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ORIGINAL ARTICLE

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Extensive hepatic replacement due to liver metastases has no effect on 5-fluorouracil pharmacokinetics

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Abstract *Purpose*: The influence of liver metastases on the pharmacokinetics of 5-fluorouracil (5-FU) and its metabolite 5,6-dihydrofluorouracil (DHFU) was studied in patients with liver metastases from gastrointestinal cancer ($n=16$) and compared with a control group of patients with nonmetastatic gastrointestinal cancer ($n=18$). *Methods*: Patients were assigned to two different groups based on the presence of liver metastases. The percentage of hepatic replacement was determined with CT and ultrasonography and classified as $<25\%$, 25–50% or $>50\%$ of the total liver volume. Chemotherapy consisted of leucovorin 20 mg/m^2 per day plus 5-FU 425 mg/m^2 per day, both for 5 days. Blood sampling was carried out on the first day of the first chemotherapy cycle. 5-FU and DHFU were quantified in plasma by HPLC. A four-compartment parent drug-metabolite model with nonlinear Michaelis-Menten elimination from the central compartment of the parent drug (5-FU) was applied to describe 5-FU and DHFU pharmacokinetics. *Results*: No effect of liver metastases on 5-FU clearance was observed. The effects of 18 covariables on pharmacokinetic parameters were also studied in a univariate correlation analysis. Body surface area was positively correlated with the distribution volume of 5-FU in the central compartment and with V_{max} ($r=0.65$ and $r=0.54$, respectively). *Conclusions*: There is no need for dose adjustment of 5-FU as a standard procedure in patients with liver metastases and mild to moderate elevations in liver function tests.

Keywords Fluorouracil · Pharmacokinetics · Toxicity · Liver function · Liver metastases

Abbreviations *5-FU:* 5-fluorouracil · *AIC:* Akaike information criterion · *ALP:* alkaline phosphatase · *ALT:* alanine aminotransferase · *AST:* aspartate aminotransferase · *AT-III:* antithrombin III · *AUC:* area under the curve · *BSA:* body surface area · *DHFU:* 5,6-dihydrofluorouracil · *DPD:* dihydropyrimidine dehydrogenase · *FBAL:* fluoro-β-alanine · *FUPA:* fluoro-β-ureidopropionic acid · *HPLC:* high-performance liquid chromatography · *LBM:* lean body mass · *LDH:* lactate dehydrogenase

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Introduction

5-Fluorouracil (5-FU) is widely used in chemotherapeutic regimens for the treatment of breast, colorectal, and head and neck cancer. The cytotoxic mechanism of 5-FU is complex, requiring intracellular bioconversion of 5-FU to cytotoxic nucleotides. Inhibition of thymidylate synthase by the metabolite 5-fluoro-2′-deoxyuridine-5′-monophosphate (FdUMP) is thought to be the main mechanism of cytotoxicity [24]. The cytotoxicity is caused by only a small part of the administered 5-FU dose, as the majority of the 5-FU is rapidly metabolized into inactive metabolites (see Fig. 1). The initial and rate-limiting enzyme in the catabolism of 5-FU is dihydropyrimidine dehydrogenase (DPD), which catalyzes the reduction of 5-FU to 5,6-dihydrofluorouracil (DHFU). Subsequently, DHFU is degraded to fluoro-β-ureidopropionic acid

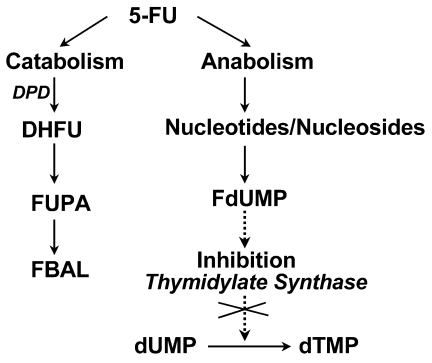

Fig. 1 Metabolism of 5-FU. 5-Fluoro-2′-deoxyuridine-5′-monophosphate (FdUMP) is the cytotoxic product resulting from a multistep 5-FU activation route. FdUMP inhibits the enzyme thymidylate synthase (TS), which leads to intracellular accumulation of deoxyuridine monophosphate (dUMP) and depletion of deoxythymidine monophosphate (dTMP). This causes arrest of DNA synthesis. The initial and rate-limiting enzyme in the catabolism of 5-FU is dihydropyrimidine dehydrogenase (DPD) which catalyzes the reduction of 5-FU to 5,6-dihydrofluorouracil (DHFU). Subsequently, DHFU is degraded to fluoro-β-ureidopropionic acid (FUPA) and fluoro-β-alanine (FBAL)

(FUPA) and fluoro-β-alanine (FBAL) [13]. Several groups have suggested a major role of DPD in the regulation of 5-FU metabolism and thus in the amount of 5-FU available for cytotoxicity [3, 6, 8, 12, 19]. DPD is present in many tissues, but the highest activity is found in the liver and, since liver blood flow is relatively high, this organ is considered the major site for 5-FU degradation [13, 14]. In recent decades the role of liver metastases and liver function impairment on 5-FU pharmacokinetics has been the subject of debate.

The effects of liver dysfunction on the pharmacokinetics of drugs are generally difficult to predict. Liver dysfunction is usually diagnosed on the basis of liver function tests, but for most drugs the correlation between test values and drug metabolism is only weak. Liver dysfunction due to liver metastases is an even more complicated issue. Liver metastases displace healthy liver tissue and this may affect the metabolic capacity of the liver directly due to tissue loss, but also indirectly due to tissue damage caused by cholestasis as a result of compression of surrounding structures including bile ducts. Furthermore, liver dysfunction may affect plasma volume, serum albumin, drug protein binding, and hepatic blood flow, all of which can influence pharmacokinetic parameters in complex ways.

In the last decade, several groups have studied the effects of liver metastases on 5-FU clearance, in particular during continuous infusion. In an early small study, a reduction in clearance of continuously infused 5-FU was found in four patients with gastrointestinal carcinoma and hepatic metastases [10]. In contrast to this, others have found no correlation between drug clearance and hepatic function tests in a larger study with 187 patients receiving 5-FU as a continuous infusion [9]. More recently, Etienne et al. have studied several covariables affecting 5-FU clearance during continuous infusion in 104 patients with various cancers [7]. They found no effect of liver metastases in a subgroup of seven patients, but did not specify further the involvement of concurrent liver dysfunction. Although these studies suggest that liver metastases do not affect 5-FU clearance during continuous infusion, it is important to realize that the pharmacokinetic behavior of 5-FU after bolus injection or short-duration infusion differs from that during continuous infusion. After rapid infusion, 5-FU displays nonlinear pharmacokinetic behavior [4, 5, 21, 26], probably due to saturation of the DPD enzyme at higher plasma levels, although the exact mechanism is still unclear [11]. Thus, data on 5-FU clearance obtained during continuous infusion do not necessarily predict the situation after bolus injection. So far, however, there are only a few reports regarding the effects of liver metastases and/or liver dysfunction on the pharmacokinetics of bolus-injected 5-FU [4, 23, 25].

Christophidis et al. studied the bioavailability of 5-FU after oral and intravenous administration in 12 patients with liver metastases, and concluded that the bioavailability is not related to liver function test abnormalities or metastatic deposits [4]. Nowakowska-Dulawa also found no effect of liver metastases on 5-FU clearance in 20 patients with colorectal cancer (compared to 8 controls) [23]. Unfortunately, in both studies patient characteristics and liver function test results were not further specified. More recently, Terret et al. studied the dose and time dependencies of 5-FU pharmacokinetics in 21 patients and also included some liver function parameters in their analysis [25]. Their data suggest that 5-FU clearance might increase with the volume of hepatic replacement.

Since in most studies information regarding the extent of liver metastatic involvement is limited or lacking, we decided to design a protocol to study the effects of this parameter on the pharmacokinetics of 5-FU and DHFU after bolus injection. It was hoped that this study would provide more insight into potential interactions between liver function and 5-FU pharmacokinetics.

Patients and methods

Patients

Patients, aged 18 years and older, scheduled to receive adjuvant or palliative 5-FU treatment for gastrointestinal cancer, and formerly chemotherapy-naive, were included. Patients with anemia (Hb <6 mmol/l), known disorders of hemostasis (e.g. hemophilia), severe renal failure (GFR <30 ml/min) or a history of alcohol or drug abuse were excluded. Patients were assigned to two groups based on the presence of liver metastases identified and measured by ultrasound and/or CT imaging. Other pretreatment measurements were body weight, height, blood cell counts, standard liver function tests (ALT, AST, LDH, ALP, bilirubin) and markers for the liver synthesis function (pseudocholinesterase, albumin and AT-III). Chemotherapy consisted of leucovorin 20 mg/m^2 per day administered as a short-duration infusion, followed by 5-FU

425 mg/m^2 per day administered as a bolus intravenous injection over 2 min. Both drugs were given on five consecutive days in a 28-day cycle (Mayo regimen). On the day of blood sampling, leucovorin was infused after the last sample. On the following 4 days, the same 5-FU dose was administered as a short-duration infusion (10–15 min) after the administration of leucovorin. During the first chemotherapy cycle, toxicity was scored according to the Common Toxicity Criteria. The study was approved by the Institutional Medical Ethics Review Board in the participating hospitals and written informed consent was obtained from all patients.

Quantification of liver metastatic involvement

The diameters of the metastases were measured using standard CT and ultrasound imaging software. The maximum diameter of each lesion was measured. This diameter was used to calculate the volume of the metastatic lesions in relation to the total liver volume. Four levels were defined for semiquantification of the extent of liver metastatic disease, according to the procedure described by Hunt et al. [15]. Absence of liver metastases was classified as level 0 (control group), less than 25% liver metastatic involvement as level 1, 25–50% as level 2, and more than 50% as level 3.

Collection of blood samples

For pharmacokinetic sampling, a cannula was placed intravenously in the arm of the patient contralateral to the side of drug administration. Blood samples of 5 ml were collected in heparinized tubes just before, and 2, 5, 10, 20, 30, 45, 60, 80, 100, 120, 150 and 180 min after 5-FU injection. The samples were immediately placed on ice and subsequently centrifuged at 2500 *g* for 10 min at 4°C and stored at –80°C until analysis. The plasma samples were analyzed for 5-FU and DHFU concentrations by high-performance liquid chromatography (HPLC).

Chemicals

5-FU and chlorouracil were obtained from Sigma Chemical Co (Zwijndrecht, The Netherlands). 5,6-dihydro-5-fluorouracil was kindly provided by Roche Laboratories (Basel, Switzerland). Human heparinized plasma was obtained from the Red Cross Blood Bank (Groningen, The Netherlands). All other chemicals were of analytical grade.

Reversed-phase HPLC analysis

5-FU and DHFU concentrations were measured by HPLC using a modification of the method described by Ackland et al. [1]. Briefly, 100 µl chlorouracil internal standard solution (80 mg/l in water) was added to 1 ml plasma sample, and this mixture was vortexed and subsequently deproteinated with 50 µl of a 50% (w/v) trichloroacetic acid solution. After centrifugation at 8000 *g* for 2 min the supernatant was transferred into a 20-ml centrifuge tube and neutralized with 1 ml 1 *M* sodium acetate solution. Then 5 ml ethyl acetate was added and the mixture was vortexed for 10 min. After separation of the organic and aqueous layers by centrifugation at 5000 *g* for 5 min, the ethyl acetate layer was transferred to a 10-ml tube and evaporated under a stream of nitrogen at 25°C. The residue was dissolved in 100 µl ultrapure water and 20 µl was injected. 5-FU and DHFU standards ranging from 0.5 to 20 mg/l were prepared in human plasma. The chromatographic system consisted of a Waters 616 pump equipped with a Waters 717$^+$ autosampler. The separation of 5-FU and DHFU was accomplished by gradient elution at ambient temperature on a Phenomenex Prodigy ODS 3 column (ID 250×4.6 mm, 5 µm) equipped with a guard column (30×4.6 mm) of the same material (both purchased from Bester, Amstelveen, The Netherlands). Mobile phase A consisted of 1.5 m*M* K_3PO_4 and 1% (v/v) methanol in water (pH 6.0), and mobile phase B of 1.5 m*M* K_3PO_4 and 5% (v/v) methanol in water (pH 6.0). The gradient was programmed as follows: 100% A for 2 min; 100% A → 100% B over 0.5 min; 100% B for 7 min; 100% B → 100% A over 0.5 min; and 100% A for 10 min. Drug was detected using a Waters 996 photodiode array UV detector interfaced with a Millennium 2010 Chromatography Manager Workstation. Spectra were acquired in the 201–300 nm range. 5-FU was monitored at 266 nm and DHFU at 205 nm. The internal standard chlorouracil was monitored at both wavelengths. The limit of quantification in plasma was 0.1 mg/l for both 5-FU and DHFU.

Pharmacokinetic analysis

The pharmacokinetic analyses were performed using the ADAPT II Maximum Likelihood Parameter Estimation program (version 4.0; University of Southern California, Los Angeles, Calif.). The pharmacokinetic data of the first 15 patients were tested in eight different parent drug-metabolite pharmacokinetic models characterized by linear or nonlinear (Michaelis-Menten) parent drug (5-FU) elimination from a central compartment and distribution of 5-FU and metabolite (DHFU) over one or two compartments. The variance of the observations was assumed to be proportional to the measured values and was set at 10%. In each model patient's data were fitted individually and for each data set the AIC was calculated [2]. The model with the lowest summarized AIC value was selected as the best. The area under the curve ($AUC_{0\rightarrow 3h}$) of 5-FU and DHFU was calculated using the trapezoidal rule. The total clearance of 5-FU was calculated by dividing the administered dose by the AUC.

Statistical analysis

Patient data were analyzed as two groups based on the presence of liver metastases. Clinical chemistry and pharmacokinetic data in both groups were compared using a two-sided Student's *t*-test. In the case of unequal variances as indicated by the Kolmogorov-Smirnov test, the log-transformed data were used, or data were tested with the non-parametric Mann-Whitney *U*-test.

The study was powered (>80%) to detect a 25% difference in population means, assuming a standard deviation in pharmacokinetic parameters of 35%. Correlations between clinical chemistry, demographic and pharmacokinetic data were tested by Spearman's correlation analysis. Statistical significance was at the $P<0.05$ level. Analyses were performed using the SYSTAT 7.0 statistical program (SPSS, Chicago, Ill., 1997).

Results

Patients

Patients in this study were treated in the Martini Hospital Groningen, the Bethesda Hospital Hoogeveen or the Diaconessen Hospital Meppel. From December 1997 to January 2001, 18 patients were included in the control group and 16 in the liver metastasis group. In one patient belonging to the control group, largely reduced clearance of 5-FU was observed. DNA sequence analysis of the gene encoding DPD revealed that this patient was heterozygous for a G→A point mutation in the DPYD gene. The resulting protein from the mutated allele is inactive and total DPD activity in this patient was low. Data on this patient have been published elsewhere [20]. The statistical analyses were performed

both with and without inclusion of this patient in the control group. The liver metastatic involvement of nine patients in the metastasis group was classified as level 1, that of four patients as level 2 and that of three patients as level 3. An overview of the patient characteristics is represented in Table 1. An overview of treatment-related toxicity observed during the first cycle is shown in Table 2.

Pharmacokinetics

The mean pharmacokinetic curves of 5-FU and DHFU as measured in both treatment groups are shown in Fig. 2. The model selected for calculating 5-FU and DHFU pharmacokinetics of the patients in this study was a four-compartment parent drug-metabolite model with Michaelis-Menten elimination from the first towards the third compartment (see Fig. 3). The model was described by four differential equations:

$$\frac{dX_1}{dt} = -\left(\frac{V_{\max}}{V_1 K_m + X_1} + k_{12} + k_{urine}\right) X_1 + k_{21} X_2 + R_{\inf}$$

$$\frac{dX_2}{dt} = k_{12} X_1 - k_{21} X_2$$

$$\frac{dX_3}{dt} = \left(\frac{V_{\max}}{V_1 K_m + X_1}\right) X_1 + k_{43} X_4 - (k_{30} + k_{34}) X_3$$

$$\frac{dX_4}{dt} = k_{34} X_3 - k_{43} X_4$$

Compartments 1 and 2 represent the central and peripheral compartment for 5-FU (parent drug) pharmacokinetics, compartments 3 and 4 are the central and peripheral compartment for DHFU (metabolite) pharmacokinetics. The X values indicate the amount of drug in each compartment. Data are imported into the model as plasma drug concentrations, measured in compartment 1 (5-FU) and compartment 3 (DHFU), respectively. The volumes of compartments 1 and 3 are

Table 1 Patient characteristics. Data are presented as range (median), except gender (number of patients)

Parameter	Normal range	Liver metastases ($n=16$)	Controls ($n=18$)	Subgroups based on percentage of liver metastatic involvement		
				$<25\%$ ($n=9$)	25–50% ($n=4$)	$>50\%$ ($n=3$)
Gender (M/F)		9/7	13/5	4/5	4/0	1/2
Age (years)		45–78 (64)	45–80 (66)	57–78 (64)	45–76 (64)	47–70 (64)
Weight (kg)		60–94 (78)	56–85 (73)	63–90 (78)	60–94 (79)	75–79 (76)
Serum creatinine (μmol/l)	40–100	53–131 (77)	62–184 (77)	53–131 (75)	71–94 (88)	61–81 (71)
AST (U/l)	<48	12–201 (42)*	13–24 (20)	12–60 (34)*	26–137 (59)*	89–201 (111)*
ALT (U/l)	<42	8–234 (56)*	5–44 (31)	8–58 (37)*	38–202	50–234 (66)*
LDH (U/l)	200–500	234–2662 (554)*	173–396 (272)	234–1035 (449)*	348–1165 (689)*	839–2662 (2357)*
ALP (U/l)	<125	65–1221 (146)*	54–108 (79)	65–163 (107)*	121–266 (181)*	344–1221 (454)*
Bilirubin total (μmol/l)	<17	3–293 (13)	5–14 (9)	3–13 (11)	8–59 (13)	31–293 (40)*
Albumin (g/l)	35–55	24–39 (36)	25–43 (36)	31–39 (37)	36–38 (37)	24–30 (26)*
AChE-ase ($\times 10^3$ U/l)	5.4–13.2	1.2–8.3 (4.4)	1.9–6.5 (3.9)	3.0–8.3 (4.9)*	1.2–6.3 (3.7)	1.5–2.8 (2.1)
AT-3 (%)	80–120	52–137 (92)	82–126 (96)	83–137 (96)	81–100 (90)	52–119 (57)

*$P<0.05$ (Mann Whitney U-test)

Table 2 Overview of side effects during the first cycle. The values represent the number of patients suffering from a particular type of toxicity (graded according to the Common Toxicity Criteria)

Toxicity	CTC grade								Total number (%) of patients	
	Metastases ($n=15$)				No metastases ($n=18$)				Metastases ($n=15$)	No metastases ($n=18$)
	I	II	III	IV	I	II	III	IV		
Gastrointestinal										
Nausea	6	0	0	0	5	0	0	0		
Vomiting	3	0	0	0	2	0	0	0		
Diarrhea	1	0	0	0	4	2	0	0		
Mucositis	3	4	0	0	2	3	0	0		
'Flu-like symptoms										
Fever	1	1	0	0	1	0	1	0		
Malaise	1	1	0	0	6	1	0	0		
Others										
Dermatological	1	0	0	0	2	0	0	0		
Eyes	1	0	0	0	2	0	0	0		
All toxicities[a]									10 (66%)	13 (72%)

[a]Toxicity of any kind at any grade

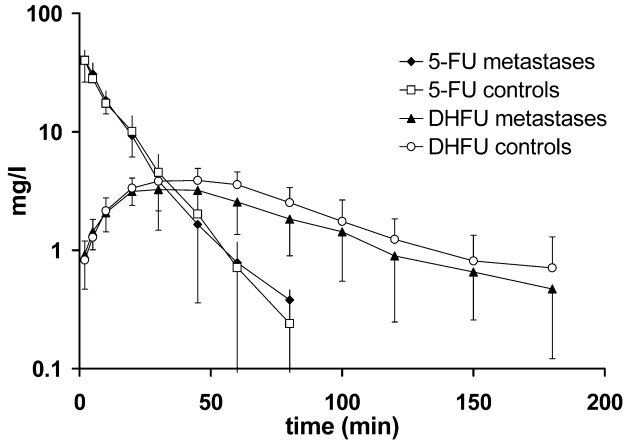

Fig. 2 Pharmacokinetics of 5-FU. Shown are 5-FU and DHFU plasma levels in control patients ($n = 18$) and in patients with liver metastases ($n = 16$). Values are means ± SD

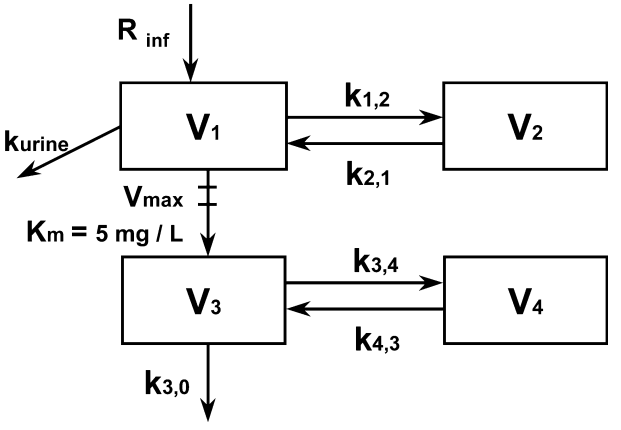

Fig. 3 Four-compartment parent drug-metabolite pharmacokinetic model describing 5-FU and DHFU pharmacokinetics

calculated by dividing the drug amount by the drug concentration. The k values represent linear distribution and elimination rate constants, and the V_{max} and K_m values represent Michaelis-Menten constants for nonlinear elimination from the first compartment. The K_m value was kept constant during fitting of patient data. To determine the best-fitting value, this parameter was varied between 0.5 and 15 mg/l. A K_m of 5 mg/l was selected as the optimal value based upon the lowest summarized AIC. R_{inf} represents the infusion rate of 5-FU in milligrams per hour. There were no differences in model parameters between the two treatment groups and there were no correlations between individual model parameters and patient characteristics. Therefore, the calculated model parameters are listed in Table 3 as mean values obtained from all 34 patients in the study. The interindividual variation in 5-FU clearance was considerable, resulting in a factor of 3 between the lowest and the highest 5-FU AUC (not including the patient with DPD deficiency).

Table 3 Pharmacokinetic parameters

Model parameter	Mean	SD
V_{max} (h^{-1})	1472	356
V_1 (l)	15.5	5.3
k_{12} (h^{-1})	7.73	4.13
k_{21} (h^{-1})	6.24	2.77
V_3 (l)	97	42
k_{34} (h^{-1})	6.18	12.83
k_{43} (h^{-1})	4.91	7.38
k_{30} (h^{-1})	1.80	1.71
AUC 5-FU (mg·h/l)	10.1	3.7
Cl 5-FU (ml/min)	1485	537
AUC DHFU (mg·h/l)	5.6	2.0

Correlation between patient covariables and pharmacokinetic parameters

We identified 18 patient covariables that were each tested in a univariate Spearman's correlation analysis. Tested covariables were sex, age, height, weight, BSA, LBM, creatinine, urea, level of liver metastatic involvement, AST, ALT, ALP, LDH, bilirubin, albumin, AT-III, pseudocholinesterase and 5-FU dose. Positive correlations were found between BSA and V_{max} and V_1 values, regardless the level of liver metastatic involvement ($r = 0.65$ and $r = 0.54$, respectively).

Discussion

The persistent uncertainty regarding the effects of liver metastases and liver dysfunction on the pharmacokinetics of bolus-injected 5-FU led us to design the current study. We decided to target the study on the extent of liver metastatic involvement and also decided to include a detailed characterization of the liver function in the study design. We eventually included 34 patients of whom 16 had liver metastases. We chose to classify the extent of liver metastatic involvement in these patients as categorical rather than as a continuous variable, according to the procedure used Hunt et al. [15], since percentage hepatic replacement is difficult to measure accurately. More subtle differences between patients cannot be detected with this approach, but this was not considered disadvantageous, since small differences would probably be clinically irrelevant.

All patients received treatment according to the Mayo Clinic's scheme. The 5-FU dose was administered as a short-duration infusion (5–10 min) according to common practice in the participating hospitals, but on the day of blood sampling, 5-FU was given as 2-min bolus injection to ensure precise and standardized drug administration. The short half-life of 5-FU necessitated this standardization, since uncertainty in this parameter can hamper pharmacokinetic calculations.

To describe the nonlinear pharmacokinetics, we applied a relatively complex model with Michaelis-Menten elimination from the central compartment, based on the model proposed by Collins et al. [5]. Our model was

selected on the basis of 'best fit' (objectified by the AIC) from a series of eight different variants on the Collins model. The final model used was almost identical to the model proposed by Terret et al. [25] in their analysis of 5-FU pharmacokinetics. We also included the metabolite DHFU in our model, but the additional value of this seemed limited, since large 95% confidence intervals were found around the calculated k_{34}, k_{43} and k_{30} values.

The consequences of nonlinear Michaelis-Menten pharmacokinetics are most profound at plasma levels exceeding the K_m value. In the case of 5-FU, such plasma levels are reached after bolus injection but not during continuous infusion. A reduction in liver DPD capacity due to liver metastases and/or liver dysfunction might result in lower V_{max} values and thus in a lower 5-FU clearance immediately after bolus injection. Our results do not confirm this, as patients in both treatment groups displayed similar pharmacokinetics. No significant correlations were found between pharmacokinetic parameters, including overall 5-FU clearance, and liver function parameters.

The fact that most patients with liver metastases had mild to moderate liver dysfunction might explain our observations. However, in three patients with extensive (level 3) metastatic disease accompanied by cholestasis as indicated by high bilirubin and ALP levels, 5-FU clearance also was unchanged. These patients further displayed high transaminase levels (indicating cell damage) and low albumin and AT-III levels (indicating loss of function). These observations suggest that the influence of extensive liver metastatic disease, including liver damage, on 5-FU pharmacokinetics is at least not dramatic. Recently, Terret et al. performed a NONMEM analysis to identify covariables that affect 5-FU model parameters, and they observed that their V_{max} values tend to increase with the volume of liver metastatic involvement [25]. In our study this correlation was only weak ($r = 0.21$, see Fig. 4) and at least clinically irrelevant. These results suggest that the metabolism of 5-FU in metastatic tumor tissue at least equals that in healthy liver tissue. Extensive 5-FU uptake in metastatic tissue has indeed been demonstrated during ^{18}F-labelled fluorouracil positron emission tomography in patients with liver metastases from colorectal cancer [22]. Although the DPD activity in liver metastases from colon cancer seems to be lower than in adjacent normal liver tissue [16], hepatic arterial blood flow is generally increased in liver metastatic disease [15, 18]. Since the elimination rate of drugs with a very large extraction ratio is strongly dependent on the hepatic blood flow, an increase in liver blood flow in metastatic disease might compensate for a reduced DPD activity in parts of the liver replaced by metastases.

As was more or less expected on the basis of the almost identical pharmacokinetic profiles, treatment-related toxicity was comparable in the two treatment groups. The incidence of diarrhea and malaise was somewhat higher in the control group, but this probably occurred by chance. One patient in the control group experienced excessive toxicity as a result of decreased 5-FU clearance due to DPD deficiency. A full description of the pharmacokinetics of 5-FU in this patient has been published elsewhere [20]. Interestingly, we found that irrespective of metastatic status, 5-FU clearance was significantly lower in patients experiencing mucositis (1696 ± 640 vs 1209 ± 290 ml/min, $P < 0.05$; see Fig. 5). Such a trend was not observed for nausea. This finding might be coincidental, but it might also be possible that late toxic effects such as mucositis are more related to pharmacokinetics than direct toxic effects such as nausea. It has been shown that the extent of salivary

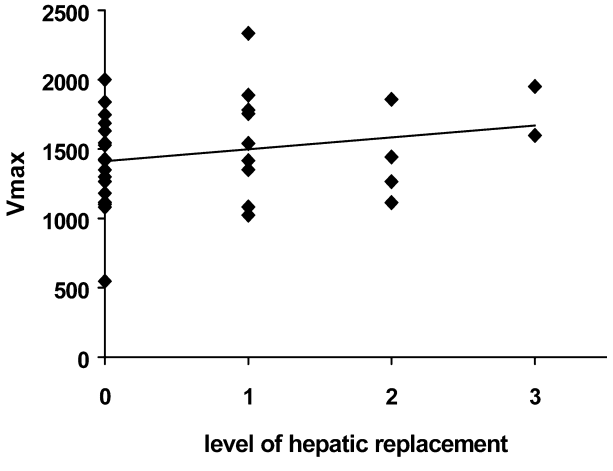

Fig. 4 Correlation between level of hepatic replacement and calculated V_{max} value (per hour)

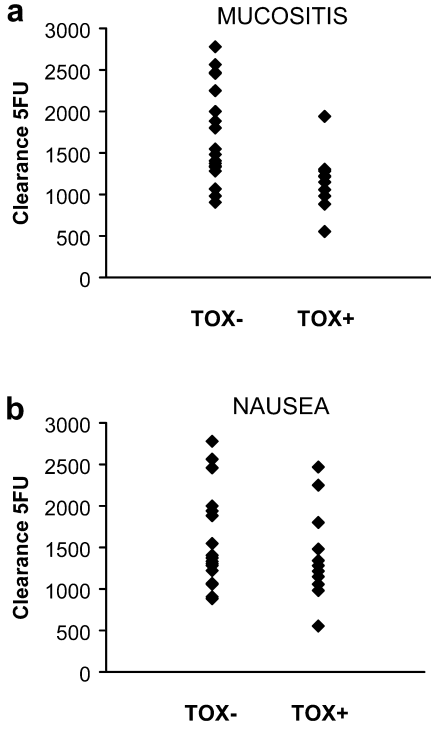

Fig. 5a, b Correlation between 5-FU clearance (millilitres per minute) and the occurrence of mucositis (**a**) and nausea (**b**)

excretion is a predictor of the development of mucositis, and salivary excretion is generally higher in patients with low drug clearance [17].

Based on the current data, we conclude that there is no need for dose adjustment of 5-FU in patients with liver metastases and mild to moderate elevations in liver function tests. Both the extent of liver metastatic involvement and liver function parameters were included as parameters in this study to allow a more comprehensive evaluation of the effect of liver metastatic disease on 5-FU pharmacokinetics. We believe that there is no reason to expect increased 5-FU toxicity in patients with liver metastases due to a reduced 5-FU clearance. Therefore, we do not recommend 5-FU dose reduction as a standard procedure in such patients.

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