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Original Articles

Pharmacokinetics of Ftorafur After Intravenous and Oral Administration

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Summary. *The pharmacokinetics of ftorafur (FT), an antineoplastic agent, has been studied in seven cancer patients by determining concentrations of the unchanged compound in serum after single IV and PO doses of 2 g FT. Serum drug concentrations were determined by a new quantitative thin-layer chromatographic method. After IV administration, the mean half-lives of the distribution phase and elimination phase were 1.0 h and 7.6 h, respectively. Total serum clearance was 69 ml/h · kg and the apparent volume of distribution was 0.66 l/kg. Following PO administration there was a short lag-time, 11 min, before the appearance of FT in peripheral serum, and the maximum concentration in peripheral serum was achieved in 3.2 h. Oral absorption was complete and no significant first-pass metabolism could be observed. FT elimination, measured in serum taken from the portal vein and a peripheral vein, occurred substantially at the same rate after IV and PO administration. In contrast, after the PO dose FT appeared in the portal serum significantly earlier than in the peripheral serum, resulting in a difference of 1.7 h in the time of maximum serum concentration. This indicates fast gastrointestinal absorption of FT but hepatic retention (without metabolism) before the appearance of FT in the peripheral serum.*

Introduction

Ftorafur [FT, R,S-1-(tetrahydro-2-furanyl)-5-fluorouracil] is an anticancer agent that has been succesfully used for treatment of several inoperable neoplasms. The drug is considered to be a prodrug that is slowly metabolized to 5-fluorouracil (5-FU) in vivo [5, 8, 13]. Two separate metabolic pathways of FT activation to 5-FU have been presented, one that is mediated by the hepatic cytochrome P-450 enzyme system and another that occurs in target tissues without the action of cytochrome P-450 [1].

The pharmacokinetics, especially metabolism, of parenterally administered FT in man has been extensively studied during last few years [e.g., 2, 4]. Little, however, is known about the bioavailability and other pharmacokinetic parameters of orally administered drug.

The present study was undertaken to evaluate FT pharmacokinetics after IV and PO administration in seven patients with liver cancer. In four patients serum drug levels were simultaneously determined in the portal vein and a peripheral vein.

Materials and Methods

Subjects. Five female and two male patients with primary or secondary liver cancer were investigated (Table 1). The diagnosis of each case was verified histologically from a biopsy sample taken during laparotomy. All had inoperable tumors and antineoplastic therapy with FT was indicated. None was anemic and all had normal serum creatinine levels, but most patients had alterations in liver function tests (Table 1). Informed consent was given by all the subjects before the study.

Table 1. Characteristics of the patients

Patient	Age (years)	Sex	Weight (kg)	Type of liver cancer	Liver function tests					
					bil	AFOS	ALAT	ASAT	alb	thromb
1	30	M	58	Metastases of sarcoma	5	434	33	30	41	52
2	36	F	41	Hepatoma	21	704	29	105	34	41
3	51	F	61	Metastases of colon cancer	8	480	54	49	40	100
4	55	M	62	Gallbladder cancer	5	245	28	17	39	66
5	62	F	48	Hepatoma	15	568	57	137	36	25
6	65	F	55	Metastases of colon cancer	7	471	11	18	39	100
7	72	F	65	Metastases of pancreatic cancer	46	1,751	135	318	41	28

Abbreviations: bil, total serum bilirubin (normal values in our laboratories: 3–17 μmol/l); AFOS, serum alkaline phosphatase (50–250 U/l); ALAT, serum alanine aminotransferase (40 U/l); ASAT, serum aspartate aminotransferase (40/l); alb, serum albumin (37–50 g/l); thromb, thrombotest (> 70%)

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Study Protocol. Single doses of 2.0 g of commercial product of FT (Ftorafur, Farmos Group Ltd, Finland) were used. For IV administration (infusion time 2–4 min) the drug was dissolved in 200 ml of saline. The PO dose was given in five capsules. All patients received an IV and a PO dose separated by 5–7 days. Blood samples were taken before and 5, 10, 15, and 30 min and 1, 2, 4, 8, 12, 24, and 30 h after administration from an antecubital vein in all subjects. An effective cytostatic content in the liver tissue can be achieved by giving the drug directly into the hepatic portal vein by means of an implanted catheter. It was thus possible to collect blood samples from the portal vein simultaneously with the peripheral blood samples in four patients in whom catheters had been implanted. Serum separated by centrifugation was stored frozen (−20° C) until analyzed.

Drug Assay. Serum FT concentrations were determined by a novel quantitative thin-layer chromatography technique. A 0.5-ml aliquot of serum was adjusted to pH 4.0 with 1.0 ml Sörensen citrate buffer and was extracted for 10 min with 1.0 ml ethylacetate on a reciprocating shaker. After a brief centrifugation, 20 µl of the organic phase was applied to a silica gel TLC plate with an automatic spotter (Linomat III, Camag, Switzerland). The plate was developed with ethylacetate : methanol : 25% aqueous ammonia (75 : 25 : 5) and scanned with a chromatogram spectrophotometer (KM3, Zeiss, FRG) in the reflectance mode at 274 nm. Quantification was achieved by comparison of the integrated peak areas for samples and standards. The limit of detection of this method was 1 µg FT/ml serum, and the precision in the concentration range 5–100 µg/ml, given by the relative standard deviation, was in the range of 3%–5%. The extraction recovery of FT was 90%.

Calculations. After IV administration the serum FT concentration/time data were analyzed using a linear two-compartment open model (eq. 1). After PO administration a linear one-compartment open model with first-order absorption and correction for lag-time was utilized (eq. 2):

$$C_t = A\ e^{-\alpha t} + B\ e^{-\beta t} \quad (1)$$

$$C_t = A'\ [e^{-k_e(t-t_0)} - e^{-k_a(t-t_0)}]. \quad (2)$$

In these equations, C_t is FT concentration in serum at time t after dosing, A, B, and A' are hybrid intercept terms, and α, β, k_a, and k_e are rate constants representing the phases of drug absorption (k_a), distribution (α), and elimination (β and k_e). t_0 is the lag-time elapsing prior to the start of first-order absorption. Initial estimates of the coefficients and exponents were obtained using the AUTOAN-2 program [12] and a nonlinear least-squares fit to the data was performed by use of the NONLIN program [10] on a Honeywell H66/60P computer system. The reciprocal of the concentrations was used as a weighting factor. Model-dependent pharmacokinetic parameters were calculated from the curve-fitting data [14]. The area under the concentration/time curve (AUC) was estimated by linear trapezoidal approximation with extrapolation to infinity, and the bioavailability (F) was calculated by dividing AUC_{PO} by AUC_{IV}. Half-life values were obtained by dividing ln 2 by the appropriate rate constant. Total serum clearance (CL) was calculated from IV data by dividing the dose by AUC and body weight, apparent volume of distribution (Vd_β) by dividing CL by the elimination rate constant (β), and apparent volume of central compartment (V_c) by dividing dose by term $A + B$.

The *t*-test for paired samples was used in the statistical analysis of the results.

Results

Figure 1 gives the FT levels in serum after IV and PO administration. Results of the pharmacokinetic analysis are shown in Tables 2 and 3.

Following IV dosing, serum FT levels declined biexponentially, indicating a two-compartment disposition. A short distribution phase, with $t_{1/2}$ = 1.0 ± 0.3 h (mean ± SE), was followed by a longer elimination phase with $t_{1/2}$ = 7.6 ± 0.9 h. The total clearance of the drug from serum was 69 ± 12 ml/h · kg, the apparent volume of distribution was 0.66 ± 0.04 l/kg, and the volume of the central compartment was 0.44 ± 0.02 l/kg.

After PO administration there was a distinct lag-time, 11 ± 4 min, between dosing and the appearance of FT in peripheral serum. Thereafter, the concentration rose slowly with a half-life of 0.7 ± 0.2 h, so that the time of peak concentration was 3.1 ± 0.4 h. After the peak, the disposition was monoexponential with a half-life of 9.2 ± 1.0 h. Comparison of AUC_{IV} and AUC_{PO} shows that the absolute FT bioavailability was 115% ± 8%.

Serum FT levels in peripheral and portal blood samples after IV and PO administration are presented in Fig. 2, and calculated pharmacokinetic parameters from the PO study in Table 4.

After IV dosing, FT concentrations in serum from peripheral and portal veins were substantially the same. In

Table 2. Pharmacokinetic parameters of ftorafur in seven patients after IV administration

Patient	α (h^{-1})	$t_{1/2\alpha}$ (h)	β (h^{-1})	$t_{1/2\beta}$ (h)	AUC_0^∞ (mg · h/l)	CL (ml/h · kg)	Vd_β (l/kg)	V_c (l/kg)
1	1.80	0.39	0.073	9.56	952	36.2	0.50	0.42
2	0.50	1.38	0.070	9.89	803	60.7	0.87	0.55
3	2.40	0.29	0.210	3.29	248	132.0	0.63	0.41
4	0.38	1.80	0.085	8.20	673	47.9	0.57	0.45
5	4.04	0.17	0.132	5.24	466	89.4	0.68	0.44
6	0.41	1.71	0.088	7.90	570	63.8	0.73	0.48
7	0.74	0.94	0.077	8.96	604	50.9	0.66	0.48
Mean		0.95		7.58	617	68.7	0.66	0.46
SE		0.26		0.92	86	12.3	0.04	0.02

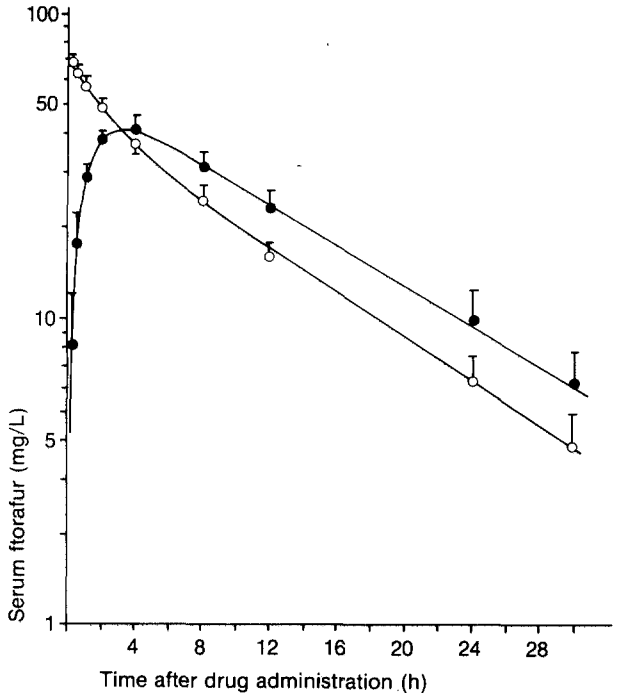

Fig. 1. Mean (± SE) serum levels of ftorafur in seven patients with liver cancer after IV (○) and PO (●) administration of 2.0 g

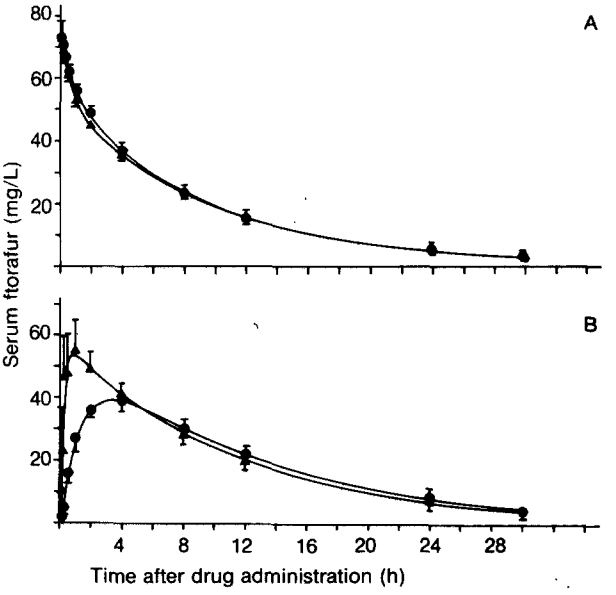

Fig. 2A and B. Mean (± SE) serum levels of ftorafur in portal (▲) and peripheral (●) vein of four cancer patients after IV **(A)** and PO **(B)** administration of 2.0 g

Table 3. Pharmacokinetic parameters of ftorafur in seven patients after PO administration

Patient	t_0 (h)	k_a (h^{-1})	$t_{1/2a}$ (h)	t_{max} (h)	k_e (h^{-1})	$t_{1/2e}$ (h)	AUC_0^∞ (mg · h/l)	F (%)
1	0	1.48	0.47	2.32	0.054	12.74	1046	108
2	0.44	1.03	0.68	3.98	0.066	10.42	1068	128
3	0.19	1.24	0.56	2.18	0.131	5.29	283	114
4	0.10	0.43	1.58	4.59	0.091	7.61	699	101
5	0.13	1.51	0.46	2.45	0.093	7.48	519	111
6	0.39	2.92	0.24	2.26	0.075	9.23	536	93
7	0.05	0.78	0.89	3.63	0.061	11.42	932	153
Mean	0.19		0.70	3.06		9.17	726	115
SE	0.06		0.17	0.37		0.97	113	8

Table 4. Pharmacokinetic parameters of ftorafur in four patients determined in portal and peripheral serum after PO administration

Patient	Sampling	t_0 (h)	$t_{1/2a}$ (h)	t_{max} (h)	$t_{1/2e}$ (h)	AUC_0^∞ (mg · h/l)
4	Portal	0	1.12	2.49	8.10	712
	Peripheral	0.10	1.58	4.59	7.61	689
5	Portal	0	0.16	0.71	6.02	504
	Peripheral	0.13	0.46	2.45	7.48	520
6	Portal	0.17	0.05	0.42	7.49	560
	Peripheral	0.39	0.24	2.26	9.23	536
7	Portal	0	0.06	0.51	11.36	994
	Peripheral	0.05	0.89	3.63	11.42	923
Mean	Portal	0.04	0.35	1.03	8.23	692
	Peripheral	0.17	0.79	3.23	8.94	667
SE	Portal	0.04	0.26	0.49	1.12	110
	Peripheral	0.08	0.30	0.54	0.92	94
Significance level		$P < 0.05$	$P < 0.05$	$P < 0.01$	NS	NS

contrast, after PO administration concentrations in the portal serum rose faster than in the peripheral serum. There were statistically significant differences ($P < 0.05$) in lag-time, absorption rate, peak time and peak concentration in peripheral and portal serum. No significant differences, however, were found in elimination rate or in bioavailability calculated from AUC values.

Discussion

There are several techniques for determination of FT in biological fluids; e.g., gas chromatography [6, 11, 15] and high-performance liquid chromatography [3, 7, 9]. This paper gives an alternative method, based on thin-layer chromatography, which permits rapid and precise determination of FT in serum. Interference by the known metabolites of FT is unlikely because their concentrations in serum are negligible [2] compared with FT concentrations.

In previous studies the pharmacokinetics of FT was evaluated after IV administration [2, 4]. In these studies, as in the present one, the disposition of FT was biphasic, and the calculated parameters (elimination half-life 6–16 h, plasma clearance 22–95 ml/kg · h, volume of distribution 0.4–0.8 l/kg) were comparable with the present data (Table 2). In this study the distribution half-life varied from 0.2 to 1.8 h. The distribution phase, however, has little significance in FT disposition kinetics because it comprises only 7% of the total AUC. There was a three-fold variation in the elimination rate of FT. This variation seems to be explicable by individual differences in hepatic drug metabolism rate (E. A. Sotaniemi et al., 1982, unpublished work). The apparent volume of distribution (0.52–0.80 l/kg) was only slightly larger than the volume in the central compartment (0.41–0.55 l/kg), implying that FT is mainly distributed in the body water.

FT is completely absorbed from the PO dose. This was shown here by the bioavailability data, which ranged from 93% to 153%. These values also indicate the lack of significant first-pass metabolism. When evaluated on the basis of FT levels in peripheral serum, oral absorption seems to be slow with a short lag-time. However, the rapid increase of FT concentration in portal serum indicates that absorption from the gastrointestinal tract starts immediately and is fast. Differences in the rate of appearance of FT in portal and peripheral serum indicate that some hepatic binding takes place during the passage of the drug through the liver. The similarity of the AUC values calculated from portal and peripheral concentration data proves, however, that there is no significant FT metabolism before its appearance in the systemic circulation. After administration via a peripheral vein, FT appears rapidly in portal serum, as shown by the equal FT levels in the two veins.

This study demonstrates that FT is well absorbed from the GI tract and is distributed into the body water. This indicates that there is no need to give the drug IV unless very high concentration in a target organ is required.

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