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Françoise Bressolle · Jean M. Joulia
Frédéric Pinguet · Marc Ychou · Cécile Astre
Jacqueline Duffour · Roberto Gomeni

Circadian rhythm of 5-fluorouracil population pharmacokinetics in patients with metastatic colorectal cancer

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Abstract *Purpose*: The purpose of this work was to estimate the population pharmacokinetic parameters of 5-fluorouracil (5-FU) in patients with advanced colorectal cancer using circadian change kinetics. *Methods*: Eighty-five patients (32 females, 53 males) were enrolled onto this study. All patients received folinic acid (200 mg/m^2) by intravenous infusion over 2 h followed by a 5-FU loading dose (400 mg/m^2) and then continuous infusion (600 mg/m^2) for 22 h. This whole regimen was repeated on day 2 and was given on a 14-day cycle. Plasma 5-FU determinations were performed by high-performance liquid chromatography with ultraviolet absorbance detection. Pharmacokinetic analyses were performed using the NONMEM computer program through the Visual-NM graphical interface. An open one-compartment pharmacokinetic model with zero-order input rate was used to describe the kinetics of 5-FU; moreover, circadian time-dependent changes in 5-FU concentrations were taken into account in the model. The circadian model was defined as the sum of two cyclic components; the amplitude of the first cyclic component (over 24 h) was about 30% of the average clearance and the amplitude of the second cyclic component (over 12 h) was about 50% of the amplitude of the first component. The acrophase (peak) times of the first and the second periodic component were 04 h 12 m and 00 h 25 m, respectively. The potential sources of variability on the population parameters (65 patients) were investigated using patient's sex, body area, age, body weight, height, liver enzymes and serum creatinine as covariables. *Results*: Only the estimated clearance circadian changes were different for the two sexes. The population parameter estimates of mean clearance (CL_{mean}) and initial volume of distribution (V), were as follows: the male subgroup showed a CL_{mean} value twice larger (125 l/h) than the value observed in the female subgroup (65 l/h), and V = 21 l. A validation group of 20 additional patients was used to evaluate the predictive performances of the population parameters. The individual pharmacokinetic parameters were computed by means of a Bayesian fitting procedure. From the resulting individualized parameter values, concentrations of 5-FU in the plasma were calculated. To evaluate the performance of the Bayesian estimation, the experimental concentrations were compared with the predicted ones. *Conclusion*: In conclusion, a chronomodulated delivery schedule of 5-FU should be performed, using a perfusion rate inversely proportional to the circadian variations of clearance in order to maintain stable 5-FU plasma levels. Such a treatment schedule may result in increased effectiveness of the treatment and decreased occurrence of drug-associated side-effects. The present study develops a complete procedure to efficiently estimate 5-FU clearance in order to optimize dosage regimens in individual patients.

Key words Colorectal cancer · 5-Fluorouracil · Population pharmacokinetics · Circadian rhythm

F. Bressolle (✉) · J.M. Joulia · R. Gomeni[1]
Department of Clinical Pharmacokinetics,
Faculty of Pharmacy, Montpellier I University,
15 Avenue Ch. Flahault,
F-34060 Montpellier Cedex 2, France
Tel./Fax: +33-4-67-54-80-75

J.M. Joulia · F. Pinguet · C. Astre
Department of Oncological Pharmacology, Pharmacy Service,
Val d'Aurelle Anticancer Centre,
parc Euromedecine, Montpellier, France

M. Ychou · J. Duffour
Digestive Oncology Unit, Val d'Aurelle Anticancer Centre,
parc Euromedecine, Montpellier, France

Present address:
[1] Astrazeneca Laboratories,
Cergy Pontoise,
France

Introduction

Continuous infusion of some anticancer drugs provides the means to increase their anti-tumour efficacy and

decrease their toxicity [17]. 5-Fluorouracil (5-FU) is an anti-neoplastic agent widely used alone or in combination chemotherapy regimens for the treatment of advanced gastrointestinal cancer, breast cancer and several other types of cancer [5]. Administration of a bolus of 5-FU and folinic acid is the reference treatment for metastatic colorectal cancer [24, 26]. Folinic acid optimizes inhibition of thymidylate synthetase by stabilizing the ternary complex formed between thymidylate synthetase, 5-fluorodeoxyuridine monophosphate (5-FU anabolite) and a reduced folate. Similar anti-tumour activity was also achieved by continuous infusion of 5-FU for 5 days or for 30 days or more [18, 39]. However, a regimen of short infusions of folinic acid followed by a 5-FU bolus loading dose and then continuous infusion for 48 h every 2 weeks appeared to be much better tolerated but equally effective [3, 4, 14]. This protocol is the most frequently used treatment schedule in this type of pathology.

The pharmacokinetics of 5-FU have been widely studied [7, 8, 13, 15, 28, 30, 34, 35, 37, 38]. Both linear [15] and non-linear (Michaelis-Menten) [30, 38] eliminations have been used to fit the data. These studies have shown significant intra- and interpatient variations in pharmacokinetic parameters. Moreover, a circadian rhythm following continuous infusion has been reported, that is, a peak at 0400 hours and a trough at 1300 hours [12, 20, 23]. In the body, 5-FU is rapidly metabolized, particularly by the liver, to give various metabolites with well-known anti-neoplastic properties [25]. Renal clearance accounts for less than 15% of the total 5-FU clearance. Total body clearance is high, from 776 to 3023 ml min^{-1} m^{-2} [15]. The elimination half-life ranged from 4.5 to 10 min [15, 28].

Recently, Gamelin et al. [9] showed that individual 5-FU dose adjustment with pharmacokinetic monitoring provided a high survival rate and percentage of responses, with good tolerance. Pharmacokinetic population studies have been developed to describe intra- and interindividual variabilities. Among the available methods, Bayesian estimation allows satisfactory model parameter estimation with a limited number of sampling points and thus reduces hospitalization time as well as the cost of pharmacokinetic studies. Such methodological schemes associating Bayesian estimation with a population study have been performed for several drugs, including some anti-cancer agents.

The purpose of the present study was to estimate the population pharmacokinetic parameters of 5-FU using a one-compartment open model and circadian change kinetics in a population of 65 patients with advanced colorectal cancer. A non-linear mixed-effect modelling approach (NONMEM software) was used to estimate the population pharmacokinetic parameters. To verify the predictive performances of this method, subsequent 5-FU concentrations were predicted in an independent group of 20 patients and then compared to the measured concentrations.

Patients and methods

Selection of patients and treatment schedule

Data collected from 1994 to 1998 were used to perform an analysis of the population pharmacokinetics of 5-FU. Eighty-five patients (32 females, 53 males) with advanced, inoperable, histologically proven colorectal cancer participated in this study. Forty-two patients were studied during two cycles with a 14-day interval; the other patients were studied during just one cycle of the allocated treatment. Patients had altered performance status [<2, World Health Organization (WHO) classification], a serum creatinine level of <130 μM, a normal blood-liver test (bilirubin <3.0 mg/100 ml and aspartate aminotransferase <2 times normal) or normal liver echography. In addition, all of them had adequate bone marrow function (WBC $\geq 3000/mm^3$ and platelets $\geq 100\,000/mm^3$). Complete history, physical examination, chemistry panel, complete blood count and platelet count, and evaluation of the extent of tumour (using appropriate investigations) were required prior to study entry. Toxicity documentation, complete blood count and platelet count and liver function studies were evaluated before each cycle.

All patients received folinic acid followed by 5-FU daily for 2 consecutive days with a controlled flow pump according to the treatment schedule reported by de Gramont et al. [3, 4] at 1400 hours. The treatment was given as folinic acid [200 mg/m^2 in 0.9% (w/v) sodium chloride] by intravenous (IV) infusion for 2 h followed by a 5-FU loading dose (400 mg/m^2 in 5% dextrose) and then continuous infusion (600 mg/m^2) for 22 h. This whole regimen was repeated on day 2 and was given on a 14-day cycle.

The subjects included were randomly allocated into a model building set (65 patients, population group) and a test-data set (20 patients, validation group). Potential explanatory covariables such as patients' age, weight, height, body area, gender and serum creatinine were included in the original data files.

Study design

Sparse data (53 patients) and rich data (32 patients) were used. Kinetic data for each patient consisted of several venous blood samples (4 to 14) drawn into heparinized tubes before, just after the IV bolus, at various time after the start of each 5-FU infusion, and 15 min and 120 min after the end of each treatment. Forty-two percent of the patients had plasma sampling at or around 0400 hours. Immediately after collection, blood samples were centrifuged (2000 *g*) at $+4$ °C for 10 min then the plasma was stored at -40 °C until assay.

Determination of 5-fluorouracil concentrations

Plasma 5-FU determinations were performed by high-performance liquid chromatography with ultraviolet absorbance detection as described elsewhere [16]. Precision expressed as percentage coefficient of variation ranged from 2.7 to 13% and the mean recovery from 94 to 105%. The limits of quantification and of detection were 20 ng/ml and 10 ng/ml, respectively.

Population analysis

Pharmacokinetic analysis was performed using the non-linear mixed-effect modelling approach as implemented in the NONMEM computer program (Version 4.0, level 2.1) [2] through the Visual-NM graphical interface [11]. The population characteristics of the pharmacokinetic parameters (fixed and random effects) were estimated using the First Order (FO) method using the sub-routines ADVAN1 and TRANS2 from the library of programs provided with the NONMEM-PREDPP package.

5-FU concentration-time data were fitted by a one-compartment structural pharmacokinetic model with zero-order input rate using sequentially a first-order elimination [15] and a Michaelis-Menten elimination [30, 38]. Preliminary analysis showed that a two-compartment model provided biased parameter estimates. The use of a one-compartment model with linear elimination kinetics significantly improved the goodness-of-fit criteria (Akaike, residual distribution). For this reason, it was not appropriate to use a Michaelis-Menten model to fit the data.

Moreover, circadian time-dependent changes in 5-FU concentrations, due to a time-dependent change in the drug clearance, were taken into account in the model according to the results published by Metzger et al. [20]. This paper showed that the average plasma concentrations varied rhythmically on each day during a 5-day 5-FU constant infusion (600 mg/m^2/day), with a mean trough at 1300 hours and a peak at 0400 hours. The steady-state time-varying clearance (CL_{ss}) was computed from the published steady-state concentrations (C_{ss}) as:

$$CL_{ss} = \frac{Dose/\tau}{C_{ss}} \quad (1)$$

where τ is the duration of the infusion.

These data were fitted to a circadian function defined as the sum of two cyclic components of 12- and 24-h periods, respectively:

$$CL_{ss} = CL_{av} + CLA_1 \cdot \cos\left[(t - t_{z1}) \cdot \frac{2\pi}{24}\right] + CLA_2 \cdot \cos\left[(t - t_{z2}) \cdot \frac{2\pi}{12}\right] \quad (2)$$

where CL_{av} is the average clearance; CLA_1 and CLA_2 the amplitude of the first and the second periodic component, respectively; t_{z1} and t_{z2} are the acrophase (peak) times of the first and the second periodic components, respectively.

The pharmacokinetic fixed effect parameters estimated by the program were the total plasma clearance (CL) and the volume of distribution (V). Measurement errors (random effects) were assessed according to a proportional error model associated to each fixed-effect parameter; thus, for example, the volume of distribution (V) of the jth subject was described by the relationship:

$$V_j = V_{mean} \cdot \exp(\eta_{Vj}) \quad (3)$$

where V_{mean} is the population mean and η_{Vj} is the difference between the population mean and the jth subject; η_V is assumed to be a Gaussian random variable with mean zero and variance σ^2_η. The concentration-time profile in the jth individual was assumed to be affected by an additive error described by the relationship:

$$C_{ij}(t) = f(p_j, D_j, t_{ij}) + \varepsilon_{ij} \quad (4)$$

where p_j are the pharmacokinetic parameters (such as clearance, volume, etc.) of the jth subject, t_{ij} is the time of the ith measurement, D_j is the dosing history of the jth subject, f is the pharmacokinetic model, and ε_{ij} represents the residual departure of the model from the observations and contains contributions from intra-individual variability, assay error and model misspecification; ε is assumed to be a random Gaussian variable with mean zero and variance σ^2_ε.

The following covariables were considered pertinent to this study: sex, body area, age, body weight, height, liver enzymes and serum creatinine. The results were compared with the ones obtained when on the one hand the circadian rhythm was not taken into account and on the other hand the influence of covariable factors was not considered; the evaluation criterium used was the log-likelihood value.

From the empirical Bayesian individual estimate of the pharmacokinetic parameters, plasma concentrations of 5-FU were calculated for each patient. To assess the posterior distribution properties of the residuals (difference between experimental and estimated values), the Student's t-test was used to compare the mean residual value to 0; the Kolmogorov-Smirnov test was used to compare the sampled distribution to the expected one (N(0,1)) [19].

Performance of Bayesian individual parameter estimates

Twenty patients not included in the calculation of population parameters were used to evaluate the performance of the Bayesian estimation. These patients were enrolled in the study according to the same experimental design (dose, route and sampling times) as the 65 patients included in the population study. For these patients, individual pharmacokinetic parameters were estimated by NONMEM using the *post hoc* Bayesian option together with the parameters of the final population model.

To evaluate the performance of the Bayesian estimation, the experimental values (C_{REF}) were compared to the predicted ones (C_{TEST}). Predictive performance was assessed in terms of bias (mean prediction error, ME) and precision (root mean square prediction error, RMSE) and the associated 95% confidence intervals [31, 32].

$$\text{Bias} = \frac{1}{n}\sum_{i=1}^{i=n}\left[C_{TEST(i)} - C_{REF(i)}\right] \quad (5)$$

$$\text{Precision} = \sqrt{\frac{1}{n}\sum_{i=1}^{i=n}\left[C_{TEST(i)} - C_{REF(i)}\right]^2} \quad (6)$$

In these expressions, the index i refers to the individual concentrations and n is the total number of values. Statistical comparisons were assessed using the paired Student's t-test.

Results

Patients and toxicity

The patients' characteristics are displayed in Table 1. The majority of subjects had undergone prior chemotherapy including irinotecan (eight patients) and oxaliplatin (eight patients); thirty one patients had previously received 5-FU. No toxicity greater than WHO Grade III was observed. The toxicity was never life threatening (Table 2).

Table 1 Demographic and biological characteristics of the patients (mean ± SD). *SD* standard deviation, *CEA* carcino embryonic antigen, *CA* carbohydrate antigen

	Sex	Age (years)	Weight (kg)	Height (cm)	Body area (m^2)	Serum creatinine level (μmol/l)	CEA (ng/ml)	CA (ng/ml)
Population group ($n = 65$)	Females: 23 Males: 42	61.1 ± 10.7	67.1 ± 13.1	168 ± 7.4	1.75 ± 0.18	84.8 ± 19.8	300 ± 575	470 ± 701
Validation group ($n = 20$)	Females: 9 Males: 11	61.0 ± 9.0	66.5 ± 15.3	166 ± 8.2	1.73 ± 0.20	78.9 ± 20.0	197 ± 354	55.6 ± 43.3

Table 2 Pattern of toxicity. *WHO* World Health Organization

	WHO grade Number of patients (population group/ validation group)			
	0	1	2	3
Nausea/vomiting	50/16	9/3	4/0	2/1
Diarrhoea	57/18	4/1	4/1	0/0
Mucositis	63/18	2/0	0/1	0/1
Leucopenia	59/18	4/2	2/0	0/0
Thrombopenia	63/19	1/0	1/0	0/1
Anaemia	59/18	4/1	1/1	1/0

Circadian variation on clearance

The circadian model defined as the sum of two cyclic components was fitted to the average CL_{ss} and the goodness-of-fit analysis revealed that this model was definitely more accurate in describing the observations than a single-cycle model or a double-cycle model with an equal periodicity of 24 h. The results of this analysis were: CL_{av} = 111 l/h, CLA_1 = 38 l/h, t_{z1} = 4.19 h, t_{z2} = 0.41 h, CLA_2 = 19.1 l/h. These values indicate that the amplitude of the first cyclic component (over 24 h) was about 30% (0.34) of the CL_{av} and the amplitude of the second cyclic component (over 12 h) was about 50% of the amplitude of the first component.

Population characteristics

The population database consisted of 562 5-FU concentrations. A reference population analysis was performed using a standard compartmental model without considering the circadian variation on clearance. The results of this analysis are presented in Table 3. An additional model was then defined to account for the influence of the circadian variation on clearance. The clearance variation was assumed to have the acrophase times (t_{z1} and t_{z2}) equal to the ones estimated in the previous CL_{ss} analysis. The amplitudes (CLA_1 and CLA_2) were assumed to be in the same proportion to the CL_{av}as previously estimated. In this approach the clearance was defined as:

$$CL = CL_{mean} + 0.34 \cdot CL_{mean} \cdot \cos\left[(t - t_{z1}) \cdot \frac{2\pi}{24}\right] + 0.17 \cdot CL_{mean} \cdot \cos\left[(t - t_{z2}) \cdot \frac{2\pi}{12}\right] \quad (7)$$

where CL_{mean} was the only unknown parameter.

The inclusion in the model of a circadian rhythm significantly reduced the maximum likelihood (455.4 instead of 460.8, $P < 0.05$). The relationship between the posterior individual estimates and the covariables was investigated by using both graphical exploratory analysis and multiple linear stepwise regression. Only the covariable 'sex', which showed a correlation with CL, was retained in the analysis.

In the final analysis, a second stage linear model was used to relate the sex and CL_{mean}:

$$CL_{mean} = sex \cdot \theta_1 + \theta_2 \quad (8)$$

where θ_1 and θ_2 were the model parameters. The standard log-likelihood ratio test based on the χ^2 statistics showed a significative improvement on the maximum likelihood ($P < 0.05$) after the inclusion of sex in the model. The final population parameters are given in Table 3 and the estimated CL circadian changes for the two sexes are displayed in Fig. 1. The goodness of fit was assessed by the analysis of the scatter plot of the empirical Bayesian predicted values versus the individual observed values (Fig. 2), and by the frequency distribution histogram of the normalized residuals which revealed a distribution very close to the expected one (normal with zero mean and unitary variance) (Fig. 3).

Evaluation of the Bayesian pharmacokinetic parameter prediction

For the patients of the test group individual pharmacokinetic parameters were calculated using the population characteristics. The scatter plot of estimated and observed 5-FU concentration values (104 data) is given

Table 3 Population characteristics of kinetic parameters estimated from observations in 65 patients. V distribution volume, CL total plasma clearance, CL_{mean} mean clearance value, θ_1 and θ_2 are the model parameters of the linear relationship between CL_{mean} and sex

Kinetic parameters	Population mean	Interindividual variability, CV (%)	Population mean	Interindividual variability, CV (%)	Population mean	Interindividual variability, CV (%)
	Without the circadian rhythm		With the circadian rhythm			
			Without covariables		With covariables	
V (l)	18.4	114	17.9	101.5	21.2	105.8
CL (l/h)	128	56	–	–	–	–
CL_{mean} (l/h)	–	–	99.2	54.1	–	55.7
θ_1 (l/h)	–	–	–	–	60.2	–
θ_2 (l/h)	–	–	–	–	65.0	–
Residual variability	0.432		0.428		0.416	
Objective function	460.8		455.4		440.1	

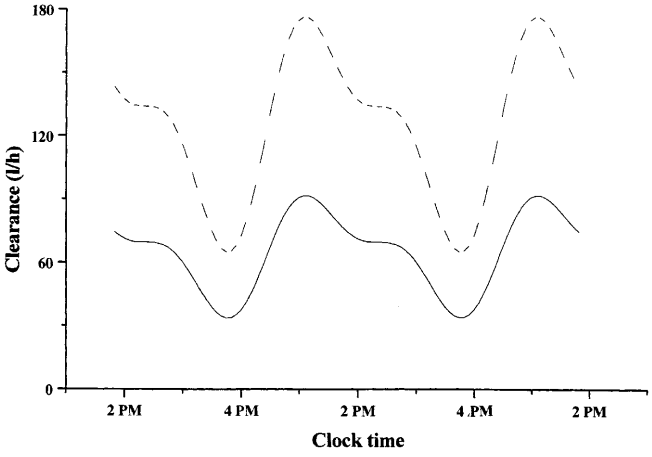

Fig. 1 Circadian variations in mean plasma concentration of 5-fluorouracil. Males (- - - -); females (——)

in Fig. 4. A typical posterior individual fitting is displayed in Fig. 5. Table 4 shows the performance of Bayesian estimation expressed by bias and precision. Bias was not statistically different from zero (student's *t*-test) and the 95% confidence interval included the zero value. We can also note that the precision on the concentration prediction remains lower than the interindividual standard deviation (Table 4).

Discussion

The present study develops a complete procedure to efficiently estimate pharmacokinetic parameters with a minimal clinical cost. Bayesian estimation of the pharmacokinetic parameters is the most valuable and accurate tool for adjusting drug dosage in an individual patient. The Bayesian approach, proposed by Sheiner et al. [33] to individualize the dosage of drug regimens, combines population characteristics of the parameters to be estimated with drug concentrations measured in the individual concerned, such that the individual pharmacokinetic parameters can be estimated.

In the present paper, a population analysis of the kinetics of 5-FU was investigated using a mixed data set arising from a group of patients with rich and sparse data. A one-compartment model was used to fit the data. Moreover, it has been published that 5-FU exhibited a prominent group circadian rhythmicity; the mean double amplitude was 82% and its acrophase time was located near 0400 hours [20]. Thus, in the present population approach, a circadian rhythm was included in the model. The circadian function was defined as the sum of two cyclic components of the 12- and 24-h period, respectively. The amplitude of the first cyclic component (over 24 h) was about 30% of the average clearance (CL_{av}) and the amplitude of the second cyclic component (over 12 h) was about 50% of the amplitude of the first component. The acrophase (peak) times of the first and the second periodic components were 0414 and 0025 hours, respectively.

Several investigators have pointed out that interindividual variations in 5-FU clearance are linked to a risk of developing more or less severe drug-related toxicities [33]; thus, identification of individual factors that can influence 5-FU pharmacokinetic parameters is essential [3, 14, 10, 21, 27]. Consequently, the potential sources of variability on the population parameters were investigated in this study using patient's sex, body area, age, body weight, height, liver enzymes and serum creatinine as covariables. Only the covariable 'sex' showed a cor-

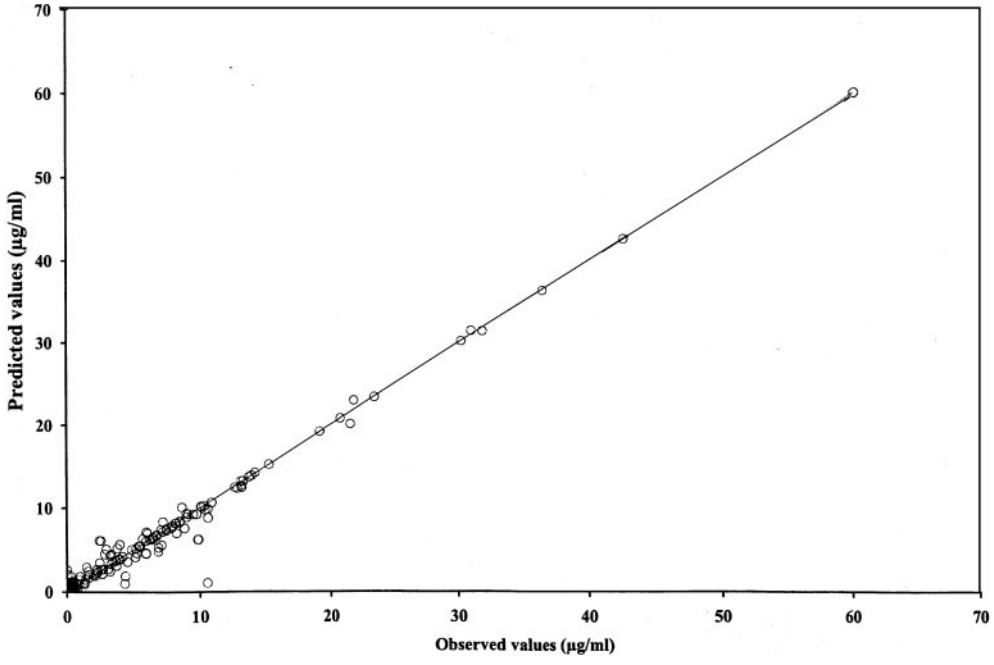

Fig. 2 Scatter plot of predicted concentrations (Bayesian estimates) versus observed concentrations (population group)

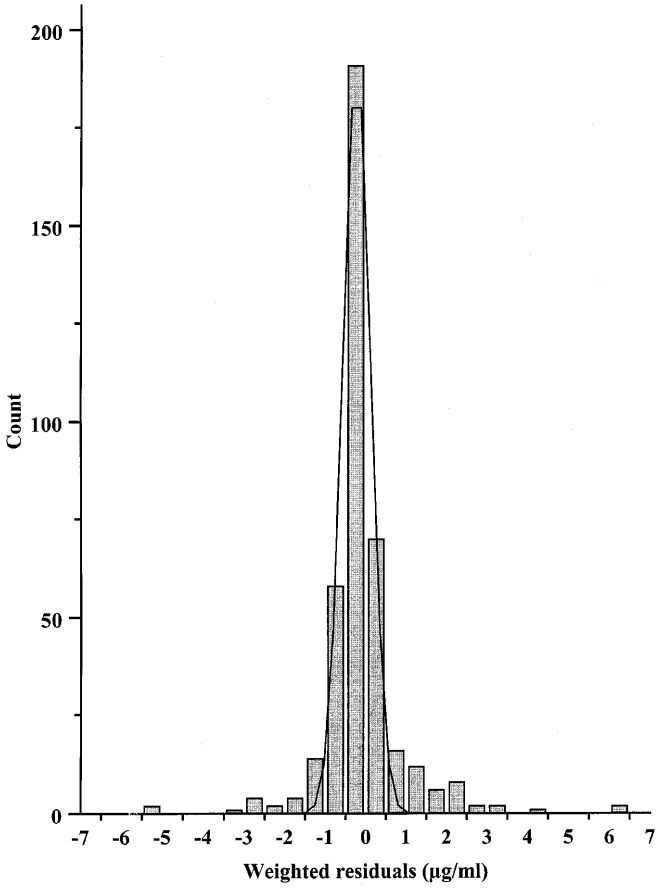

Fig. 3 Frequency distribution of standardized residuals

relation with CL_{mean}; the estimated mean clearance values and the associated circadian changes were different for the two sexes. On average, the male subgroup showed a CL_{mean} value twice larger (125 l/h) than the value observed in the female subgroup (65 l/h). These results were in accordance with those found by Milano et al. [22], who reported a significantly lower clearance in women than in men. As has been reported, the sex-related differences in 5-FU clearance should be related to dihydropyrimidine dehydrogenase (DPD) activity [22, 36]. Bayesian estimates of the pharmacokinetic parameters in the population group showed that the intrapatient variability in the pharmacokinetic parameters over 2 successive days of treatment are relatively low and do not exceed 20%.

The Bayesian methodology developed in this study enables the estimation of individual 5-FU pharmacokinetic parameters from patients with rich or sparse data (two blood sampling times over a 24-h period, i.e. *t* 10–15 min and *t* 20 h) in order to optimize the best therapeutic dose regimen for each patient. Peak values and concentrations during the 22-h infusion period were well estimated. Bias was not statistically different from zero. The precision of the estimate (1.72 µg/l, Table 4) remained lower than the interindividual standard deviation (10.6 µg/l). Using such an approach, it is possible to estimate accurately individual pharmacokinetic parameters, and consequently the exposure to the drug. In this case, dosage can be adjusted between two courses of chemotherapy to optimize drug efficacy or decrease side-effects. Theoretically, for an efficient estimation of *CL* and *V*, two sampling times are needed [1]. The first sample should be taken as early as possible after the maximum drug concentration, and the other as late as possible [6]. The first sample should be taken 10 min after the end of the loading dose, and the second sample about 2 h before the end of the long-term infusion, as performed in the patients of this study with sparse data.

Since 5-FU plasma levels are associated with drug-induced side-effects [29], knowledge of the circadian

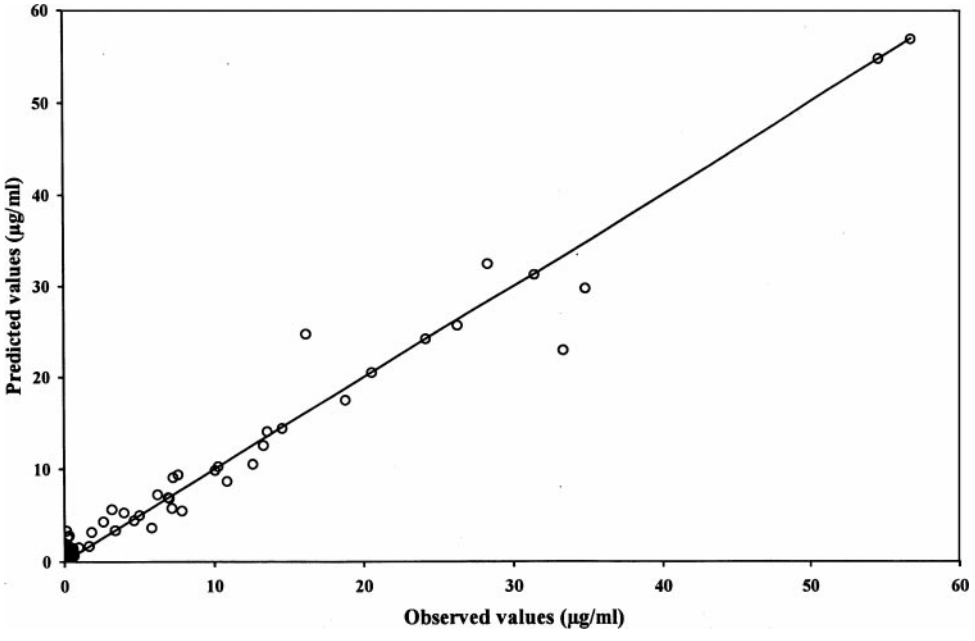

Fig. 4 Scatter plot of predicted concentrations (Bayesian estimates) versus observed concentrations (test group)

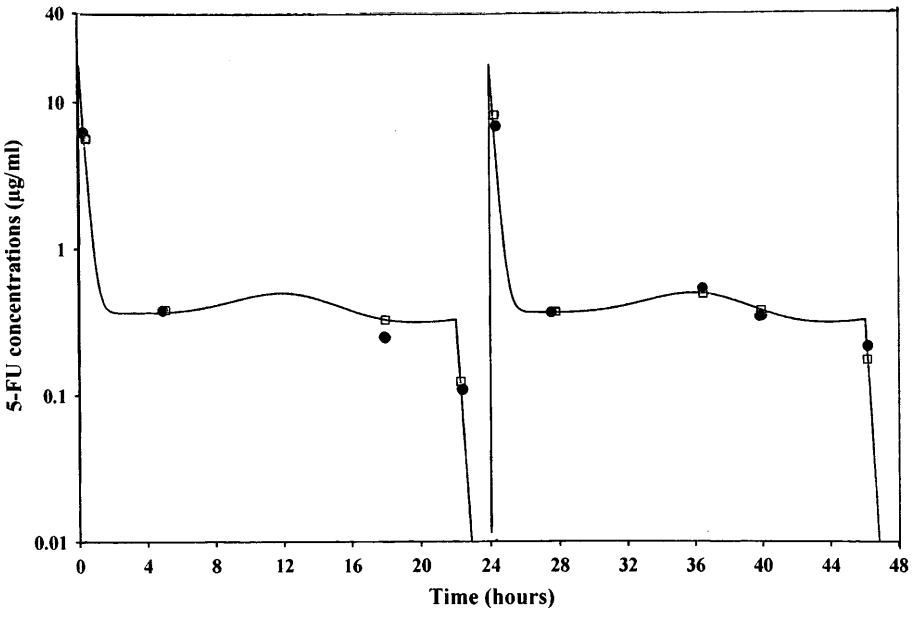

Fig. 5 Typical posterior individual fittings. ● Observed values, □ predicted values, *5-FU* 5-fluorouracil

Table 4 Statistical analysis after Bayesian estimation[a]. The values in parentheses represent the 95% confidence intervals. *n* number of samples, *SD* standard deviation

Predicted concentrations	5.41 ± 10.2
Mean ± SD (µg/ml)	(*n* = 104)
Range (µg/ml)	0.037 to 56.9
Bias* (µg/ml)	−0.305 (−0.6325 to 0.0225)
Precision (µg/ml)	1.72 (−0.763 to 4.209)

[a] Reference concentration values: 5.11 ± 10.6 µg/ml (range: 0.034 to 57.0 µg/ml)
* Not statistically different from 0 (Student's *t*-test)

variation of plasma drug levels in individual patients may allow more precise planning of time-modified schedules of drug delivery which, in turn, may result in increased effectiveness of the treatment and a decreased occurrence of drug-associated side-effects. A chronomodulated schedule delivery of 5-FU should be performed, using a perfusion rate inversely proportional to the circadian variations of clearance (Eq. 2) in order to maintain stable 5-FU plasma levels. In conclusion, the present study has developed a complete procedure for efficiently estimating 5-FU clearance in order to optimize dosage regimens in an individual patient. This population approach should be carried out regardless of the protocol of chemotherapy used.

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