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A mathematical model of the kinetics of 5-fluorouracil and its metabolites in cancer patients

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Summary. A compartmental model of the kinetics of 5-fluorouracil (5-FU) and its catabolites in humans is proposed. This model was developed using data from a previous study in which plasma levels and urinary amounts of unchanged drug and metabolites were quantitated after i.v. bolus injection of 500 mg/m^2 5-FU in ten patients. Biliary excretion was also quantified in two subjects. The different processes, biochemical transformations, and urinary and biliary excretion were adequately described by first-order kinetics. The technique of multiresponse modelling was used for global fitting of all data for each patient. Satisfactory agreement was achieved between measured and predicted values. This model enabled accurate avaluation of pharmacokinetic parameters that could not be adequately calculated using a model-free analysis. The total clearance and elimination half-life of 5-FU and its catabolites are reported for all subjects. The estimated mean half-life was 6.9 ± 3.9 min for unchanged 5-FU and 225 ± 352, 7.6 ± 4, and 9.6 ± 7.7 min, respectively, for the three measured catabolites dihydrofluorouracil (FUH_2), α-fluoro-β-ureidopropionic acid (FUPA), and α-fluoro-β-alanine (FBAL). The percentage of anabolic, catabolic, urinary, and biliary elimination in total clearance was also quantitated. Anabolic clearance accounted for 39% ± 14% of total 5-FU clearance, with substantial variation occurring among patients. Urinary clearance represented 6.5% ± 3.2%, 0.8% ± 0.9%, 13.2% ± 4.7%, and 98.2% ± 2.5% of total clearance for 5-FU, FUH_2, FUPA, and FBAL, respectively. The model was also satisfactorily fitted to the data of a patient deficient in dihydropyrimidine dehydrogenase, an enzyme previously thought to be the rate-limiting step for 5-FU catabolism. In this case, catabolism was highly reduced and urinary excretion of 5-FU increased up to 64% of total drug clearance. This first global model of the kinetics of 5-FU and all of its catabolites in patients given an i.v. bolus infusion of 500 mg/m^2 5-FU represents a further step toward detailed comprehensive modeling of the kinetics of this drug.

Introduction

5-Fluorouracil (5-FU) is widely used in the treatment of solid tumors. The kinetics of unchanged 5-FU have been extensively studied [3]. This drug is metabolized by two major pathways that directly compete for 5-FU as a substrate: anabolism and catabolism. Anabolism is the clinically relevant pathway of cytotoxic activity, including the conversion of 5-FU to nucleosides and nucleotides, but the quantitation of 5-FU anabolites cannot be measured in biological fluids, as these metabolites are primarily intracellular. The description and quantitative assessment of catabolism appears to be essential, as it is an important component of 5-FU metabolism [3, 4]. The development of a specific high-performance liquid chromatography (HPLC) methodology has enabled the quantitation of 5-FU and its major catabolites dihydrofluorouracil (FUH_2), α-fluoro-β-ureidopropionic acid (FUPA), and α-fluoro-β-alanine (FBAL) [16]. Using this HPLC technique, catabolism of 5-FU was examined in isolated rat hepatocytes [16, 17]. Intracellular and extracellular concentrations of 5-FU and its catabolites were measured at specified time points following exposure of cells to radiolabelled 5-FU. A compartmental model was proposed that quantitatively describes the transport, transformation, and exchanges of 5-FU and its catabolites in rat liver cells [13].

With the use of a similar HPLC technique, the metabolism of 5-FU was subsequently investigated in ten cancer patients following i.v. bolus administration of 5-FU [10]. The time course of plasma levels and urinary excretion of 5-FU and its metabolites (FUH_2, FUPA, and FBAL) was measured. In two of these subjects who had external biliary

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catheters, a novel metabolite was detected in bile. This was subsequently identified as a conjugate of FBAL and cholic acid: *N*-cholyl-2-fluoro-β-alanine (CFBAL) [19]. The time course of 5-FU plasma concentration and urinary excretion was also studied in a patient who was deficient in dihydropyrimidine dehydrogenase (DPD), the enzyme responsible for conversion of 5-FU to FUH_2. This study enabled the examination of 5-FU kinetics in a patient with altered pyrimidine catabolism [6].

The data from the above studies were used to develop a compartmental model of the kinetics of 5-FU and its metabolites in cancer patients after i. v. bolus administration of 500 mg/m^2 of 5-FU. Such a model enables a unified description of metabolic processes using a small number of mathematical equations and the estimation of important pharmacokinetic parameters of 5-FU metabolism and excretion. The present report describes the general assumptions of the model, the statistical methods used, and the estimated pharmacokinetic parameters, including the catabolic clearances, renal clearances, and half-lives of the unchanged drug and its metabolites for the ten patients. A further assumption about biliary excretion led to an estimation of the anabolic fraction of 5-FU clearance and of FBAL biliary clearance. The present study has for the first time enabled a comprehensive analysis of the formation and elimination of 5-FU and all of its catabolites in humans at a clinically relevant therapeutic dose of 500 mg/m^2.

Patients and methods

Experimental data. Ten patients participated in the study. The experimental procedures have been described in detail in a previous report [10]. In brief, 500 mg/m^2 5-FU was injected over 1 min by i. v. bolus. Blood samples were collected at 0, 2, 5, 8, 12, 20, 30, 45, 60, 180, and 360 min following injection and also at 1.5, 2, 4, 8, and 24 h for the last four patients. Only detectable plasma levels of 5-FU, FUH_2, FUPA, and FBAL were used in the pharmacokinetic analysis, for an average of 8, 7, 6, and 8 values, respectively. For eight of the ten patients, urine was collected over 24 h in 2 h fractions for 8 h and then in 8 h fractions for 16 h. The detectable amounts of 5-FU, FUH_2, FUPA, and FBAL excreted in urine were also taken into account for the fitting of the model, for an average of 2, 2, 6, and 6 values, respectively. For two of the patients with external biliary catheters, bile was collected over 48 h in 15-min fractions for 1 h, in 30-min fractions for 1 h, in 2 h fractions for 4 h, in 6 h fractions for 18 h, and in 12 h fractions for 24 h. The detectable amounts of CFBAL excreted in bile were incorporated in the fitting for an average of 10 values. Data from a subsequent study were analyzed separately. A single patient who was deficient in DPD was given a test dose of 25 mg/m^2 5-FU over 1 min by i. v. bolus [6]. Blood samples were collected at 0, 2, 5, 8, 12, 20, 30, 45, 60, 90, 120, 240, 360, and 480 min following injection, and urine was collected over 24 h in 2 h fractions for 8 h and in 8 h fractions for 16 h. No 5-FU catabolites were detected in plasma.

General Assumptions of the pharmacokinetic model. The mathematical model is based on existing knowledge of 5-FU catabolism based on animal in vitro data [13] and human data [10]. The delivered dose is assumed either to be converted to nucleosides and nucleotides or to follow degradation through the catabolic pathway [16]. Each catabolite is then excreted in urine. In addition, FBAL is assumed to be excreted only in bile as a conjugate identified as CFBAL. An attempt was made to develop a minimal compartmental model that would be sufficient for an adequate description of the data in a unified manner and that would enable an estimation of the pharmacokinetic parameters. Each compartment represents one compound in a given medium. The exchanges between compartments represent flows from one compartment to another such that either a biochemical transformation or a transfer of a given compound from one space to another can be modelled [9]. Since only one dose was studied, linear first-order kinetics was first assumed.

Mathematical formulation of the model. Compartmental models are described by a set of state variables following mass-balance differential equations. For an n-compartment model based on first-order kinetics, the equation is:

$$\frac{dX_i}{dt} = \sum_{j=1}^{n} k_{j-i} X_j - \sum_{j=0}^{n} k_{i-j} X_i \quad \text{for } i = 1,\ldots, n,$$

where X_i is the state variable representing the amount of drug or catabolite in compartment i, k_{i-j} is the rate constant from compartment i to compartment j ($k_{i-j} = 0$ if there is no transfer from i to j), and k_{i-0} is the rate constant from compartment i to the environment [8]. The initial conditions of this system are: $X_i(0) = 0$, $i = 1,\ldots, n$. The administration of an initial dose X_0 by i. v. bolus over a duration τ_0 is modelled by a constant rate ($R_0 = X_0/\tau_0$). This term is added to the equation describing the administration compartment during the infusion time.

The set of differential equations describes the time course of amounts of unchanged drug and of each catabolite. For comparison of the values predicted by the model with the actual experimental data, plasma concentrations were obtained by dividing instantaneous amounts by the apparent volume of distribution of each catabolite, V_i. Data for urine and bile were calculated as the amount excreted from the time of the previous sample collection to the current time.

The vector θ of the pharmacokinetic parameters that describes the model is thus composed of the apparent volumes of distribution with respect to plasma (V_i) and the rate constants (k_{i-j}).

Statistical methods. For each patient, data for unchanged drug and metabolites were analyzed jointly using a multiresponse modeling approach [18]. The vector of unknown parameters θ was estimated by maximal likelihood analysis of the full set of individual data. The measurement error for a data point, $z_i(t_{i,k})$ was assumed to arise from a zero mean gaussian distribution with a known variance, $\sigma_i^2(t_{i,k})$, depending on the variable (i) and the time ($t_{i,k}$). The errors on separate variables and successive data points were assumed to show no correlation. Accordingly, maximization of the likelihood of the data with respect to the parameters is equivalent to minimization of the following weighted least-squares function:

$$J(\theta) = \sum_{i=1}^{p} \sum_{k=1}^{m_i} \frac{[y_i(t_{i,k}, \theta) - z_i(t_{i,k})]^2}{\sigma_i^2(t_{i,k})},$$

where θ is the vector of parameters to be estimated; p is the number of sampled compartments of the model; m_i is the number of sample collections in the i^{th} compartment; z_i and y_i, $i = 1,\ldots, n$ are the observed and model-predicted values in the i^{th} compartment, respectively; $t_{i,k}$, $k = 1,\ldots, m_i$, are the m_i dates of measurement in compartment i; and $\sigma^2_i(t_{i,k})$ is the variance of the measurement error.

The following formula for the variance of experimental error was used to provide the weights in the least-squares function:

$$\sigma_i^2(t_{i,k}) = A_i^2 + [B_i\, y_i(t_{i,k})]^2.$$

Over most of the data range, the standard deviation of the error is approximately proportional to the experimental data with a coefficient of variation B_i. It is lower-limited by A_i for low measured values. These assumptions are in agreement with the accuracy of the HPLC assay. The A_i value was set to 1 μmol/l for plasma concentrations, 50 μmol /min for urinary levels and 0.5 μmol/min for amounts in bile. The B_i value was set to 0.05 and 0.1 for 5-FU and FBAL plasma concentrations, respectively, and to 0.2 for all other variables.

The standard error of each parameter estimate was calculated from the approximate variance-covariance matrix [1]. The Akaike Information

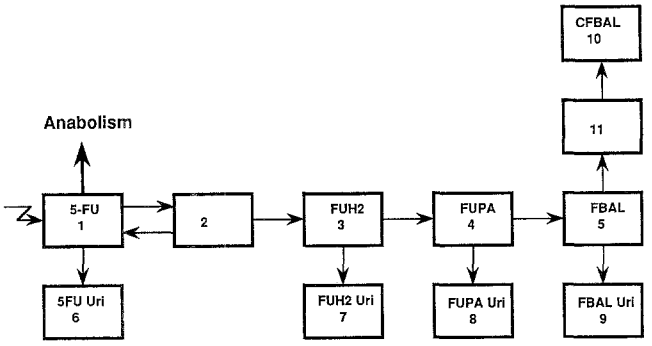

Fig. 1. Compartmental model for the metabolism and excretion of 5-FU and its catabolites in man after i. v. bolus administration of 5-FU. Compartments *1, 3, 4* and *5* represent 5-FU and its catabolites FUH_2, FUPA and FBAL in the body, including plasma. Compartments *6, 7, 8* and *9* represent 5-FU, FUH_2, FUPA and FBAL excreted in urine. Compartment *10* represents CFBAL excreted in bile. All exchanges were modeled by first order kinetics

Criterion (AIC) was used to assess the best model. This criterion can be viewed as the sum of a measure of the godness of fit and a "penalty" function proportional to the number of parameters ($n\theta$) in the model. The model with the smallest AIC is the most adequate according to a parcimony principle. Using weighted least-squares with uncorrelated gaussian errors, the criterion is defined as $AIC = \min[J(\theta)] + 2n\theta$ [7].

Numerical methods. Estimation of the parameters was performed using a Fortran 77 computer program, PHACIN [21], on a DEC VAX 8810 computer. The set of differential equations was integrated numerically with a fourth-order variable-step method [14]. Minimization of the weighted least-squares criterion was performed using Marquardt's second-order algorithm [11].

Results

The model

The mathematical model of 5-FU metabolism in humans after administration of 500 mg/m^2 was constructed step by step. In the first step only the plasma concentrations of unchanged 5-FU were considered. The biexponential decline suggested by inspection of the experimental data was confirmed through fitting. As compared with a one-compartment model, the two-compartment model improved the fit, the global AIC for all patients decreasing from 382 to 194 with 122 measurement points. In describing the kinetics of FUH_2, two three compartment models were compared: (1) a model with an compartment intermediate between 5-FU and FUH_2 and (2) a model in which the second compartment for 5-FU is peripheral. The AIC with 232 data points for all patients was 489 for the first model

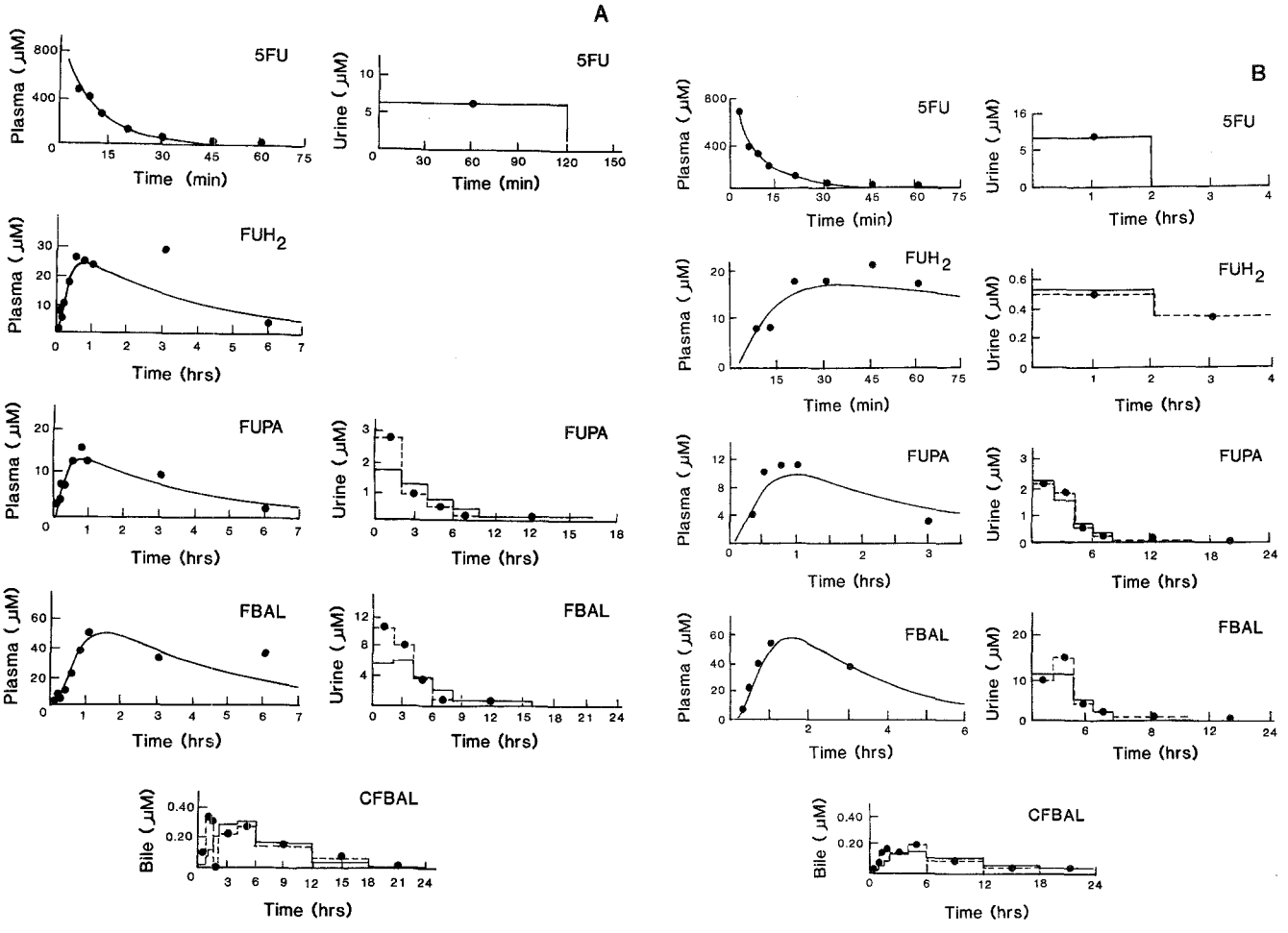

Fig. 2 A, B. Global multiresponse fitting of the model of 5-FU metabolism to the set of data for patients **A** WM and **B** WM /Jr after i. v. bolus administration of 500 mg/m^2 5-FU. *Dot symbols* represent the experimental plasma concentrations and urinary rates of excretion of 5-FU, FUH_2, FUPA and FBAL as well as biliary rates of excretion of CFBAL; *solid lines* represent the time profiles predicted by the model

Table 1. Estimated values of the parameters of 5-FU catabolism in two patients[a]

		WM Jr1		WM 1	
V_1 (l)		6.3	(1.1)	8.26	(1.5)
V_3 (l)		227.7	(23)	120.6	(23)
V_4 (l)		33.99	(10)	1.89	(0.47)
V_5 (l)		6.85	(2.1)	4.87	(1.5)
k_{1-0}	(min^{-1})	0.042	(0.011)	0.047	(0.009)
k_{1-2}	(min^{-1})	0.181	(0.062)	0.053	(0.023)
k_{1-6}	(min^{-1})	0.016	(0.004)	0.01	(0.004)
k_{2-1}	(min^{-1})	0.116	(0.051)	0.029	(0.046)
k_{2-3}	(min^{-1})	0.114	(0.014)	0.139	(0.059)
k_{3-4}	(min^{-1}, × 100)	0.645	(0.077)	0.458	(0.071)
k_{3-7}	(min^{-1}, ×1,000)	0.188	(0.14)	0[b]	
k_{4-5}	(min^{-1})	0.058	(0.017)	0.4	(0.15)
k_{4-8}	(min^{-1}, × 100)	0.904	(0.34)	8.543	(4.1)
k_{5-9}	(min^{-1})	0.041	(0.012)	0.035	(0.009)
k_{5-11}	(min^{-1}, × 100)	0.103	(0.034)	0.232	(0.075)
k_{11-10}	(min^{-1}, × 100)	0.299	(0.029)	0.619	(0.17)

[a] The estimates and the standard errors (shown in parentheses) were obtained by fitting the model to the concentrations of 5-FU and its catabolites measured after i. v. bolus administration of 500 mg/m² drug (see Fig. 1 for the structure of the compartmental model)

[b] Urinary amounts of FUH_2 not detected

Table 2. Estimated total clearance and half-lives of 5-FU and its catabolites in patients given an i. v. bolus infusion of 500 mg/m² 5-FU

Patients	5-FU		FUH_2		FUPA		FBAL	
	$t_{1/2}$ (min)	Cl (l/min)	$t_{1/2}$ (min)	Cl (l/min)	$t_{1/2}$ (min)	Cl (l/min)	$t_{1/2}$ (min)	Cl (l/min)
WM /Jr	4.69	0.93	105	1.51	9.9	2.28	16.49	0.29
WM	6.81	0.84	151	0.55	1.44	0.92	18.56	0.17
UT	5.26	0.94	80	1.66	11.55	2.76	ND	0.45
LH	4.72	0.47	17	1.9	6.93	5.03	0.71	0.37
CK	2.84	0.52	119	ND	NE	ND	16.69	ND
RH	5.63	0.65	90	1	4.95	0.45	ND	0.84
WA	6.16	1.18	115.6	0.1	4.95	0.19	8.5	0.02
JC	8.18	0.91	121	1.21	13.86	2.31	0.11	0.26
DJ	17.05	0.83	NE	0.57	NE	0.5	NE	0.07
SB	7.36	0.78	187	ND	6.93	ND	6.21	ND
Mean	6.87	0.81	225	1.05	7.56	1.59	9.61	0.31
SD	3.88	0.21	352	0.62	4.01	1.45	7.74	0.26

ND, Not determined; NE, not evaluable

and 1,335 for the second. The model with an intermediate compartment added between the 5-FU and FUH_2 plasma compartments, which most adequately accounted for the time course of FUH_2 concentrations, was thus chosen.

The plasma concentrations of FUPA and FBAL were considered in the next step, with later inclusion in the data analysis of the amounts of each product excreted in urine. Finally, to describe the amounts of CFBAL excreted in bile, an intermediate compartment was added between the FBAL plasma compartment and the biliary CFBAL compartment. This compartment was necessary for modeling of the conjugation of FBAL with cholic acid to CFBAL and its transport into bile.

According to the previous assumptions, the complete model of the kinetics of 5-FU and its catabolites in man after i. v. bolus administration of 500 mg/m² 5-FU is composed of 11 compartments (Fig. 1). Connections are accounted for by 12 rate constants. This model was fitted to the full set of data for two patients for whom both plasma concentrations and urinary excretion rates of 5-FU, FUH_2, FUPA, and FBAL as well as biliary excretion of CFBAL had been quantitated. Figure 2 presents the data for the nine responses together with the corresponding time courses generated by the pharmacokinetic model. The predicted values approximated well the measured data for all sampled compartments. The estimated values of the parameters with standard errors are presented in Table 1. The small size of the standard errors for most parameters demonstrates the accuracy of the estimates.

Evaluation of pharmacokinetic parameters for all patients

For eight patients, lack of data for some outputs of the model (urinary or biliary excretion) made the full model structurally nonidentifiable. In these cases, the volumes of distribution for FUH_2, FUPA, and FBAL could be estimated only up to a proportionality constant. Nevertheless, estimates for the elimination rate constants of 5-FU and its metabolites and for the corresponding half-lives as well as the total clearance of 5-FU could be obtained. When urinary data were available, the renal clearances of 5-FU and its catabolites could be estimated.

Results from the two reference patients with complete sets of data (Table 1) show that biliary elimination was

Table 3. Percentage of anabolic, catabolic, urinary, and biliary elimination in total clearance for 8 patients given an i. v. bolus infusion of 500 mg/m² 5-FU

	5-FU			FUH_2		FUPA		FBAL	
	Anabolic	Catabolic	Urinary	Catabolic	Urinary	Catabolic	Urinary	Biliary	Urinary
Mean	38.9	54.6	6.5	99.2	0.8	86.7	13.2	1.8	98.2
SD	14.4	13.7	3.2	0.9	0.9	4.7	4.7	2.5	2.5
Minimum	14	37	2	97.4	0[a]	80	5	0.1	92.5
Maximum	59	80	11	100	2.6	95	20	7.5	99.9

[a] Urinary amounts of FUH_2 not detected in two patients

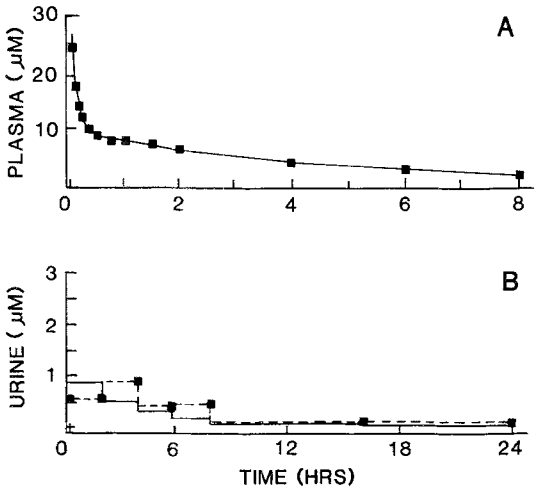

Fig. 3 A, B. Fitting of a submodel to the data of a DPD-deficient patient after i. v. bolus administration of 25 mg/m^2 5-FU. *Square symbols* represent the experimental plasma concentrations and urinary rates of excretion of 5-FU; *solid lines* represent the time profiles predicted by the model

<15 times lower than urinary elimination. Biliary excretion appeared to be a minor pathway of elimination of 5-FU and catabolites. An additional assumption was introduced in the model, with the rate constant for biliary elimination of FBAL (k_{5-11}) being fixed to 0.0015 min^{-1}, the mean of the estimates in the two reference patients (Table 1). Based on this assumption and the availability of urinary data, all parameters of the model were estimated. The pharmacokinetic half-lives and total clearances of 5-FU and its catabolites in patients given 500 mg/m^2 5-FU are presented in Table 2. Table 3 shows the average percentage of 5-FU total clearance due to anabolic, catabolic, or urinary elimination; of FUH_2 and FUPA total clearance attributable to catabolic or urinary elimination; and of FBAL total clearance due to biliary or urinary elimination.

Patient deficient in DPD. No catabolites were detected in the plasma of the patient who was deficient in DPD after receiving an i. v. bolus of 25 mg/m^2 5-FU. A submodel for unchanged drug disposition and elimination that was derived from the complete model was used to fit the 5-FU plasma concentrations and urinary exretion data for this experiment (Fig. 3). For this patient, the renal drug clearance was estimated to be 0.092 l/min; this value was consistent with the mean renal clearance of the other patients (0.06 ± 0.03 l/min). In contrast, the total clearance of 5-FU for this patient was 0.14 l/min, which was approximately 6 times lower than that in patients with normal catabolism. In this case, the renal clearance represented 64% of total clearance as compared with 6.5% for the other patients. Elimination of unchanged drug in the DPD-deficient patient was much slower (note the difference in the time scale between Fig. 2 and Fig. 3) and occurred primarily via the kidney.

Discussion

The technique of multiresponse modeling was used to describe the pharmacokinetics of 5-FU and its catabolites. At each step in the development of the mathematical model, the fittings were satisfactory and the parameters were estimated within comparable ranges for the different patients. The ranges of estimated parameters remained unchanged when new data were included to fit the submodel corresponding to the next step of development. The pharmacokinetic model constructed from data obtained in ten cancer patients also adequately predicted 5-FU kinetics in a patient deficient in DPD, with a set of parameters being consistent with the expected biochemical changes. The additional assumption of setting the rate constant of biliary excretion k_{5-11} to 0.0015 min^{-1} in patients without biliary drainage enabled estimation of both the anabolic clearances of 5-FU and the catabolic clearances of its catabolites. The values for the remaining parameters were compatible with those obtained in the two subjects whose data enabled complete estimation of the model (Table 2). It should be noted that the clearances of 5-FU and its catabolites were similar when data were fitted with various values of the rate constant k_{5-11} between 0 and 0.005 min^{-1} (results not shown). Thus, any additional minor pathway of elimination of FBAL, such as potential trapping of FBAL in tissues, would have only a slight influence on the clearances of 5-FU and its catabolites and was not included in the model.

In previous studies of 5-FU pharmacokinetics in humans in which 5-FU levels alone were measured and no catabolites were quantitated, dose-dependent kinetics has been observed [2, 4, 12, 20, 22]. Attempts to model 5-FU kinetics have used a Michaelis-Menten equation so as to describe the conversion of 5-FU to FUH_2 [2, 4, 12, 22]. The cellular pharmacokinetics of 5-FU in isolated rat hepatocytes also involved a nonlinear kinetic step [13]. In this previous in vitro study, the Michaelis-Menten constant K_m was estimated to lie between 12 and 36 μM for the conversion of 5-FU to FUH_2.

In the present clinical study, the modeling of 5-FU elimination by Michaelis-Menten kinetics, with K_m being fixed to the value of 15 μM reported in previous studies [4], led to fittings that did not improve the data description (data not shown). A two-compartment model based on linear kinetics was sufficient to describe 5-FU disposition kinetics at a dose of 500 mg/m^2. Furthermore, other authors have reported that the dose-dependent changes in half-life observed in 5-FU kinetics are not consistent with a capacity-limited or Michaelis-Menten process, but that nonlinear elimination could be attributable to product-inhibited metabolism [15]. The present data, which were collected following the administration of a unique dose of 5-FU (500 mg/m^2), do not enable confirmation of this hypothesis.

The total clearance values for 5-FU (0.81 ± 0.21 l/min) estimated by this model were consistent with those calculated using a noncompartmental analysis of the same data [10] as well as with those previously reported by Diasio and Harris [5] in nine different studies after the administration of an i.v. bolus at several dosages of 5-FU (range,

0.8–1.9 l/min). As shown in Table 3, renal clearance of 5-FU represented <10% of total clearance. The anabolic fraction of 5-FU clearance showed a mean value of 39% with, apparently, substantial interpatient variations (14%–70%). This estimated average percentage of 5-FU undergoing anabolism was higher than the value of 20% that is usually cited [3]. It should be noted that this value was indirectly obtained by measuring $^{14}CO_2$ in the expired air of one patient who had been given 7.5 mg/kg [^{14}C-2]-5-FU (approximately 300 mg/m^2) [23]. The lack of precise quantitation of the catabolic products of 5-FU using this methodology may have led to an underestimate of the percentage of 5-FU anabolism in the lower range of our estimates. However, it has recently been suggested that the lungs may be involved in 5-FU elimination [15]. In fact, k_{1-0} represents all non-catabolic or urinary routes of elimination and, therefore, incorporates pulmonary elimination. This might also partly explain the disparity between the anabolic clearance estimated in this study and previous data [23].

The main purpose of our modeling was to provide for the first time a quantitative insight into the pharmacokinetics of 5-FU catabolites in man. Clearly, i.v. administration of the catabolites would be more informative. Such a study would require preliminary synthesis or isolation of 5-FU catabolites, which raises ethical concerns. Multiresponse fitting of unchanged drug and metabolite data can, to a certain extent, provide an estimate of 5-FU pharmacokinetic parameters of catabolites without necessitating further clinical studies. It can be seen that the renal clearance of FUH_2 was minimal, with the catabolic clearance accounting for the major proportion of total clearance. Large variations in renal and catabolic clearance were observed for FUPA, a transient 5-FU catabolite [16]. This possible reflects the low amounts of FUPA that were found, requiring measurement near the limit of sensitivity of the HPLC method. Also, the estimation of the parameters involved was less accurate because the variance of the experimental error was larger for FUPA than for 5-FU or FBAL. Table 3 also shows that FBAL is essentially excreted unchanged in urine, with only a small percentage being excreted in bile.

The estimated elimination half-lives of FUPA and FBAL were shorter than the values previously derived as apparent half-lives from the terminal phase of the concentration time course [10]. The present model indicates that both compounds, in fact, have elimination half-lives of 8–10 min, comparable with that of 5-FU but much shorter than that of FUH_2 (Table 2). The disposition kinetics of FUPA and FBAL appears to be rate-limited by their formation from FUH_2. In such a case, the model-independent estimate of half-life derived from the terminal data of the product actually represents the half-life of the precursor. This model thus enabled for the first time an estimation of the real elimination half-lives "in vivo" of catabolites of 5-FU. The model also established that the longer half-life of FUH_2 is attributable to the distribution of this catabolite, since its clearance value was in the same range as that of the unchanged drug and its other catabolites.

In conclusion, a mathematical model of the metabolism of 5-FU in cancer patients after the administration of an i.v. bolus is proposed. This first complete set of data enabled the development of a global model of 5-FU catabolism. It also enable an estimation of the pharmacokinetic parameters of 5-FU metabolism at a therapeutically relevant dose of 500 mg/m^2, which cannot be achieved through noncompartmental data analysis or separate fittings of plasma level data. The existing models involving nonlinear disposition of 5-FU are restricted to the plasma kinetics of the parent drug alone. The present study is a further step towards a detailed comprehensive modeling of the kinetics of 5-FU and its catabolites; data at other doses and other input rates are clearly needed to achieve that purpose.

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