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Clinical report

Sparse-data set analysis for irinotecan and SN-38 pharmacokinetics in cancer patients co-treated with cisplatin

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The clinical pharmacokinetics of the antineoplastic agent irinotecan (CPT-11) are associated with substantial inter-patient variability. The degree to which this variability in CPT-11 exposure impacts upon the response and toxicity of the drug has not yet been properly determined. In general, the area under the plasma concentration–time curve (AUC) is an appropriate indicator of exposure, but requires collection of up to 17 timed blood samples. This presents difficulties if large-scale population samplings are required. The present study involved the development and validation of a strategy to estimate the AUCs of the lactone and total (i.e. lactone *plus* carboxylate) forms of CPT-11 and its active metabolite SN-38 from a limited number of blood samples in patients co-treated with cisplatin. Using data from 24 patients, univariate and multivariate regression analyses were employed to generate the models. The best predictive models for simultaneous estimation of CPT-11 and SN-38 AUCs were obtained with three time points at 0.5, 1.67 and 5.50 h after start of the 90 min i.v. infusion of CPT-11. The models were tested separately in another group of 24 patients receiving the same combination treatment. This validation set demonstrated that CPT-11 and SN-38 AUCs after standard dose administration could be predicted sufficiently unbiased and precisely with three timed samples to warrant clinical application. [© 1999 Lippincott Williams & Wilkins.]

Key words: Cisplatin, irinotecan (CPT-11), limited sampling models, pharmacokinetics, SN-38.

Introduction

The antineoplastic agent irinotecan (CPT-11; 7-ethyl-10-[4-(1-piperidino)-1-piperidino] carbonyloxycamptothecine) is a promising water soluble semisynthetic derivative of camptothecin, a plant alkaloid from the Chinese tree *Camptotheca acuminata*.[1,2] The drug displays potent antitumor activity against a variety of tumors, and has recently been approved for the treatment of refractory colorectal and ovarian carcinomas in several countries.[3] The mechanism of action of CPT-11 and its structurally related analogs is thought to be related to inhibition of the intranuclear enzyme topoisomerase I, thereby indirectly impeding DNA replication and RNA transcription.[4]

CPT-11 and its active metabolite SN-38 (7-ethyl-10-hydroxycamptothecine; Figure 1) are both subject to a rapid, reversible, pH-dependent hydrolysis of a lactone ring moiety in the molecule, generating an open-ring carboxylate.[5] At neutral or physiologic pH, e.g. in blood, the equilibrium between the two drug species favors the pharmacologically less active carboxylate for most camptothecines.[6] However, the relative importance of the lactone-carboxylate interconversion of CPT-11 and SN-38 with respect to pharmacodynamic outcome is still not completely understood. Furthermore, the clinical pharmacokinetic behavior of CPT-11 is associated with a substantial degree of interindividual variability. Thus, careful measurement of both drug forms is clearly warranted in order to fully characterize the clinical pharmacology of these agents.

The major dose-limiting toxicities encountered with single-agent CPT-11 therapy were neutropenia and diarrhea.[7] Relationships for CPT-11 and SN-38 between clinical pharmacokinetics and pharmacodynamic outcome are extremely complex and not thoroughly discerned (reviewed in Takimoto and Arbuck[8]). Based on the knowledge of camptothecin pharmacology,

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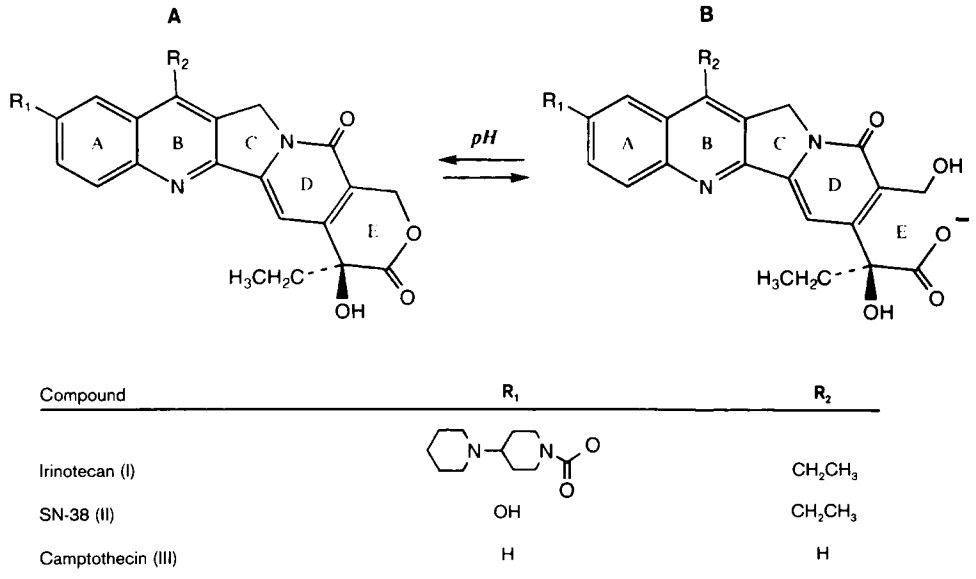

Compound	R_1	R_2
Irinotecan (I)		CH_2CH_3
SN-38 (II)	OH	CH_2CH_3
Camptothecin (III)	H	H

Figure 1. Chemical structures of the lactone (A) and carboxylate (B) forms of CPT-11, its active metabolite SN-38, and the related compound camptothecin.

CPT-11-induced myelosuppression probably occurs due to the inhibition of topoisomerase I by SN-38 lactone in bone marrow cells. In contrast, acute CPT-11-mediated diarrhea is most likely caused by the anticholinesterase activity of the parent compound. Supporting this theory are reports that the area under the plasma concentration-time curve (AUC) of SN-38 correlated with myelosuppression and the AUC of CPT-11 correlated with diarrhea.[8,9] However, some studies have not found such associations, indicating that additional studies applying selective analytical methods are essential to help clarify these contrasting results. Such studies will likely involve large numbers of patients and generally require the collection of up to 17 timed blood samples after i.v. drug administration.[10] Thus, the objective of the current study was to develop a model for prediction of the AUCs of CPT-11 and SN-38 from a limited blood sampling schedule in patients with advanced solid cancer receiving the drug in combination with cisplatin.

Materials and methods

Patients and treatment

The pharmacokinetic models were developed and validated in 48 patients with proven malignant solid tumors, participating in a phase I and pharmacokinetic study of combined chemotherapy with CPT-11 and cisplatin.[9] Detailed clinical and toxicological profiles will be reported separately. Inclusion criteria included the following: (i) no more than one prior combination chemotherapy regimen or two single agent regimens; (ii) off previous anticancer therapy for at least 4 weeks (6 weeks if nitrosoureas, mitomycin or radiotherapy); (iii) no prior treatment with topoisomerase I inhibitors or platinum derivatives; (iv) age between 18 and 70 years; (v) WHO performance status ≤ 2; (vi) life expectancy greater than 12 weeks; and (vii) adequate bone marrow, liver and renal functions and symptomatic peripheral neurotoxicity graded 1 or less (according to NCI common toxicity criteria). Written informed consent was obtained from all patients prior to treatment in accordance with the guidelines of the Institutional Review Board.

CPT-11 was provided by Rhône-Poulenc Rorer (Antony, France) as an aqueous formulation containing *d*-sorbitol, lactic acid and sodium hydroxide with a final pH value of 3.5. The drug was administered at dose levels ranging from 175 to 300 mg/m^2 as a 90 min i.v. infusion. Cisplatin was given as a 3 h i.v. infusion directly after the end of the CPT-11 infusion.

Pharmacokinetic analysis

For CPT-11 and SN-38 pharmacokinetic analysis heparinized blood samples were drawn from an

indwelling cannula at 0.5, 1.5, 1.67, 1.83, 2.0, 2.5, 3.5, 4.5, 5.0, 5.5, 6.5, 8.0, 12.0, 25.5, 32.0, 49.5 and 56.0 h after the start of the infusion. The plasma fraction was obtained by centrifugation and analyzed for CPT-11 and SN-28 using a validated reversed-phase high-performance liquid chromatography system (HPLC) with fluorescence detection.[11] The lower limits of quantitation were 0.5 ng/ml for the lactone forms (1 ml samples) and 2.0 ng/ml for the total forms (0.25 ml samples), respectively. The percentage deviation from the nominal value and the between-run and within-run precision were always less than 15.0%.

CPT-11 and SN-38 (lactone and total) concentration-time data of all patients were fitted to a tri-exponential equation, using Siphar version 4.0 (SIMED, Créteil, France), based on discriminating tests described elsewhere.[12] All compartmental analyses were obtained by inverse square weighting of the observed concentration. The terminal drug disposition half-life [$t_{1/2}(\gamma)$] and the AUC from time zero to infinity were determined on the basis of the best fitted curves, whereas the peak plasma concentration (C_{max}) was determined graphically from semi-logarithmic concentration-time plots.

Model development and validation

Limited sampling models were constructed on a training data set that contained 24 patients, randomly assigned from each separate dose level to avoid bias in the predictive values of one set to another. The models were constructed by assuming that concentration(s) at a fixed time could predict the AUC of each of the compounds of interest simultaneously. Simple linear correlations were initially determined between the concentrations at each time point (independent variables) and the corresponding AUC (dependent variable) by a univariate linear-regression analysis, to find the optimal single-sample time point for each substance measured. Next, forward stepwise multivariate regression analyses were undertaken to develop the best linear equation describing the association between concentrations at more than one time point and AUC, to increase the precision of the method. The optimal model was eventually identified on the basis of Pearson's correlation coefficient (r) and root mean square residual values as determined from the regression.[13]

The pharmacokinetic data from the remaining 24 patients was used to validate the applicability of the constructed models. This was achieved by comparing actual AUCs from the tri-exponential computer fit with estimated AUCs using the best single or multiple time-point models developed from the training set. The predictive performance of the developed models was evaluated using calculations of bias (or percentage mean predictive error; %MPE) and precision (or percentage root mean square error; %RMSE). Due to missing concentrations in this data set at the relevant time points, three patients were excluded from validation. Pearson's correlation coefficient was used to rank the concordance between measured and predicted AUCs. Differences in patient demographics and pharmacokinetics between training and validation set patients were evaluated by using Student's t-test. All statistical calculations were performed with the Number Cruncher Statistical System software version 5.X (Dr JL Hintze, Kaysville, UT, 1992).

Results

Pharmacokinetic studies were completed in 48 patients with various types of solid tumors, treated with a 90 min i.v. infusion of CPT-11, directly followed by a 3 h infusion of cisplatin. The total group of patients was composed of 31 males and 17 females, with a mean age 53 years and a median Eastern Cooperative Oncology Group (ECOG) performance status of 0 (Table 1). Patients were randomly divided in two groups, a training set and a validation set, both containing 24 patients. No significant differences were observed between both groups in patient characteristics (Table 1).

The mean plasma concentration-time curves for the lactone and total forms of CPT-11 and SN-38 in all patients treated at a dose level of 200 mg/m^2 of CPT-11 are shown in Figure 2. During the drug infusion, the plasma concentrations of the lactone and total forms

Table 1. Patient demographics

Characteristics	Training set	Validation set
No. of patients	24	24
Age [years (range)]	53 (42–69)	52 (36–68)[a]
Sex (male/female)	16:8	15:9
ECOG performance status (0/1/2)	17:7:0	14:9:1
Primary tumor site		
colorectal	12	9
lung	3	3
pancreas	2	0
mesothelioma	2	0
tonsil	2	1
unknown	2	4
other	1	7

[a]Results expressed as mean value (range).

of CPT-11 and SN-38 increased steadily, after which a decrease was observed with a decay best described by a tri-exponential equation. Relatively large amounts of CPT-11 and SN-38 were continually present in the lactone forms of these substances, as described for these compounds previously.[14] The terminal elimination phases of CPT-11 lactone and total were more rapid than those of the SN-38 forms, which resulted in prolonged biological half-lives for the active metabolite relative to CPT-11. A summary of the main pharmacokinetic parameters, including AUC, C_{max} and $t_{1/2}(\gamma)$ of CPT-11 and SN-38 between the two patient groups is presented in Tables 2 and 3, respectively. There were no significant differences in any pharmacokinetic parameter between the two groups as shown by an unpaired two-sided Student's *t*-test (Tables 2 and 3). Interpatient variability in the concentrations of CPT-11 and SN-38 in the training and validation sets at each of the 17 sample time points was large [coefficient of variation ranged from 64% (0.5 h) to 96% (1.67 h)]. The interpatient variability in corresponding AUCs of CPT-11 and SN-38 was slightly dependent on the dose level, and ranged from 46 to 64%.

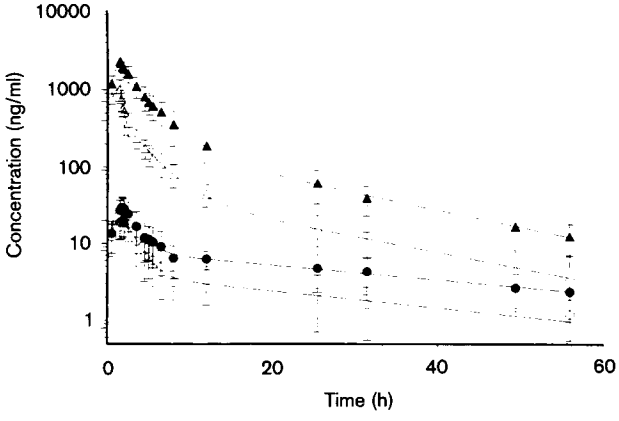

Figure 2. Plasma concentration–time curves of CPT-11 (triangles) lactone and total and of SN-38 (circles) lactone and total in 17 patients given CPT-11 at 200 mg/m^2 as a 90 min i.v. infusion. The open symbols represent the lactone forms and the closed symbols represent the total forms of CPT-11 and SN-38. All pharmacokinetic curves were fitted to a tri-exponential equation, using Siphar version 4.0 (SIMED), assuming a three-compartment model for distribution and elimination of the compounds. Data are presented as mean values (symbols) ± SD (error bars).

CPT-11 and SN-38 (both lactone and total) concentrations at each sample time point were correlated with their AUC by using univariate regression analysis for the training data set (Table 4). The correlation coefficient ranged from 0.396 to 0.938 for CPT-11 lactone, from 0.611 to 0.968 for CPT-11 total, from 0.362 to 0.823 for SN-38 lactone and from 0.097 to 0.743 for SN-38 total (Table 4). The best correlation was found at the sample time point of 5.50 h, taking all substances into account simultaneously. Following this univariate regression, multivariate regression with a restriction to models with no more than two additional time points was evaluated. In the trivariate models, sample time point combinations with the highest correlation and precision (lowest %RMSE), were found at different sample time points for CPT-11 total, CPT-11 lactone, SN-38 total and SN-38 lactone (data not shown). Assuming the lactone forms being most predictive for toxicities of the given drug, the best sample time points for the combination of CPT-11 lactone and SN-38 lactone were used for further model development.

Table 2. Summary of the plasma pharmacokinetic parameters of CPT-11 total and lactone after a 90 miun i.v. infusion of CPT-11 in the training (A) and validation (B) sets

Dose level (mg/m^2)	Set	*n*	$AUC_{0-\infty}$ total (μg·h/ml)	$AUC_{0-\infty}$ lactone (μg·h/ml)	C_{max} total (μg/ml)	C_{max} lactone (μg/ml)	$t_{1/2}$ (γ) total (h)	$t_{1/2}$ (γ) lactone (h)
175	A	1	6.53	2.03	1.37	0.60	12.14	12.80
	B	2	7.77, 15.9	2.36, 4.78	2.39, 3.16	1.07, 1.80	8.48, 11.1	5.43, 7.94
200	A	9	11.5±3.75	3.79±0.98	2.49±0.35	1.04±0.22	14.2±7.80	17/3±10.4
	B	7	12.8±3.01	3.66±0.78	2.51±0.41	1.12±0.22	13.6±5.82	12.2±5.65
230	A	3	13.1±2.65	4.32±1.43	2.98±0.72	1.50±0.68	9.21±2.20	13.4±3.72
	B	4	17.7±2.05	5.02±1.11	3.32±0.30	1.39±0.29	11.5±2.22	9.62±2.61
260	A	6	13.5±4.65	4.01±1.07	2.61±0.65	1.31±0.30	12.6±5.86	12.8±4.21
	B	6	13.6±5.88	4.86±2.19	2.70±0.72	1.38±0.43	11.4±1.81	11.2±2.41
300	A	5	22.3±13.3[a]	6.20±2.96	4.04±1.45[a]	1.71±0.59	11.5±2.97[a]	12.9±3.67
	B	5	21.2±5.92	7.27±2.61	4.17±1.22	1.97±0.59	12.5±1.72	12.0±2.64

All parameters were obtained from a non-linear three-compartment computer-fitted model with 1/(concentration)^2 weighting. Results are shown as mean ± SD.
n, number of data sets. [a]*n*=4.

Table 3. Summary of the plasma pharmacokinetic parameters of SN-38 total and lactone after a 90 min i.v. infusion of CPT-11 in the training (A) and validation (B) sets

Dose level (mg/m^2)	Set	*n*	$AUC_{0-\infty}$ total ($\mu g \cdot h/ml$)	$AUC_{0-\infty}$ lactone ($\mu g \cdot h/ml$)	C_{max} total (ng/ml)	C_{max} lactone (ng/ml)	$t_{1/2}$ (γ) total (h)	$t_{1/2}$ (γ) lactone (h)
175	A	1	0.13	0.07	11.43	6.52	7.72	6.76
	B	2	0.29, 0.35	0.16, 0.17	44.6, 47.4	27.5, 27.7	16.87, 10.3	13.9, 13.2
200	A	9	0.43±0.20	0.21±0.08	36.7±10.9	25.1±7.33	30.4±15.1	24.8±7.61
	B	7	0.30±0.08	0.16±0.05	29.2±7.25	20.8±7.35	20.3±7.64	19.3±5.09
230	A	3	0.39±0.16	0.16±0.04	27.4±3.50	18.4±5.43	42.0±35.2	18.3±7.99
	B	4	0.79±0.46	0.27±0.08	57.9±25.8	42.8±26.5	29.9±14.5	23.4±6.83
260	A	6	0.34±0.18	0.22±0.07	40.3±15.8	25.7±11.3	23.1±10.6	29.8±15.5
	B	6	0.51±0.22	0.31±0.13	44.4±14.5	31.5±8.00	26.9±10.9	23.0±5.80
300	A	5	0.43±0.25	0.33±0.21	47.9±27.6	36.7±27.2	29.9±18.0	39.9±19.3
	B	5	0.51±0.22	0.35±0.14	51.2±18.5	38.4±12.5	29.8±14.6	30.8±11.7

All parameters were obtained from a non-linear three-compartment computer-fitted model with $1/(concentration)^2$ weighting. Results are shown as mean±SD.
n, number of data sets.

Table 4. Univariate correlation of CPT-11 and SN-38 (lactone and total) concentrations at each sample time point with the corresponding AUC in the training data set

Time point (h)	CPT-11 lactone		CPT-11 total		SN-38 lactone		SN-38 total	
	n	*r*	*n*	*r*	*n*	*r*	*n*	*r*
0.5	23	0.633	23	0.611	17	0.362	24	0.097
1.5	22	0.607	22	0.790	22	0.478	23	0.332
1.67	21	0.422	23	0.841	19	0.823	23	0.523
1.83	22	0.676	23	0.923	22	0.505	24	0.611
2.0	24	0.473	23	0.929	24	0.691	24	0.651
2.5	23	0.766	23	0.942	22	0.477	24	0.686
3.5	22	0.883	23	0.954	20	0.690	24	0.637
4.5	23	0.857	23	0.959	24	0.686	24	0.712
5.0	23	0.886	23	0.968	23	0.742	24	0.636
5.5	23	0.920	23	0.965	24	0.598	23	0.743
6.5	23	0.873	22	0.950	22	0.486	23	0.661
8.0	21	0.938	21	0.946	20	0.621	22	0.586
12.0	21	0.619	21	0.873	20	0.419	20	0.621
25.5	23	0.842	23	0.898	23	0.426	15	0.480
32.0	20	0.756	22	0.894	19	0.477	12	0.528
49.5	23	0.481	22	0.723	20	0.378	8	0.223
56.0	23	0.396	23	0.712	18	0.377	8	0.126

n, number of data sets at that specific time point.
r, Pearson's correlation coefficient.

Table 5. Limited-sampling models for the prediction of the AUCs of CPT-11 lactone and total and of SN-38 lactone and total models

Model	Training set			Validation set		
	r	%MPE	%RMSE	*r*	%MPE	%RMSE
A	0.953	0.34	7.88	0.936	0.36	11.3
B	0.982	0.22	6.83	0.966	0.10	3.31
C	0.903	0.52	7.94	0.443	1.06	31.7
D	0.764	0.85	21.1	0.869	1.08	29.8

r, Peason's correlation coefficient.
$C_{0.5}$, $C_{1.67}$ and $C_{5.5}$ are the plasma concentrations in $\mu g/ml$ at 0.5, 1.67 and 5.5 h after start of infusion.
Models:
A: $AUC_{CPT\text{-}11\ lactone}$ ($\mu g \cdot h/ml$)=1.11*$C_{0.5}$+0.0531*$C_{1.67}$+16.53*$C_{5.5}$+0.439
B: $AUC_{CPT\text{-}11\ total}$ ($\mu g \cdot h/ml$)=1.84*$C_{0.5}$+1.19*$C_{1.67}$+11.5*$C_{5.5}$+0.215
C: $AUC_{SN\text{-}38\ lactone}$ ($\mu g \cdot h/ml$)=2.46*$C_{0.5}$+2.36*$C_{1.67}$+9.66*$C_{5.5}$+0.0521
D: $AUC_{SN\text{-}38\ total}$ ($\mu g \cdot h/ml$)=−6.27*$C_{0.5}$+3.72*$C_{1.67}$+20.2*$C_{5.5}$+0.121

The most predictive sample time points were found at 0.5, 1.67 and 5.5 h after the start of infusion. In the training data set, the models of all substances demonstrated little bias, with values for the %MPE ranging from 0.22 to 0.85 (Table 5). In this set, the correlation coefficient of SN-38 total was estimated at 0.764 with a %RMSE of 21.1%, suggesting less correlation and lower accuracy than found for the other compounds (correlation coefficients ranging from 0.903 for SN-38 lactone to 0.982 for CPT-11 total and %RMSE ranging from 6.83 for CPT-11 total to 7.94 for SN-38 lactone).

Next, we used the validation data set, containing the remaining 24 patients to evaluate the predictive performance of the developed models. For CPT-11 lactone and total, correlation coefficients were 0.936 and 0.966, respectively, with the %MPE (0.36 and 0.10 respectively) and the %RMSE (11.30 and 3.31 respectively) being low, indicating minor bias and excellent precision (Table 5 and Figure 3). For SN-38 total, similar acceptable data could be obtained using the same model. However, in the validation data set SN-38 lactone data showed poor results for the correlation coefficient, %MPE and %RMSE, due to a poor correlation between AUC and concentrations at the higher

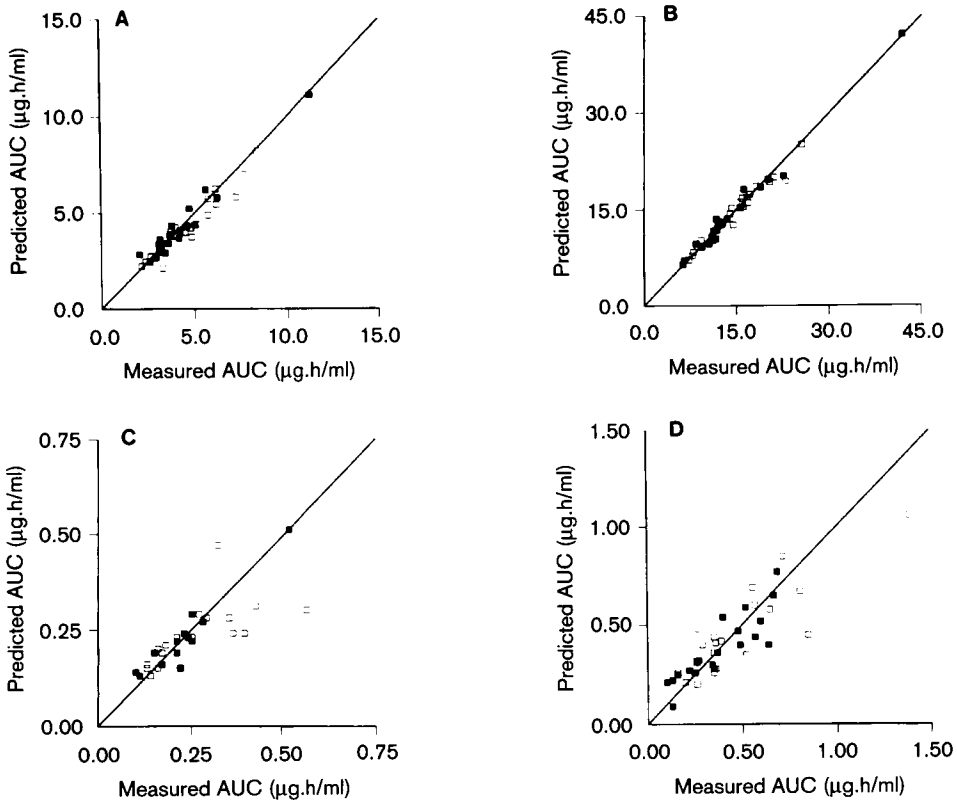

Figure 3. Observed correlations between the measured AUC using a non-linear three-compartment computer-fitted model with 1/(concentration)^2 weighting and the predicted AUC from the limited sampling models (Table 5) for CPT-11 lactone (A), CPT-11 total (B), SN-38 lactone (C) and SN-38 total (D). In all models plasma samples were taken at sample time points of 0.5, 1.67 and 5.5 h after the start of infusion. Closed symbols represent data from the training set and open symbols data from the validation set. Pearson's correlation coefficients in the training and validation sets were 0.953 and 0.936 for CPT-11 lactone, 0.982 and 0.966 for CPT-11 total, 0.903 and 0.443 for SN-38 lactone, and 0.764 and 0.869 for SN-38 total, respectively. The solid lines represent the lines of identity.

dose levels of CPT-11 (230-300 mg/m^2). Hence, the limited-sampling model was not suitable for prediction of SN-38 lactone AUCs in patients treated at dose levels of CPT-11 higher than 230 mg/m^2.

We also performed an additional analysis to evaluate the use of CPT-11 and SN-38 total concentrations for prediction of the AUCs of the respective lactone drug forms. In general, the best models demonstrated deteriorated correlations and poor accuracy, with values for the %RMSE of up to 42% (data not shown).

Discussion

In recent years, various statistical models have been developed for antineoplastic agents to predict pharmacokinetic parameters from a limited blood sample schedule.[15] Previous studies have indicated that such strategies are also feasible for the estimation of CPT-11 and SN-38 pharmacokinetics with the drug given by i.v. infusion, although no differentiation has been made so far between the lactone and carboxylate forms of the compounds.[16-19] In view of the discrepant data published on relationships between drug levels and the observed toxicity, further investigations of CPT-11 kinetics including separate quantitation of the lactone and the total forms of CPT-11 and SN-38 are clearly needed. Previously described limited-sampling models differed considerably in administered dose and infusion duration, and are only valid for CPT-11 given as a single agent. In our current study, the follow-up period for sample collection after infusion was much longer as compared to the other studies, resulting in more reliable pharmacokinetic data. Moreover, our limited-sampling models are the first applicable for CPT-11 given in combination with another drug, in this case cisplatin.

To achieve high predictive values for the developed models, i.e. high correlation coefficients and precision with low bias,[12] at least three sample-time points were required in all models. Although inclusion of additional samples might have upgraded the predictive performance of the models, fewer samples are more cost-effective and convenient for the patients. In addition, sampling over shorter periods enables pharmacokinetic-pharmacodynamic studies during day-time treatment in an outpatient setting, even in multi-institutional clinical trials.

The pharmacokinetic behavior of SN-38, the principal (active) metabolite of CPT-11, is markedly different from that of the parent drug. The objective of our approach was to accurately predict the AUCs of CPT-11 and SN-38 simultaneously in both lactone and total drug forms, from only three sample time points. The best compromise for the concurrent determination of the AUCs was found at the sample time points at 0.5, 1.67 and 5.5 h after the start of infusion. In selecting these sample time points, clinical constraints were also taken into consideration. For example, the samples have to be taken as early as possible after infusion, in view of the potential future usage of CPT-11 in clinical practice with drug-level monitoring for adaptive controlled dosing. In addition, a late sample time point is not clinically convenient as it makes outpatient treatment difficult or even impossible. For all four limited-sampling models developed, the first sample time point (at 0.5 h) is critical, for it is part of the ascending part of the concentration-time curves. The second point (at 1.67 h) lies just after the end-of-infusion time point, and is indicative for near-maximum plasma concentrations of CPT-11 and SN-38. The third sample point (at 5.5 h) is also important for it is part of the descending part of the concentration-time curves. Theoretically, limited-sampling strategies employing other sample time points which are also predictive could have been constructed, but would probably lack the above-mentioned advantages.

The CPT-11 total AUC is an important pharmacologic parameter, essential for the calculation of the total body clearance and for the calculation of individual metabolic ratios. The active lactone forms, especially that of SN-38, are important as they are assumed to be the real cytotoxic species and responsible for the toxic effects of CPT-11 therapy.[8] The proposed models for estimation of the AUCs of CPT-11 lactone and total and SN-38 total were shown to be valid, with excellent predictive utility in a large group of patients given CPT-11 at different dose levels in combination with cisplatin. In case of SN-38 lactone, however, the AUC estimates were slightly biased and less predictable especially at dose levels above 230 mg/m^2. In combination therapy studies, for instance with cisplatin, these high dose levels of CPT-11 may be less relevant for clinical practice and therefore this model can still be considered useful in a normal clinical setting. Other studies confirmed the variable and lower predictive behavior of SN-38 in limited-sampling model development, probably due to the complex pharmacokinetics of this metabolite.[20-22]

In future clinical studies, our limited-sampling models will enable prediction of the systemic exposure to CPT-11 and SN-38. Studies to examine the relationships between CPT-11 and SN-38 pharmacokinetics and pharmacodynamics could be explored conveniently using our model and sampling strategy. In our continued investigations, we will be examining these relationships in a future clinical phase II trial with combined CPT-11 and cisplatin chemotherapy.

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