Comparative Pharmacokinetic Analysis of 5-Fluorouracil and Its Major Metabolite 5-Fluoro-5,6-dihydrouracil after Conventional and Reduced Test Dose in Cancer Patients

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ABSTRACT

The aim of this study was to investigate the clinical pharmacokinetics of 5-fluorouracil (5-FU) and its major metabolite 5-fluoro-5,6-dihydrouracil (5-FDHU) in 20 colorectal cancer patients given two dose levels of 5-FU, 250 and 370 mg/m², administered by i.v. bolus. A reverse-phase high-performance liquid chromatographic method was used for the simultaneous assay of 5-FU and 5-FDHU in plasma samples obtained at baseline and at multiple time points from 5 min to 4 h after 5-FU bolus as well as to assess the activity of dihydropyrimidine dehydrogenase (DPD) in peripheral blood mononuclear cells (PBMCs) before 5-FU dosing. Plasma pharmacokinetic parameters of patients given 250 mg/m² 5-FU were significantly different from those receiving 370 mg/m²; main differences were observed in the trapezoidal areas under the plasma levels-versus-time curve from t₀ to the last measurable concentration (area under the curve, 3.77 ± 0.21 versus 13.61 ± 2.3 h × µg/ml), peak plasma concentration (Cₘₐₓ, 18.15 ± 1.35 versus 48.41 ± 7.69 µg/ml), and total body clearance (CLₜₚ, 54.64 ± 3.54 versus 25.43 ± 2.3 l/h/m²). Significant differences were also observed in the main pharmacokinetic parameters of 5-FDHU after 250 and 370 mg/m² 5-FU including the area under the curve from t₀ to 4 h (5.39 ± 0.32 versus 8.75 ± 1.24 h × µg/ml), Cₘₐₓ (3.60 ± 0.16 versus 5.26 ± 0.55 µg/ml) and time to Cₘₐₓ (Tₘₐₓ, 0.45 ± 0.03 versus 0.69 ± 0.06 h). The mean DPD activity in PBMCs in this group of patients was 205.7 ± 36.4 pmol of 5-FDHU/min/mg of protein and was within the normal range; however, no significant correlations were found between 5-FU or 5-FDHU pharmacokinetic parameters at two dose levels and DPD activity of PBMCs. The results of the present study provide the first detailed comparison of the distribution of 5-FU and its major metabolite 5-FDHU at the therapeutic level as well as at reduced test dose levels to obtain pharmacokinetic data to be used as reference values for the identification of patients at risk of major 5-FU toxicity due to impaired metabolism to 5-FDHU.

INTRODUCTION

5-FU³ is widely used as a single drug as well as in combination with other chemotherapeutic agents to treat solid tumors of the gastrointestinal tract (1). To increase the therapeutic efficacy of 5-FU, several modalities of drug administration, including i.v. bolus injections or continuous infusion for extended time have been investigated (2). The clinical pharmacokinetics of single doses of 5-FU from 300 to 600 mg/m², administered as i.v. bolus, has been characterized previously (3). Schaaf et al. (4) described the nonlinear disposition of 5-FU in colorectal cancer patients, as demonstrated by the nonproportional increase in the AUC and corresponding decrease in CLₜₚ after the increase of drug dose. The nonlinear pharmacokinetics of 5-FU was confirmed in additional studies, and drug AUC was related to the toxicity profile (5). However, a similar systematic analysis of the plasma disposition of its major metabolite, 5-FDHU, in patients is lacking with the exception of the study by Heggie et al. (6), who described the disposition of 5-FU and 5-FDHU in patients following i.v. bolus of [¹⁴C]5-FU, and reported a Cₘₐₓ of 5-FDHU in the range of 20–40 µM and a longer t₁/₂ b (40–60 min) than the parent compound (t₁/₂ b for

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3 The abbreviations used are: 5-FU, 5-fluorouracil; AUC, area under plasma levels-versus-time curve; CLₜₚ, total body clearance; 5-FDHU, 5-fluoro-5,6-dihydrouracil; t₁/₂ b, terminal half-life; DPD, dihydropyrimidine dehydrogenase; PBMC, peripheral blood mononuclear cell; HPLC, high-performance liquid chromatography; Cₘₐₓ, peak plasma concentration; Tₘₐₓ, time to Cₘₐₓ; Vdₜₚ, volume of distribution at steady state; tₛ/₃ b, half-life of initial phase.
5-FU, 6–22 min). However, the administration of a radiolabeled drug is unlikely to be used for population pharmacokinetic studies, and the availability of a nonradioactive assay method is highly desirable.

The cytosolic enzyme DPD (EC 1.3.1.2) is widely expressed in both normal and tumor tissues (7, 8) and represents the initial and rate-limiting enzyme of the metabolic pathway leading to the degradation of the pyrimidine bases uracil and thymine (7–9). The detoxification of 5-FU in vivo is mainly due to hepatic DPD (70–80% of the administered dose) through the formation of 5-FDHU followed by fluoroureidopropionic acid and α-fluoro-β-alanine (Fig. 1; Ref. 9), whereas 10–20% of the drug is excreted unchanged in the urine (2). The biochemical basis of severe 5-FU toxicity has been attributed to impaired drug catabolism, resulting in a markedly prolonged 5-FU plasma t1/2 and almost complete absence of drug catabolites (10). In family studies on pediatric and cancer patients with thymine-uricururia, an autosomic recessive pattern of inheritance for DPD deficiency was identified based on measurements of en-

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of patients</th>
</tr>
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<tbody>
<tr>
<td>No. of patients</td>
<td>20</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>14:6</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Median 66, Range 41–75</td>
</tr>
<tr>
<td>ECOG* performance status</td>
<td>Median 0, Range 0–1</td>
</tr>
<tr>
<td>Tumor primary site</td>
<td>Colon 13, Rectum 7</td>
</tr>
<tr>
<td>Body surface area, (m²)</td>
<td>Median 1.71, Range 1.5–1.9</td>
</tr>
</tbody>
</table>

*ECOG, Eastern Cooperative Oncology Group.

The aim of the present study was to characterize the pharmacokinetics of 5-FU and 5-FDHU in colorectal cancer patients given a reduced test dose of 5-FU (250 mg/m²) followed by the conventional therapeutic dose (370 mg/m²). The use of a test dose may be proposed as a preliminary screening procedure to assess the pharmacometabolic profile of patients who are candidates for 5-FU adjuvant treatment and to prevent full-dose administration in those patients with impaired metabolic clearance of 5-FU that depends on a DPD deficiency not otherwise detected in PBMCs.

**PATIENTS AND METHODS**

**Chemicals.** Analytical grade reagents were purchased from Sigma Chemical Co. (St. Louis, MO). 5-FU and 5-FDHU for calibration standards were a generous gift from Hoffman-La Roche (Basel, Switzerland); drugs were reconstituted at 1 mg/ml in 35 mM KH₂PO₄ (pH 7.4) immediately before use. Lymphosep was obtained from ICN Biomedicals (Costa Mesa, CA).

**Patients.** This study was approved by the Ethics Committee of Pisa University Hospital and was conducted according to its guidelines. Patients were informed of the procedures and aim of the study, and they were enrolled after giving written consent to participate. Twenty consecutive patients with surgically resected colorectal adenocarcinomas without evidence of metastatic sites of disease were studied (Table 1). Eligibility criteria also included age ≥ 18 years; Eastern Cooperative Oncology Group performance status ≤ 1; and adequate hematopoietic (leukocyte count ≥ 3,000/µl; absolute neutrophil count ≥ 1,500/µl; platelet count ≥ 100,000/µl; and hemoglobin level ≥ 10 g/dl), hepatic (total bilirubin level ≤ 2.0 mg/dl; aspartate aminotransferase and alanine aminotransferase ≤ 2.5 times normal upper limit), and renal (serum creatinine ≤ 1.5 mg/dl) functions.

**Drug Dosage and Administration.** Patients received a single 5-FU test dose of 250 mg/m² as i.v. bolus (≤1 min) without l-folic acid 1 week before starting the adjuvant treatment consisting of an i.v. bolus of 370 mg/m²/day 5-FU plus 100 mg/m²/day l-folic acid for 5 consecutive days, with cycles repeated every 28 days (15). 5-FU was administered undiluted (50 mg/ml) by rapid i.v. push (≤1 min); immediately after the administration, the i.v. line was flushed with 10 ml of 0.9% NaCl solution.

**Blood Collection.** Plasma disposition of 5-FU and its catabolite 5-FDHU was evaluated in patients after administration of the 5-FU test dose as well as at day 1 of the first cycle
of adjuvant therapy. Blood samples (4 ml each) for drug assays were taken between 9 a.m. and 1 p.m. from an indwelling i.v. cannula placed in an antecubital vein contralateral to the infusion site at 0 min (before the 5-FU bolus was administered) and at 5, 10, 15, 20, 30, 40, 45, 60, and 90 min, and 2, 3 and 4 h after 5-FU i.v. bolus. Blood was collected in heparinized tubes (Vacutainer tubes; Becton Dickinson Vacutainer System, Rutherford, NJ), temporarily stored for a maximum of 15 min at 4°C and then centrifuged (10 min, 4000 rpm, 4°C) to separate plasma, which was stored at −20°C and assayed within 1 week. With these conditions, no evidence of degradation of 5-FU and 5-FDHU was observed because the concentrations of 5-FU and 5-FDHU in blank samples to which they had been added were always ≥95% of the initial concentrations.

**HPLC Analysis.** The simultaneous assay of 5-FU and 5-FDHU in human plasma was performed by a validated non-radioactive reverse-phase HPLC method with UV detection (16). Briefly, 0.5 ml of plasma was mixed with 25 μl of 1 m sodium acetate (pH 4.8), 0.25 ml of anhydrous sodium sulfate (0.2 g/ml) and 50 μl of 5-bromouracil as internal standard (50 μg/ml), and extracted with 7 ml of n-propyl alcohol/diethyl ether (1:9, v/v). Samples were mixed and then centrifuged at 4000 rpm for 10 min to separate the organic phase, which was evaporated to dryness. The sample was reconstituted with 250 μl of mobile phase [50 mM KH₂PO₄ (pH 4.0)], and 50 μl of the sample were finally injected into the HPLC instrument. 5-FU and 5-FDHU were separated on Hypersil BDS C₁₈ columns (150 × 4.6 mm; 5 μm stationary phase; Alltech, Deerfield, IL), eluted with 1 ml/min of 50 mM KH₂PO₄ (pH 4.0). The chromatographic instrument was an LC Module I Plus HPLC (Waters, Milford, MA) with an UV detector set at 200 nm, and data analysis was performed by the Millenium 2.1 software (Waters). The limit of detection was 75 ng/ml for 5-FU and 5-FDHU; compounds eluted within 12 min after injection. Calibration curves were generated by adding 5-FU and 5-FDHU to 0.5 ml of a plasma blank, which resulted in final concentrations that ranged from 0.075 to 75 μg/ml; samples were extracted as described above. The mean recoveries of 5-FU and 5-FDHU were 82 and 79%, respectively, as related to the calibration curve. The 5-FU and 5-FDHU intraassay coefficients of variation were 2–9.1% and 2.3–9.5%, respectively, whereas the interassay coefficients of variation for a 4-day validation were 2–9.1% and 2.3–9.5%, respectively, over the range from 0.075 to 75 μg/ml.

**PBMC Collection and Preparation of Cytosolic Extract.** Before drug administration, 15 ml of blood were drawn from the antecubital vein of patients, collected in heparinized tubes, and diluted (1:1, v/v) with PBS. Diluted blood (4 ml) was placed on top of 3 ml of Lymphosep and centrifuged at 1500 rpm for 45 min. After centrifugation, the PBMC layer was recovered and washed twice with PBS; the remaining erythrocytes were lysed by diluting the cell pellet with an hypotonic solution (1:8, v/v) composed of 10 mM KHCO₃, 160 mM NH₄Cl, and 0.13 mM EDTA for 15 min at 20°C. The cell suspension was centrifuged at 10,000 rpm for 10 min and washed with PBS; the resulting pellet was resuspended in 35 mM potassium phosphate buffer (pH 7.4). Cells were frozen in liquid nitrogen, thawed three times, and centrifuged at 15,000 rpm for 20 min at 4°C. The supernatant was collected, and the protein concentration in the cytosolic extract was measured by the Protein Assay Kit (Sigma).

**Determination of DPD Activity.** DPD activity was assayed in the PBMC cytosolic extract as described previously with minor modifications (17). Briefly, samples containing 0.1–0.3 mg of protein were mixed with 20 μM 5-FU, 250 μM reduced β-NADPH, 2 mM β-mercaptoethanol, and 2.5 mM MgCl₂; then the volume was then adjusted to 0.5 ml with 35 mM potassium phosphate buffer (pH 7.4). Samples were incubated for 30 min at 37°C; the reaction was then quickly stopped by freezing samples in liquid nitrogen. Cytosolic samples were extracted, and 5-FDHU was measured as described above; the DPD activity was expressed as pmol of 5-FDHU formed/min/mg of protein.

**Pharmacokinetic Analysis.** Individual 5-FU and 5-FDHU concentration versus time data sets were fitted according to a two-compartment model, using nonlinear least-squares regression analysis (AP02PR version 3.03 software; MediWare, Groeningen, the Netherlands). Pharmacokinetic calculations were performed according to standard methods (18). The Cmax and Tmax were identified from the inspection of 5-FU and 5-FDHU concentration-time plots. The t1/2 was defined as the time from the peak concentration (Cmax) to the time of last measurable concentration (5-FU) or last blood sample (4 h; t4) for 5-FDHU. CL₀₁ and Vss were obtained from the equation

\[
Vss (l/m²) = \frac{\text{AUC}}{Cmax} \cdot \frac{1}{k_{10}}
\]

where \(k_{10}\) is the rate constant for the transition from the central compartment (C₀) to the peripheral compartment (C₁).

**Data Analysis.** The results are reported as the mean ± SE of 20 patients. The statistical significance of the differences between the two groups of patients was calculated with the Mann-Whitney test, and \(P < 0.05\) was considered significant.

**RESULTS**

**Pharmacokinetics of 5-FU.** Drug pharmacokinetic parameters, obtained in patients given 250 and 370 mg/m² 5-FU, are listed in Table 2. The plasma disappearance curves (Fig. 2) showed a biphasic decay at 250 and 370 mg/m² with an initial
phase characterized by a rapid decline ($t_{1/2a}$, 0.06 ± 0.01 versus 0.02 ± 0.01 h at 250 and 370 mg/m², respectively; $P < 0.05$) and a second phase with a short $t_{1/2b}$ of 0.17 ± 0.02 and 0.21 ± 0.02 h, respectively. Most patients had undetectable 5-FU levels in plasma 90 min after i.v. administration. The $C_{max}$ of 5-FU at 250 and 370 mg/m² was 18.15 ± 1.35 and 48.41 ± 7.69 μg/ml, respectively ($P < 0.05$) and was detected at the first sampling time (5 min); the AUC values for 5-FU were 3.77 ± 0.21 and 13.61 ± 2.30 h × μg/ml ($P < 0.05$), respectively. The CL_TUB values were 54.64 ± 3.54 and 25.43 ± 2.3 l/h/m² ($P < 0.05$) in patients given 250 and 370 mg/m² 5-FU, respectively, demonstrating a significant decrease in drug clearance as the dose of 5-FU increased (Table 2), a behavior typical of nonlinear pharmacokinetics depending on saturable elimination process. This finding was also confirmed by the AUC and $C_{max}$ values, which significantly ($P < 0.05$) increased in a nonproportional fashion with respect to the dose of 5-FU delivered to patients (Table 2). Likewise, the Vdss decreased from 9.14 ± 3m to 2.3 l/h/m² ($P < 0.05$) in patients given 250 and 370 mg/m² 5-FU. Furthermore, the changes in drug distribution included a significant inverse relationship between drug dose and CL_TUB and Vdss, whereas no significant changes in $t_{1/2b}$ were noted after the administration of 370 mg/m² with respect to the test dose. The AUC ratio between 5-FU and 5-FDHU significantly increased ($P < 0.05$) from 0.74 ± 0.05 (250 mg/m²) to 1.72 ± 0.27 (370 mg/m²; Table 2).

Pharmacokinetics of 5-FDHU. The pharmacokinetic parameters of 5-FDHU are listed in Table 3. 5-FDHU was measurable in plasma at the first sampling time (5 min) and was detectable 4 h after the 5-FU i.v. bolus. Following 5-FU doses of 250 and 370 mg/m², $C_{max}$ values of 3.60 ± 0.16 and 5.26 ± 0.55 μg/ml ($P < 0.05$) were achieved at 0.45 ± 0.03 and 0.69 ± 0.06 h ($P < 0.05$; Table 3 and Fig. 3), respectively. The biphasic elimination curves (Fig. 3) of the major catabolite of 5-FU showed much longer half-lives than those of the parent compound: the $t_{1/2as}$ were 0.13 ± 0.02 and 0.14 ± 0.05 h, whereas the terminal half-lives were 0.87 ± 0.13 and 0.80 ± 0.1 h after 250 and 370 mg/m² 5-FU, respectively (Table 3). The increase in 5-FU dose was associated with a delay in $T_{max}$ (0.45 ± 0.03 versus 0.69 ± 0.06 h; $P < 0.05$), whereas a significant difference between the AUCs (5.39 ± 0.32 versus 8.75 ± 1.24 h × μg/ml; $P < 0.05$) was observed.

DPD Activity. DPD activity varied widely in the PBMCs of patients, with a mean ± SE value for 5-FDHU of 205.7 ± 36.4 pmol/min/mg of protein and a median value of 132.4 pmol/min/mg of protein (range, 101.1–541.4 pmol/min/mg of protein). Furthermore, the DPD activities were similar in male and female patients [5-FDHU, (mean ± SE), 215.7 ± 46.9 versus 201 ± 59.9 pmol/min/mg of protein, respectively]. There were no statistically significant correlations ($P > 0.05$) between PBMC DPD activity and 5-FU or 5-FDHU pharmacokinetic parameters, including $C_{max}$, AUC, CL_TUB and 5-FU/5-FDHU AUC ratio, at 5-FU dose levels of 250 and 370 mg/m² (data not shown).

**DISCUSSION**

The present study reports a detailed investigation on the human plasma distribution of 5-FU and 5-FDHU in previously untreated colorectal cancer patients. The plasma levels of the parent drug and metabolite, following i.v. bolus administration of 5-FU at two dose levels, was assayed by a sensitive HPLC method that allowed the simultaneous measurement of 5-FU and 5-FDHU. The availability of pharmacokinetic data for a 5-FU test dose of 250 mg/m² versus the conventional 370 mg/m² dose would permit the rational use of this method to screen colorectal

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**Table 3** Pharmacokinetic parameters of 5-FDHU in patients treated with 5-FU at two dose levels

<table>
<thead>
<tr>
<th>Dose (mg/m²)</th>
<th>250 mg/m²</th>
<th>370 mg/m²</th>
<th>Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{max}$ (μg/ml)</td>
<td>3.60 ± 0.16</td>
<td>5.26 ± 0.55*</td>
<td>+46.1</td>
</tr>
<tr>
<td>$T_{max}$ (h)</td>
<td>0.45 ± 0.03</td>
<td>0.69 ± 0.06*</td>
<td>+53.3</td>
</tr>
<tr>
<td>$t_{1/2a}$ (h)</td>
<td>0.13 ± 0.02</td>
<td>0.14 ± 0.05</td>
<td>-7.7</td>
</tr>
<tr>
<td>$t_{1/2b}$ (h)</td>
<td>0.87 ± 0.13</td>
<td>0.80 ± 0.1</td>
<td>-8.8</td>
</tr>
<tr>
<td>AUC (h × μg/ml)</td>
<td>5.39 ± 0.32</td>
<td>8.75 ± 1.24*</td>
<td>+62.3</td>
</tr>
</tbody>
</table>

* $P < 0.05$, 250 vs. 370 mg/m² dose.
cancer patients prior to 5-FU adjuvant therapy to identify those subjects with impaired metabolism at risk of developing severe or fatal drug-related toxicity.

Previous studies described in detail the pharmacokinetics of 5-FU after i.v. administration and reported a two-compartment model to describe the distribution kinetics of 5-FU. Furthermore, the disposition of 5-FU was characterized by high drug clearance (2), a very short distribution phase (19), an elimination half-life varying from 8 to 22 min, and nonlinear pharmacokinetics (4). However, data concerning the pharmacokinetic profile of its major catabolite, 5-FDHU, which reflects the result of systemic (mainly hepatic) DPD activity rather than the enzymatic activity of PBMCs, were still lacking. Heggie et al. (6) administered a 14C-labeled dose of 5-FU to study drug distribution in human plasma, and observed a peak level of 5-FDHU about 1 h following injection, with an half-life almost five times longer (40–60 min) than that of the parent drug. The present study confirms the biphasic decay of 5-FU in plasma at both dose levels and the nonlinear pharmacokinetics of the drug. The increase in drug dose from 250 to 370 mg/m² (48%) was associated with a disproportional decrease in CL TB (−114.9%) and Vdss (−120.2%) and increases in the AUCs (261%) and Cmax (166.7%). Thus, the kinetic profile of 5-FU and 5-FDHU after the test dose of 250 mg/m² is characterized by enhanced clearance with respect to the conventional dosage of 370 mg/m², suggesting that a single, reduced test dose of 250 mg/m² may also be safe for subjects with profound DPD deficiency. Furthermore, the test dose permits the measurement of the major catabolite 5-FDHU, the product of the DPD enzyme, and thus provides a direct estimate of the systemic metabolic activity more accurately than the measurement of enzyme activity in PBMCs.

The relationship between PBMC DPD activity and 5-FU clearance revealed a weak correlation (10) unable either to predict the severity of 5-FU toxicities or to suggest dose modifications to prevent these toxicities (20). The potential advantage of measuring 5-FDHU plasma levels in patients versus the activity of DPD in a highly differentiated cellular compartment as PBMCs is obvious because the enzyme activity in bone marrow cells may not be representative of that found in other tissues, particularly the liver. This point of view was confirmed by data collected in our patient population about the lack of significant correlation between pharmacokinetic parameters and PBMC DPD activity, probably due to the profound variation in DPD activity of different human blood cell types (21). Previous pharmacokinetic studies demonstrated a reduced 5-FU clearance in patients with DPD deficiency (11). These patients were characterized by a markedly altered pharmacokinetic pattern, with no evidence of 5-FU catabolites in plasma at any of the 15 time points examined over 24 h (11), with a body clearance of 5-FU markedly lower than that in patients with normal catabolism, and with about 90% of the 5-FU dose excreted unchanged in the urine (22).

The data from the present study provide evidence that the analysis of 5-FDHU and 5-FU kinetics is feasible on a routine basis and that the data obtained may be used as reference values to identify DPD-deficient patients at the beginning of adjuvant therapy. In addition, the test dose may be implemented as a routine pretreatment screening procedure of colorectal cancer patients. This strategy is similar in concept to the study of Gamelin et al. (23), which examined the endogenous uracil/dihydrouracil ratio as a predictor of DPD activity in cancer patients. However, the use of a test dose of 5-FU might be advantageous because of the easier measurement of 5-FU and 5-FDHU compared with uracil and dihydrouracil.

5-FU is metabolized mainly in the liver, and the level of DPD activity in this tissue represents the major determinant of 5-FU metabolic clearance and toxicity. Stéphan et al. (20) described a case of lethal multifocal encephalopathy after 5-FU chemotherapy and demonstrated very high and sustained 5-FU concentrations in plasma (half-life >3 days), whereas DPD activity in the liver was markedly reduced, although the PBMCs displayed normal enzyme activity. This discrepancy points out a crucial issue, i.e., that DPD activity in the PBMCs does not necessarily reflect the ability of the body to metabolize 5-FU. Therefore, it does not offer a reliable test to predict the occur-

![Fig. 3 5-FDHU pharmacokinetic profiles in human plasma at the two 5-FU dose levels of 250 and 370 mg/m². Symbols indicate mean values; bars, SE; *, P < 0.05 (370 versus 250 mg/m²), Mann-Whitney test.](image-url)
rence of life-threatening toxicities due to 5-FU overexposure. Furthermore, the marked inter- and intraindividual variation in DPD activity of PBMCs (21, 24) represents an additional factor of concern with respect to the use of the PBMC DPD assay to predict 5-FU clearance and risk of toxicity (13). Therefore, the present pharmacokinetic data for 5-FDHU could improve the ability to recognize and select patients with a systemic impairment of 5-FU catabolism who are at risk of developing severe drug-related toxicity.

The administration of a test dose of 5-FU may thus represent an alternative and simple method to recognize a catabolism deficiency at the beginning of 5-FU treatment that may integrate or even simplify other screening methods, including the examination of cancer patients with respect of the mutant DYPD allele as suggested by Wei et al. (25) or the semi-automated radioassay of DPD activity in PBMCs as reported by Johnson et al. (26).

In conclusion, the present study represents a further step toward a detailed modeling of the kinetics of 5-FU and its catabolite 5-FDHU. In addition, this study suggests the potential clinical relevance of a pharmacokinetic analysis of a reduced 5-FU test dose of 250 mg/m² compared with the conventional dose of 370 mg/m² to identify patients with impaired metabolism and at risk of drug-related life-threatening toxicities.

ACKNOWLEDGMENTS

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REFERENCES


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