5-fluorouracil (FU) [12, 13]. Both compounds are used in the palliative treatment of solid tumors [1, 2, 12, 28]. FU is usually administered by the i.v. route [12], rarely by the oral route, as the bioavailability of oral FU is erratic, varies several-fold among patients and cannot be predicted from pretreatment liver function tests [12]. The bioavailability of FU is erratic partly because of its rapid presystemic gastrointestinal-hepatic first-pass metabolism, which is dose-dependent and saturable [12]. We compared the intrinsic clearance of FU and dFUR in rat liver and small intestine, and found that the dFUR clearance by these tissues represents <5% of the FU clearance [5]. Consistent with its low presystemic gastrointestinal-hepatic clearance, the oral bioavailability of dFUR is high, ranging from 60% in rats to 80% in man with a relatively small coefficient of variation (<30%) [6, 18]. The oral route of administration is convenient, especially for continuous long-term therapy. The high and constant bioavailability of dFUR together with its relatively long half-life in plasma make dFUR suitable for oral use. dFUR is currently used orally in Japan [28].

dFUR is activated to FU by phosphorylases. These enzymes are present in tumors and in various normal tissues. The small intestines, liver and kidney have the highest activity, while the bone marrow contains little or no activity [3, 5, 19]. The small intestines metabolize about 10% of the dFUR presented to the tissue during a single passage [5]. This represents a significant amount of FU in terms of activity, because FU is 100 times more potent than dFUR on a molar basis [4, 8, 9]. One study showed that the intestinal toxicity of dFUR in patients is higher by the oral route than by the i.v. route [28]. It is possible that the intestinal toxicity of oral dFUR is partly due to the high dFUR concentration in the intestine, resulting in localized formation and high concentration of FU. Another possible cause of the intestinal toxicity is the prolonged duration of exposure due to the long biological half-life of dFUR; it has been shown that a continuous i.v. infusion of FU produces greater gastrointestinal toxicity than a bolus i.v. injection of the same dose [12]. Because the activation of dFUR to FU by pyrimidine nucleoside phosphorylases is required for its activity [4, 8, 19], inhibition of intestinal phosphorylases may reduce the intestinal drug toxicity.

We previously showed that uridine (UR), a physiologic substrate for pyrimidine nucleoside phosphorylases, inhibits the conversion of dFUR to FU in the rat small intestines [31]. The inhibition constant of UR is about 20 μg/ml, while the Michaelis-Menten constant of dFUR phosphorolysis is about 200 μg/ml [31]. UR is currently used in patients to modulate the biological activities of fluorinated pyrimidines [22, 30], and could be implemented in clinical dFUR protocols if shown effective in reducing dFUR tox-

* Supported in part by research grants CA-37110, CA-43365 and P30CA16058-12 from the National Cancer Institute, USPHS

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icity. Based on the rapid clearance of UR in humans [22], the nearly complete extraction of UR by perfused rat livers after a single passage [16, 24] and the rapid intestinal metabolism of UR [31], we postulated that UR given orally would be eliminated by presystemic metabolism and would not enter the systemic circulation in appreciable quantities. This will allow localized inhibition and protection of the intestines and will not compromise the systemic antitumor activity of dFUR. Potential pitfalls are the effects of UR on intestinal drug absorption, presystemic intestinal and hepatic first-pass elimination, and systemic clearance of dFUR and FU. To investigate the potential of UR as a protecting agent and to find the effective UR dose, the pharmacokinetic interaction between UR and dFUR needs to be established, and was examined in the present study.

Material and methods

Chemicals and reagents. [6-^{3}H]dFUR (specific activity, 1.83 μCi/μg) was obtained from Moravek Biochem (City of Industry, Calif.), unlabeled dFUR (lot number 7445-114) from Hoffmann LaRoche, Inc. (Nutley, NJ), UR from Sigma Chemical Co. (St. Louis, Mo.) and all other high-pressure liquid chromatography (HPLC) or reagent grade chemicals and solvents from Sigma and Fischer Scientific (Cincinnati, Ohio). HPLC analysis showed that [6-^{3}H]dFUR was >98% pure, UR and unlabeled dFUR >99.5% pure.

Animal protocol. Female Fischer rats 2–3 months old were housed in metabolic cages and had access to food and water ad lib. Permanent catheters were implanted in the right jugular veins under ether anesthesia 1 day before the study. Six rats received by oral gavage 500 mg kg^{-1} dFUR alone or a combination of 300 mg kg^{-1} dFUR and 3 g kg^{-1} UR followed by 1.5 g kg^{-1} UR at 60 min on days 1 and 4 in a random crossover experiment. The administered volume was equal for both treatments. Each oral treatment was followed 5 min later by an i.v. injection of 6–12 μCi [6-^{3}H]dFUR over 1 min through the venous catheter. The drug concentrations in normal saline were 111 mg/ml dFUR, 635–800 mg/ml UR and 30 μCi/ml [6-^{3}H]dFUR. The pH of the drug solutions was adjusted to 7 with 1 *N* NaOH. Serial blood samples were withdrawn through the venous catheter and kept on ice to avoid dFUR degradation by serum phosphorylases. The pretreatment body weight of the rats was 132.2±10.9 g (mean ± SD) for dFUR alone and 138.0±9.2 g for dFUR + UR.

Dose selection was based on the following considerations. The 500 mg kg^{-1} dFUR dose is active and 7 days' treatment produces 90% cures in rats bearing transplanted dimethylhydrazine-induced colon tumors [9, 29]. A preliminary experiment established a steep dose-response of oral dFUR in rats: a 600 mg kg^{-1} dose was relatively nontoxic and produced a body weight loss of less than 10%, whereas animals died within 10 days when the dose was increased by 16% to 700 mg kg^{-1}. UR coadministration was expected to reduce the presystemic first-pass elimination and hence increase the systemic bioavailability of dFUR. To avoid potential toxicity, the dFUR dose was reduced to 300 mg kg^{-1} when it was coadministered with UR. The degradation of UR by intestinal enzymes was more rapid than that of dFUR [31]. The reason for administering a dose of UR 15 times higher than that of dFUR was to maintain effective inhibitory concentrations of UR.

Sample analysis. Blood samples were analyzed as described previously [9]. In brief, 200 μl blood was mixed with the internal standard 5-bromouridine (BU), extracted and analyzed by HPLC using a reverse-phase μBondapak C_{18} column (Waters Assoc., Milford, Mass.), and an aqueous mobile phase (pH 5.0) containing 2.5 m*M* ammonium acetate and 1.5% methanol. BU, dFUR, UR, FU and U were detected by their absorbances at 254 and 280 nm. The peak heights of BU in all samples varied by less than 20%. The maximum [6-^{3}H]dFUR concentration was <0.3% of the unlabeled dFUR. Hence, the drug concentration quantitated by UV absorbance represented >99% unlabeled dFUR and did not require correction. The standard curves established using the UV absorbance peak height ratios of the drugs to BU were linear from 25 to 2000 ng/ml for FU (r^2 = 0.998), from 2.5 to 250 μg/ml for dFUR (r^2 = 0.995), from 1 to 80 μg/ml for UR (r^2 >0.998) and from 0.5 to 50 μg/ml for U (r^2 >0.995). The coefficients of variation at the highest and lowest concentrations were 2% and 10% respectively for FU, 2% and 5% for dFUR, 2.5% and 7.3% for UR and 7.6% and 7.2% for U. [6-^{3}H]dFUR in HPLC-eluting fractions was determined by liquid scintillation counting using a Beckman model LS8100 counter with a 50% counting efficiency. The standard curve for [6-^{3}H]dFUR, established from the ratios of the dFUR radioactivity to the UV absorbance of BU, was linear from 0.2 to 100 nCi per 200 μl (r^2 = 0.9999).

Data analysis. The blood concentration-time data of [6-^{3}H]dFUR were analyzed using model-independent and model-dependent methods. In the model-independent analysis, the area under the drug concentration-time curve (AUC) was calculated by the linear trapezoidal rule. The blood clearance (Cl) of [6-^{3}H]dFUR was calculated as dose divided by AUC [25], and the volume of distribution at steady state (Vd_{ss}) by the method of Benet and Galeazzi [10]. In the model-dependent analysis, the i.v. [6-^{3}H]dFUR data were computer-fitted to a two-compartment body model using the NONLIN84 pharmacokinetic data analysis program (Metzler and Weiner, Statistical Consultants, Inc., Lexington, Ky.). This program provides the best estimates of AUC, CI, volumes of distribution, and the rate constants of distribution and elimination. The computer-fitted microconstants of intercompartmental transfer processes (k_{12} and k_{21}), and the elimination constant (k_{el}) were used together with the Loo-Riegelman analysis [23] to examine the absorption profile of dFUR after oral administration.

The bioavailability (F) of the oral unlabeled dFUR is given by Eq, 1 [25].

$$F = \frac{AUC_{oral} \times Cl_{[6\text{-}^3H]dFUR}}{Dose_{oral}} \quad (1)$$

Results

Clearance of i.v. [6-^{3}H]dFUR

The clearance of an i.v. tracer dose of a drug administered simultaneously with an oral dose gives the systemic clearance of the drug during and after its oral absorption [6]. The blood concentration-time curves of [6-^{3}H]dFUR after

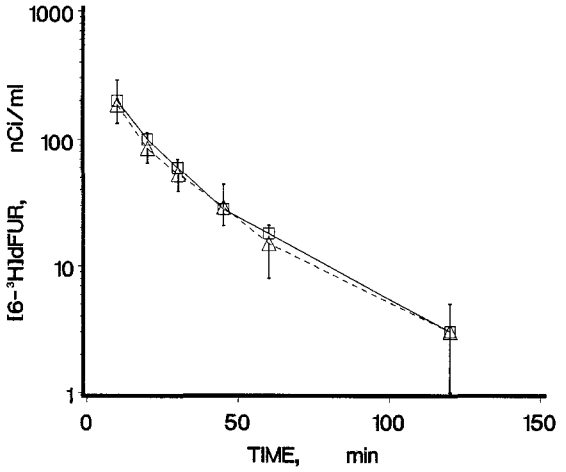

Fig. 1. Blood concentration-time profiles of [6-^{3}H]dFUR. Six rats received two oral treatments in a crossover experiment. On one occasion, the animals received 500 mg kg^{-1} dFUR alone, and on the other occasion a combination of 300 mg kg^{-1} dFUR plus 3 g kg^{-1} UR followed by 1.5 g kg^{-1} UR at 60 min. Five minutes after initiation of each treatment, an i.v. tracer dose of [6-^{3}H]dFUR (6–12 μCi, or 3.3–6.6 μg) was administered to determine the systemic pharmacokinetics of dFUR. The [6-^{3}H]dFUR concentrations during treatment with dFUR alone (*triangles*) and with dFUR + UR (*squares*) are shown. Mean and 1 SD

oral dFUR with or without UR are almost superimposable (Fig. 1). The pharmacokinetic parameters of dFUR after the two treatments were not different (Table 1), indicating that UR did not alter the systemic clearance or distribution of dFUR. The dFUR clearance of about 15–18 ml kg^{-1} min^{-1} is comparable to that previously observed [6]. The computer-predicted blood concentrations, using a two-compartment body model, differed by less than 10% from the observed concentrations, and model-dependent and model-independent calculations gave similar clearance values (Table 1), indicating that the disposition of dFUR is well described by a two-compartment body model. The intercompartmental transfer and elimination constants generated from the compartmental analysis were used to examine the oral absorption of dFUR.

Disposition of oral dFUR

Figure 2 shows the blood concentration-time profiles of unlabeled dFUR concentrations derived from the oral dose. After dFUR alone, the time for the drug concentration to reach its maximum (t_{max}) was between 1 and 2 h. The apparent t½ of the terminal log-linear slope ranged from 100 to 190 min (mean ± SD: 126.5 ± 34.5 min). After dFUR + UR, the t_{max} of dFUR concentration was approximately the same, but the dFUR concentrations were 3–5 fold lower. The apparent terminal t½ ranged from 143 to 352 min (mean ± SD: 241.8 ± 82.6 min). The terminal t½ of oral dFUR was 6-10 times longer than the terminal t½ of 24 min for i.v. dFUR. This indicates that the kinetics of oral dFUR are described by the "flip-flop" model for oral absorption, and that the absorption rate of dFUR was slower than its elimination rate [25]. UR significantly reduced the absolute oral bioavailability of dFUR (Table 2).

Absorption rate profile

The rate of absorption of dFUR over time was determined by the Loo-Riegelman analysis [23]. The absorption rate-time profiles (Fig. 3) show that the absolute rate of dFUR absorption (in μg/min) between 0 and 4 h was about 3 times lower after UR coadministration. The apparent absorption rate constants of dFUR, which are not affected by the difference in dFUR dose between the treatments, were also determined by the Loo-Riegelman analysis, and showed a 1.7-fold reduction of dFUR absorption by UR. The Loo-Riegelman analysis assumes unaltered kinetics between the i.v. and oral treatments. This condition was

Table 1. Effect of UR on the pharmacokinetics of dFUR

	Cl (ml min^{-1} kg^{-1})	Volume (ml kg^{-1})	t½ (min)	$k_{12} \times 10^4$ (min^{-1})	$k_{21} \times 10^4$ (min^{-1})	$k_{el} \times 10^4$ (min^{-1})
Model-independent analysis						
dFUR	15.7 ± 3.0 (12.0–20.0)	352 ± 43[a] (306–398)	25.5 ± 9.3 (17–42)	NA	NA	NA
dFUR + UR	15.5 ± 2.0 (11.8–17.9)	346 ± 60[a] (279–422)	23.8 ± 8.5 (12–37)	NA	NA	NA
P	NS	NS	NS			
Compartmental analysis						
dFUR	16.7 ± 3.2 (13.2–21.3)	272 ± 38[b] (226–321)	24.5 ± 9.6 (17–43)	227 ± 111 (94–427)	506 ± 221 (234–772)	623 ± 96 (517–790)
dFUR + UR	18.2 ± 1.6 (16.4–20.7)	302 ± 92[b] (203–447)	26.5 ± 9.1 (19–44)	171 ± 78 (65–245)	431 ± 163 (207–641)	603 ± 135 (464–839)
P	NS	NS	NS	NS	NS	NS

Six rats received on days 1 and 4 in a crossover experiment two oral treatments of 500 mg kg^{-1} dFUR alone and a combination of 300 mg kg^{-1} dFUR plus 3 g-kg^{-1} UR followed by 1.5 g kg^{-1} UR at 60 min. An i.v. bolus injection of [6-^{3}H]dFUR (6–12 μCi) was given 5 min after each oral treatment. The i.v. data were analyzed either by a model-independent method or by computer fitting to a two-compartment open body model. k_1, k_{21}, and k_{el} are the intercompartmental transfer and elimination constants obtained from the computer analysis. Data are presented as mean ± SD with the range in parentheses. NA, not applicable. Statistical differences were analyzed by two-tailed paired *t*-test. NS, not significant

[a] Volume of distribution at steady state

[b] Volume of distribution of central compartment

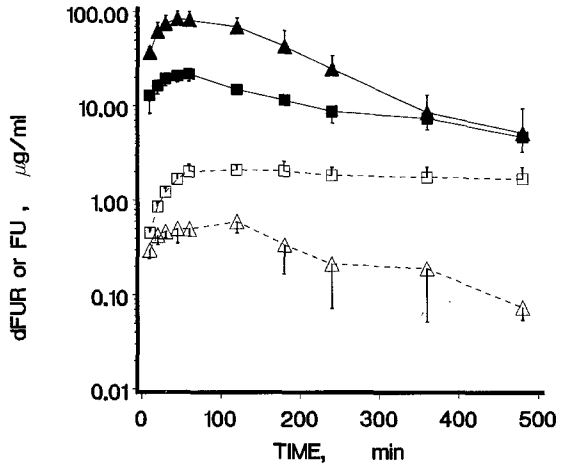

Fig. 2. Blood concentration-time profiles of unlabeled dFUR and its metabolite FU. Concentrations of dFUR (*solid symbols*) and FU (*open symbols*) obtained after oral administration of dFUR alone (*triangles*) or dFUR + UR (*squares*) are shown. See Fig. 1 for further description of the experimental design. Mean and 1 SD

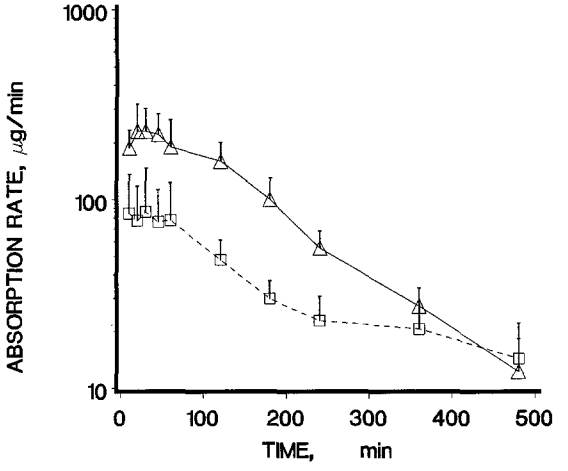

Fig. 3. Oral absorption rate-time profiles of dFUR. The computer-fitted intercompartmental transfer and elimination constants and the oral data of unlabeled dFUR were analyzed for the rate of drug absorption using the Loo-Riegelman method. *Triangles*, dFUR alone; *squares*, dFUR + UR. *Time* is mid-time. Mean and 1 SD

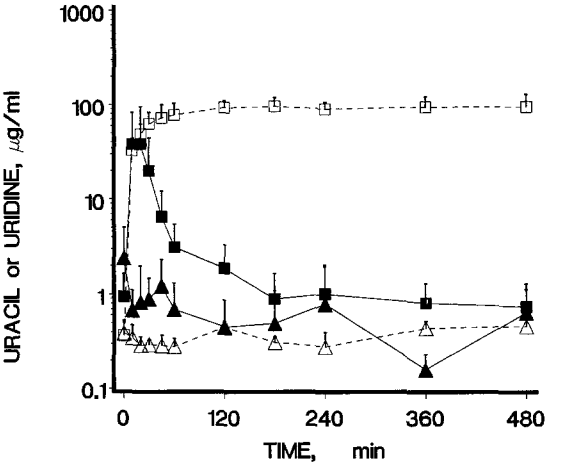

Fig. 4. Blood concentration-time profiles of UR and its metabolite U. Six rats received dFUR alone (*triangles*) and dFUR + UR (*squares*) as described in Fig. 1. Concentrations of UR (*solid symbols*) and U (*open symbols*) are shown. Mean and 1 SD

ensured by the concomitant administration of an i.v. tracer dose during the oral experiment.

Of the dFUR absorbed during the 8-h observation period, most was absorbed during the first 4 h. After dFUR alone the fraction absorbed was 93%, whereas after dFUR + UR only 77% was absorbed. Hence UR delayed the dFUR absorption. These data together with the lower dFUR bioavailability indicate that UR inhibited the rate and reduced the extent of gastrointestinal absorption of dFUR.

Systemic availability of FU

After dFUR alone, the concentrations of FU derived as a dFUR metabolite rose to a maximum at 2 h and declined by about 90% at 8 h. After dFUR + UR, the FU concentrations reached a plateau at 2 h and declined at a much slower rate, to be reduced by only <20% at 8 h (Fig. 2). Thus, UR significantly increased the terminal t½ and the systemic availability of FU (Table 2). The AUC of FU, when expressed as a fraction of the AUC of dFUR, was 20 times higher after dFUR + UR than after dFUR alone. Although no reference dose of FU was administered, these data indicate that the clearance of FU was reduced by UR coadministration.

Table 2. Effect of UR on the systemic biovailability of dFUR and its metabolite FU

	dFUR		FU	
	AUC[a] (mg min^{-1} ml^{-1})	Bioavailability (%)	AUC[a] (mg min^{-1} ml^{-1})	AUC(FU)/AUC(dFUR) (%)
dFUR	16.68±2.88 (12.2–20.2)	55.7±11.6 (36.1–66.7)	0.13±0.03 (0.10–0.18)	1.52±3.10 (0.94–1.89)
dFUR + UR	5.26±0.52 (4.48–5.81)	32.7±6.8 (25.6–43.8)	0.85±0.14 (0.62–1.04)	30.5±4.5 (26.0–38.7)
P	<0.02	<0.005	<0.005	<0.002

Six rats received two oral treatments, 500 mg kg^{-1} dFUR alone and 300 mg kg^{-1} dFUR plus UR, on days 1 and 4 in a crossover experiment. Data are presented as mean ± SD with the range in parentheses. Statistical differences were analyzed by two-tailed paired *t*-test

[a] AUC was from time zero to 480 min

Disposition of UR

The orally administered UR dose produced a maximal blood concentration ranging from 3 to 140 μg/ml, which indicates a highly variable absorption. The t_{max} was between 10 and 30 min, indicating rapid absorption. The UR concentration declined rapidly, returning to its pretreatment (endogenous) level of 1.2 μg/ml at 3 h and in most cases even earlier. However, the maximum concentration of its metabolite U ranged from 40 to 70 μg/ml and was >200 times its pretreatment level of 0.17 μg/ml. The concentrations of U reached a plateau at 2 h and did not decline significantly until after 8 h, indicating its slow elimination. After administration of dFUR alone, UR and U were not elevated.

Discussion

The absorption of UR from the gastrointestinal tract was more rapid than that of dFUR, as indicated by the shorter t_{max} for UR. UR was metabolized rapidly to U, either before its absorption by presystemic gastrointestinal and hepatic tissues and/or after its absorption. The rapidly declining UR concentrations and the high and slowly declining U concentrations are similar to the findings in mice given an oral dose of UR [20]. In humans given 300 mg kg^{-1} of UR orally, the peak plasma concentrations of UR and U were 21 and 10 μg ml^{-1} [30]. The bioavailability of UR was low (<7%). The estimated mean residence time of UR in man was 200–300 min [30], suggesting a much slower decline of UR concentration to the pretreatment level than in rats.

Coadministration of UR produced opposite effects on the elimination and availability of dFUR and its metabolite FU. The UR concentrations in plasma only transiently exceeded the concentration corresponding to the inhibition constant of dFUR phosphorolysis (20 μg ml^{-1}) in rat intestinal tissue [31]. This is consistent with the observation that UR did not alter the systemic clearance of dFUR. UR also did not alter the distribution of dFUR. However, UR did decrease the apparent absorption rate constant of dFUR from the gastrointestinal tract during the first 4 h. Based on a transit time of 6–8 h for solids in rat small intestines [21], it can be inferred that UR inhibited the dFUR absorption in the small intestine, the site of maximal drug absorption [21], and resulted in incomplete absorption and reduced absolute oral bioavailability of dFUR. The saturable transmembrane transport of dFUR [11] and gastrointestinal absorption of UR [26] further suggest that UR competitively inhibited the transport of dFUR in the small intestine.

Coadministration of UR decreased the elimination and increased the AUC of FU. dFUR is eliminated primarily by metabolism, and its conversion to FU is the major metabolic pathway [4, 9, 15, 19, 27]. When administered separately, FU is cleared 6 times faster than dFUR [9]. Hence the kinetics of FU as a metabolite of dFUR are expected to follow the formation-rate-limited metabolite kinetics characterized by a constant ratio of drug and metabolite concentrations [25]. This was the case after dFUR alone, where the FU concentrations declined in parallel with the dFUR concentrations. However, after dFUR + UR, the FU concentration had a slower terminal slope than dFUR, indicating that the FU kinetics were altered and that the elimination rate of FU was no longer limited by its formation rate. The higher AUC of FU after dFUR + UR than after dFUR alone could be due to an increased formation (from systemic and/or presystemic metabolism of dFUR) and/or reduced elimination. The unchanged dFUR clearance and decreased dFUR availability rule out an increased systemic conversion of dFUR to FU. An increased first-pass metabolism of dFUR to FU is unlikely, as UR is an inhibitor of dFUR phosphorolysis [31]. Hence the increased FU availability could not be due to an increased formation. On the other hand, FU shares the same metabolic pathways with other pyrimidine bases. U and another pyrimidine base, thymine, have been shown to competitively inhibit the degradation of FU in dogs [14] and patients [7]. Competitive inhibition of FU degradation by U is the most likely cause of the reduced elimination and increased availability of FU on coadministration of UR.

The results of this pharmacokinetic study establish the complex interactions between dFUR and UR and between their metabolites. These data are important in exploring whether potentially useful biochemical interactions in isolated cells or tissues can lead to enhanced therapeutic activity or whether the potential benefit would be compromised by a pharmacokinetic interaction in vivo. The reduction by UR of the absorption and oral bioavailability of dFUR may lower the systemic antitumor effect and toxicity of dFUR. But this will be compensated by the increased FU availability. The increase in FU availability effected by thymidine led to enhanced systemic toxicity in patients [14]. A separate experiment confirmed that UR coadministration potentiated the lethality of dFUR in rats (unpublished results). Simultaneous administration of oral dFUR and UR to mice resulted in enhanced antitumor activity and hematologic toxicity [17]. In humans, the concentrations of U after oral UR have not been described in detail, but may be lower than in rats. This raises the possibility that a combination of dFUR and UR would be more effective in humans than in rodents. The results of this study indicate that dose adjustments may be necessary and that the pharmacokinetic interaction between UR and dFUR after concomitant oral administration may need to be considered when UR is used to modulate the activity of dFUR.

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Received October 8, 1987/Accepted January 15, 1988