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Nonlinear Pharmacokinetics for the Elimination of 5-Fluorouracil after Intravenous Administration in Cancer Patients

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Summary. *Plasma concentrations of 5-fluorouracil (FU) and its primary catabolite, 5', 6'-dihydro −5 − fluorouracil (DHFU) were measured using gas-liquid chromatography after single-dose therapy with 7.2–14.4 mg/kg. Because of the limited sensitivity of the assay for drug levels in plasma, the urinary excretion of FU and metabolites was investigated using an ion-specific electrode after either a single bolus (7.0–9.6 mg/kg) or multiple-dose therapy (6.4–7.4 mg/kg/day). Half-life values for the elimination of FU from plasma (mean, 123.5 min) were greater in each patient than for the catabolite (mean, 109.2 min). Values of the area under the curve for FU profiles varied between patients (mean ± SE, 12.7 ± 1.9 μg · h/ml) by comparison with the relatively constant values for curves of DHFU concentrations (mean ± SE, 2.8 ± 0.15 μg · h/ml). In pharmacokinetic profiles of urinary excretion a transient phase of convex shape was apparent after 80%–98% of single doses of FU was excreted. Half-lives for the elimination of FU in urine were 2.6–5.9 h, which increased to 18–44 h on multiple dosing. The results demonstrate saturation in the elimination of FU after therapeutic doses, and are consistent with the proposal that reduction of FU to DHFU provides the rate-limiting step.*

Introduction

The major problem in applying pharmacokinetic principles to the design of therapeutic regimens containing FU has been the lack of knowledge of how plasma levels of the drug relate to intracellular concentrations of its active nucleotide metabolites. Following IV bolus injection, most studies have demonstrated that after a short phase of distribution with a half-life ($t_{1/2}$) of less than 5 min [5, 13, 27] a single phase of elimination of FU from plasma occurs, with $t_{1/2}$ values of 8–20 min [20]. Finn and Sadee [12] first advocated a third phase in the disposition of FU, based on the assumption that clearance of the nucleotides takes place by conversion to the parent compound and subsequent catabolism. Assessment of this terminal phase of elimination may therefore be of importance as an indirect relative measure of the active form of the drug. Although assessment of the terminal elimination phase does not provide data regarding the organ(s) from which the drug is being lost, results from animal studies [4] suggest that the tumour and small intestine contain a major portion of FU and metabolites remaining in the body at late times after treatment. The pharmacokinetic data reported to characterize the terminal phase in humans [3, 23, 27] have been limited and considerable differences in $t_{1/2}$ values have been observed compared with data from animal studies [4, 12]. The initial metabolic step in the degradation of FU to 5', 6'-dihydro-5-fluorouracil (DHFU) in the liver by dihydrouracil dehydrogenase is saturated easily [1, 19]. As a result, pharmacokinetics of the drug are dose-dependent [11, 13, 15].

The main purpose of the present investigation was to provide further data in an attempt to establish the range of pharmacokinetic parameters for the terminal phase of elimination in humans in view of its possible relevance to clinical response. In addition, we have monitored DHFU concentrations in plasma since the ability of the liver to carry out the initial catabolic step in FU degradation will in part determine the extent of exposure of sensitive tissues to the drug.

Materials and Methods

Patient Protocols. Twenty-one patients for whom FU was part of their medical treatment at the Belvoir Park Hospital, Belfast, participated with informed consent. All had metastatic breast carcinoma, post-mastectomy, except for A. McG. (unresected breast cancer), A. W. (unknown primary tumour), and T. M. (lung carcinoma). Patients A. L., K. K., D. M., and A. W. had received chemotherapy with FU previously.

Pharmacokinetics of FU and DHFU in plasma and the urinary excretion of drug and metabolites were studied in patients being treated according to 1-day and 2-day cyclical combination regimens. FU was administered in combination with methotrexate (50 mg) and vincristine (1.0–1.5 mg), together with either cyclophosphamide (300 mg) or adriamycin (25–50 mg) [8–10]. Kinetics of urinary excretion were also investigated in patients receiving FU on each day of a 5-day chemotherapeutic schedule [8, 9]. These patients also received cyclophosphamide (150–300 mg) on days 1 and 5 and vincristine (0.6–1.0 mg) on days 2 and 5. Methotrexate (7.5–10 mg) was also administered to all patients on days 1 and 4, with the exception of patients A. W. and D. M. FU was administered by rapid bolus injection. Blood specimens (10 ml) were taken from an indwelling venous cannula or by venipuncture into heparinized tubes. Plasma was separated and stored at −20° C. Sodium azide (0.1%, w/v) was used as preservative for urine specimens, which were collected when voided spontaneously. Volumes of specimens were recorded and aliquots (25 ml) stored at −20° C.

Analytical Methods. A gas-liquid chromatographic method (GLC) with electron-capture detection [28] was modified so

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that FU and DHFU could be measured simultaneously in plasma specimens [16]. DHFU was synthesized from FU (Sigma Chemical Co., St Louis, Missouri, USA) by catalytic hydrogenation using borohydride-reduced palladium [22]. FU and DHFU concentrations were measured as the ratio of their peak heights with that of the internal standard, 5-chlorouracil (Cambrian Chemicals Ltd, Croyden, England), over the ranges 0–0.3 and 0.3–2.5 μg FU/ml, containing 100 and 500 ng 5-chlorouracil, respectively.

Total FU and metabolites were estimated in urine as fluoride ion using an ion-specific electrode [17]. Organically bound fluorine in the drug and metabolites was decomposed to fluoride by combustion in an oxygen flask [24].

Preparation of samples for combustion was based on the method of Venkateswarlu [25]. Urine samples (2.0 ml) containing FU (and metabolites) were pipetted into weighed 25 ml Quickfit flasks (Corning Ltd, Staffs., Great Britain). A solution of lactose (1.2 ml) in deionized water (7%, w/v) was added to each sample prior to lyophilization. Before re-weighing of the flasks, silicon grease was removed from the necks using chloroform-impregnated tissue paper. Approximately 20 mg of each freeze-dried sample was weighed accurately and placed in the centre of a piece (2.5 cm^2) of filter paper with a 0.5 cm × 2.5 cm strip attached. The filter paper was folded to contain the sample leaving the strip free to be used as a taper for ignition. A Schoniger-type oxygen flask consisted of a Quickfit Erlenmeyer flask (1 litre) and stopper. Embedded in the stopper was a nickel wire support (13 cm × 2 mm in diameter) to which was secured a piece of platinum gauze (3.0 cm × 1.5 cm; grade 4, 36 mesh, 0.23 mm wire diameter; Johnston, Matthey and Co. Ltd, London, Great Britain). The gauze held the sample during the combustion procedure [24]. Decomposition products were dissolved deionized water (15.0 ml). An equal volume of total ionic strength adjustment buffer [21] was added to the combustion flask and the solution transferred to a plastic beaker for measurement of electrode potential. A combination fluoride electrode (Model 96-09) and a Digital Ionanalyzer (Model 701A), purchased from Orion Research Inc., Cambridge, Mass., USA, were used in conjunction with a Philips PM 8251 recorder (Pye Unicam, Cambridge, Great Britain).

Final readings were taken from the voltmeter when the electrode potential stabilized to ± 0.1 mV. Quantitative analysis was performed by reference to the electrode potentials of FU solutions ($1.0 \times 10^{-6} M - 5.0 \times 10^{-3} M$) in pooled urine, defluorinated by adsorbtion with calcium phosphate [26], which were analysed by the same procedure. The concentration of free fluoride ion in specimens was determined by comparison with electrode potentials produced by sodium fluoride solutions ($1.0 \times 10^{-7} M - 1.0 \times 10^{-3} M$) in defluorinated urine. Ionic fluoride was subtracted from total fluoride to allow calculation of the concentration of nonionic fluorine representing FU.

Pharmacokinetic Analyses. Solution of the differential equations of the multicompartment system yields the following integrated equation describing the plasma concentration-versus-time curve after rapid IV administration [7]:

$$C = \sum_{i=1}^{n} A_i \exp(-b_i t)$$

where C is the drug concentration at time, t, A_i are the intercepts on the ordinate axis, and b_i are the hybrid first-order rate constants. For the three-compartmental analysis of FU disposition, b_i values have been designated π, α, and β. A_i and b_i values were estimated from the data by conventional curve-stripping procedures [14] or by nonlinear least-squares regression analysis of pharmacokinetic profiles which were sufficiently well defined, using a computer program, NONLIN [18]. $t_{1/2}$ values were calculated as $0.693/b_i$. Values of $\int_0^\infty C\,dt$, the area under the plasma concentration-versus-time curve (AUC) were determined using the relationship AUC equals $\sum_{i=1}^{n} A_i/b_i$ for FU profiles and using the trapezoid rule [14] for DHFU profiles. The time course of total drug levels (i.e., FU and metabolites) in urine was evaluated by the 'sigma-minus' method [29], which entails plotting the logarithm of the sum of the amounts of the total drug excreted until such time as excretion may be considered to be complete minus the cumulative amount of drug excreted to a time, t. An indication of the accuracy of results from sigma-minus plots [29] was obtained using the Rate method [14], in which the logarithm of the excretion rate of the total drug was plotted versus the midpoint in time of the urine collection. The elimination rate constant of the parent drug was calculated from linear portions of the plots.

Results

Plasma Pharmacokinetics

Figure 1 shows the composite profile of FU levels in plasma for the twelve patients studied as a triphasic semilogarithmic plot. Five minutes after drug administration in seven patients FU concentrations in plasma varied 25-fold. Drug concentrations declined monoexponentially between 10 min and approximately 1 h and a further phase of monoexponential decay was apparent at times greater than 2 h. At the onset of the terminal

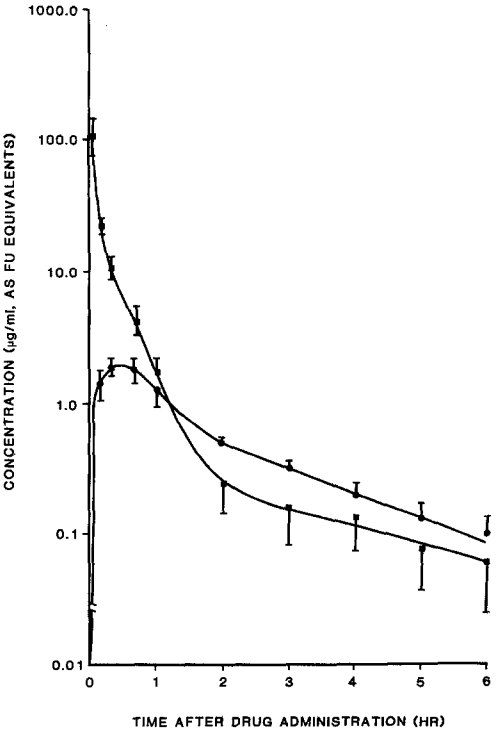

Fig. 1. Semilogarithmic plots of plasma concentrations (mean ± SE) versus time after FU dosage for FU (■) in 12 patients and for DHFU (●) in five patients following 10.0 ± 0.7 and 10.1 ± 0.8 (mean ± SE) mg/kg, respectively

Table 1. Pharmacokinetic characteristics for individual plasma concentration-versus-time profiles for FU and DHFU

Patient	Dose (mg/kg)	$t_{1/2}$ (min)				Auc, ‡ (mg · h/ml)	
		FU			DHFU		
		Phase π	Phase α	Phase β	Phase β	FU	DHFU
M. Ma.	8.6	3.8	7.7	151.1	ND	22.7	ND
C. H.	12.4	2.5	13.6	167.4	129.9	19.2	2.9
E. C.	8.7	2.1	18.4	99.0	56.9	17.5	2.4
A. M.	7.2	2.7	15.1	40.5	–	2.7	–
B. C.	13.5	ND*	13.4	63.8	ND	16.9	ND
A. L.	8.2	–+	13.9	70.9	ND	19.3	ND
M. A.	9.2	–	11.3	197.4	176.4	15.4	2.9
K. K.	11.4	–	10.2	198.2	70.8	11.8	3.3
A. McG.	14.4	–	9.8	–	–	9.7	–
M. Mu.	8.6	ND	11.2	–	–	4.2	–
M. McH.	9.6	ND	13.5	–	ND	7.8	ND
M. B.	8.7	ND	6.8	–	111.9	5.7	2.4
Mean	10.0	2.8	12.1	123.5	109.2	12.7	2.8
SE	0.7	0.4	1.0	22.2	21.4	1.9	0.15

* Not detected
+ Not determined
‡ Area under the curve, omitting the α phase

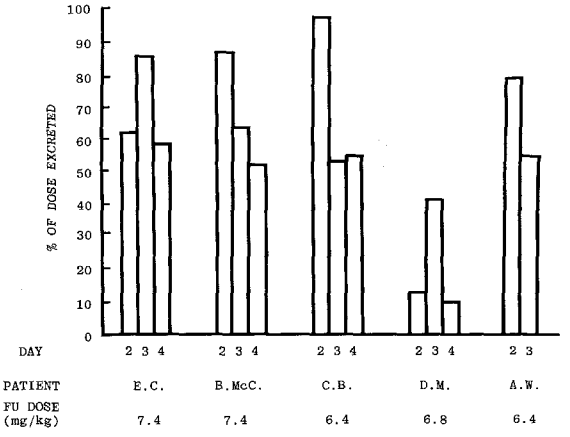

Fig. 2. Urinary excretion of total FU and metabolites in 24-h periods after administration of FU on each day of a 5-day combination regimen

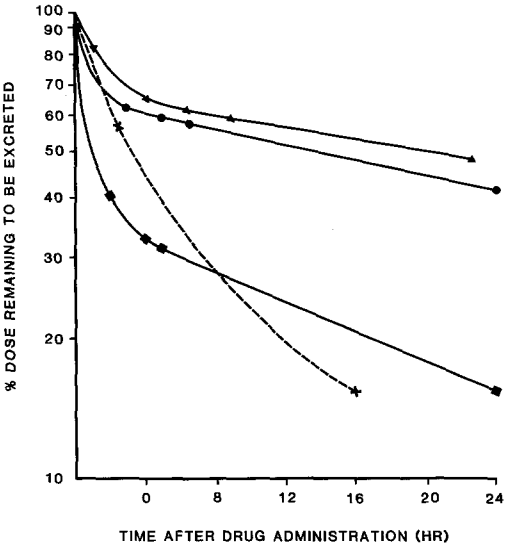

Fig. 3. 'Sigma-minus' plots for total FU and metabolites excreted by D. M. (▲) and E. C. (●) on day 3 and by A. W. on days 2 (×) and 3 (■) of a 5-day combination regimen

phase, plasma concentrations ranged from 0.2 to 2.6 μg/ml. Values of $t_{1/2}$ for the second exponential phase, with rate constant α, were determined for each patient and the parameters for the preliminary distribution phase (π) and the terminal elimination phase (β) were estimated where the data were adequate (Table 1).

The composite profile of DHFU concentrations versus time after FU administration (Fig. 1) shows considerable variation in the mean plasma levels within the first hour after dosage. The mean peak concentration of DHFU was 2.1 (range, 1.0–2.7) μg/ml, occurring between less than 10 min and up to 1 h after FU administration. Since equilibrium between FU and DHFU was attained quickly the rate constant for formation of the metabolite could not be estimated. The terminal linear portions of the profiles of DHFU concentrations were used to determine $t_{1/2}$ values of its elimination from plasma (Table 1). The AUC values for FU and DHFU in individual patients are included in Table 1.

Kinetics of Urinary Excretion

Total amounts of FU and metabolites excreted in 24-h periods after administration of FU to five patients on successive days are given in Fig. 2. Patients E. C. and D. M. excreted decreased amounts of total drug after day 3. Accumulation of the drug in patients B. McC., C. B. and A. W. occurred after day 2 of therapy. From analyses of specimens collected at timed intervals on days 2 and 3 of the multiple dosing regimen the elimination kinetics of FU in three patients were determined (Fig. 3). $t_{1/2}$ values were 37.4, 43.9, and 18.8 h for

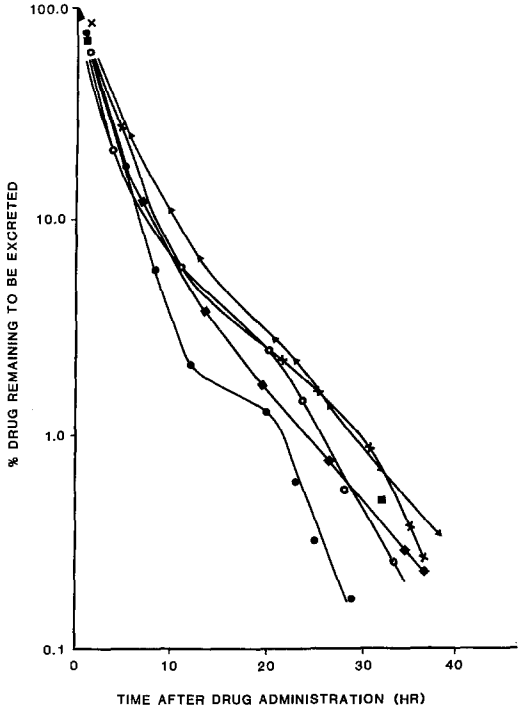

Fig. 4. 'Sigma-minus' plots for total FU and metabolites excreted by N. F. (△), E. P. (○), McK (●), P. D. (×), and S. L. (■) after single-dose therapy

Table 2. Kinetic parameters for urinary excretion of total FU and metabolites after single-dose therapy

Patient	Dose (mg/kg)	% of total dose excreted in urine‡	$t_{1/2}$ (h)	
			I*	II*
B. McK.	7.5	93.6	2.1	2.6
N. F.	7.1	57.8	3.8	4.25
E. P.	7.0	94.5	ND†	3.7
P. D.	8.7	95.7	2.8	3.1
S. L.	9.6	83.1	ND	5.9

‡ Within 48 h of drug administration
* First and second linear portions of the 'Sigma-minus' plots shown in Fig. 4
† Not detected

patients D. M., A. W., and E. C., respectively, for day 3. Total drug was eliminated in patient A. W. more quickly on day 2 than on day 3.

The kinetics of urinary excretion of FU after single dose therapy in five patients are shown in Fig. 4. Generally, each pharmacokinetic profile was composed of two linear parts and a convex portion at approximately 14–20 h after drug administration. Curvature of the sigma-minus plots occurred over periods of 5–15 h when 80%–98% of the drug had been excreted. Linearity of the profiles resumed when 1%–2% of the drug remained in the body. Table 2 shows excretion of the total dose as FU and metabolites in individual patients, and the $t_{1/2}$ values of elimination calculated from suitable parts of the pharmacokinetic curves.

Discussion

The triexponential curve of plasma concentration of FU versus time after IV administration (Fig. 1) establishes the proposal of our initial investigations [27] and other reports [3, 12] that pharmacokinetic evaluation of FU would require at least a three-compartment open-model system. The magnitude of the rate constants for the π and α phases of FU disposition (Table 1) are in agreement with those reported previously [5, 13, 20, 27]. Little inter-individual variation in the α phase has been noted, regardless of disease state, and so, exact definition of this phase is inlikely to be useful clinically [2]. This conclusion is reasonable if the second phase of FU disposition is viewed as being representative largely of a distribution process and not associated solely with elimination. The average $t_{1/2}$ value of 123.5 min for the terminal phase of FU elimination from plasma (Table 1) is longer that those reported previously of 54 min [3] and 78 min [27].

Comparison of the $t_{1/2}$ values for elimination of FU and DHFU (Table 1) shows a shorter $t_{1/2}$ value for DHFU in all patients than for the parent drug. Theoretically, assuming first-order kinetics, the $t_{1/2}$ value estimated from the terminal linear portion of a metabolite profile should be equal to or greater than the $t_{1/2}$ value for the parent drug [14]. An explanation may be given on the basis that although metabolism of FU to DHFU can be influenced by zero-order kinetics, the elimination of DHFU may not be limited. This hypothesis is inconsistent with that of Garett et al. [13], of product-limited metabolism for FU. Since the pharmacokinetic profiles for individual patients maintained a linear appearance at increased dosing it was proposed that after reduction of FU, the subsequent ring opening of DHFU may be the saturable process, resulting in accumulation of DHFU in equilibrium with FU. Further evidence that the inhibition mechanism is associated alternatively with the initial catabolic step is provided by the consistency of AUC values for DHFU by comparison with the variation in AUC values for FU (Table 1).

Saturation of the catabolic pathway would provide an explanation for the increased rates of FU accumulation during 5-day courses of treatment (Fig. 2). The nonlinearity of FU pharmacokinetics is illustrated by the data from patient A. W., which shows an increase in $t_{1/2}$ for FU elimination on successive days of therapy (Fig. 3). The kinetic parameters for FU elimination determined from the urinary excretion data shown in Fig. 3 are consistent with previous suggestions as to the duration of FU activity from animal studies [4, 12]. The greatest exposure to the active metabolites occurred at 24–72 h after dosage of mice with FU [4], which correlated with the observation of a $t_{1/2}$ of elimination of 20 h in rats [12]. However $t_{1/2}$ values calculated from the sigma-minus plots (Fig. 3) using the administered dose as the asymptote may be overestimated [29]. Nevertheless, results for patient A. W. were adequate for evaluation by the Rate plot, giving a $t_{1/2}$ value of 24 h (data not shown).

The pharmacokinetic profiles shown in Fig. 4 suggest that a temporary phase of nonlinear kinetics can occur in the elimination of FU in patients receiving therapeutic doses for breast cancer. Since the slopes of the two linear parts of each plot were similar, the profiles represent a single elimination phase, that is, the β phase observed when investigating plasma concentrations of FU versus time (Fig. 1). By comparison with data from pharmacokinetic investigations in plasma (Table 1), $t_{1/2}$ values for FU elimination after single bolus therapy were greater when determined from urinary excretion studies (Table 3). The limit of sensitivity of the GLC assay usually precluded accurate measurement of FU levels in plasma at times greater than 6 h after drug administration. As the time of

onset of the β phase occurred between 1 and 2 h, equilibrium between plasma and the intracellular anabolic pools might not be established fully at the times used for kinetic analysis of plasma data (Fig. 1), resulting in an underestimate in the calculated $t_{1/2}$ values.

Values of $t_{1/2}$ calculated in this study for patients receiving a multiple dosing regimen resulting in saturation of FU elimination were of the same magnitude as that reported for FU elimination in rats after administration of 90 mg FU/kg [12]. From a previous investigation of the urinary excretion kinetics of FU and metabolites in humans [23] after single doses of 7.6–17.0 mg/kg, $t_{1/2}$ values for FU elimination were 0.34–84.92 h (mean, 14.94 h) which differ from those of the present report. Also, we found less variation in $t_{1/2}$ values but a smaller number of patients were studied. The discrepancies may result from differences in analytical methodology. The shapes of pharmacokinetic profiles for the excretion of FU and metabolites after single doses of FU (Fig. 4) are similar to computer simulations of various types of model based on plasma data [3, 6]. Representative curves derived for FU elimination demonstrated convex behaviour but it has been emphasized that this feature, characteristic of nonlinear kinetics, may be obscured by inadequate sampling or variation in the data [6].

The practical difficulties associated with the determination of intracellular concentrations of FU and metabolites in man precludes any assessment of the relative contributions of different tissues to the observed elimination pattern of the drug. Since the liver is the major organ of FU elimination it is likely that elimination of the drug from plasma or the rate of appearance of parent drug and metabolites in urine reflects primarily hepatic drug metabolizing activity, particularly at early times after treatment. Thus our data pertaining to the relative pharmacokinetics of FU and DHFU derived from analysis of plasma samples (Table 1) probably reflects mainly hepatic elimination. However, a limited capacity of the liver to carry out the initial catabolic step in the degradation of FU will in part affect the degree of exposure of sensitive tissues to the drug. Studies using tumour-bearing mice have demonstrated that the major exposure to FU and metabolites 24–72 h after treatment occurs in tumour and small intestine [4]. It is possible, therefore, that our characterization of the terminal phase of FU elimination in man may at least in part reflect loss of parent drug and metabolites from these important tissues.

The major purpose of this study has been to further elucidate the pharmacokinetic parameters of FU in man using a novel, noninvasive analytical approach. Evaluation of clinical response in relation to drug pharmacokinetics will require a controlled study with patients preferably receiving FU alone. This work is currently in progress.

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