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ORIGINAL ARTICLE

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Limited sampling models for CPT-11, SN-38, and SN-38 glucuronide

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Abstract *Purpose*: We developed limited sampling models (LSMs) for predicting the area under the curve (AUC) of irinotecan (CPT-11) and its metabolites SN-38 and SN-38 glucuronide (SN-38G). *Patients and methods*: Regression models were developed based on data from a phase I clinical trial involving 34 patients with advanced solid tumor malignancies who received CPT-11 as a 90-min infusion on an every 3-week dosing schedule. Multiple stepwise regression procedures were supplemented by all possible subsets regression analysis. Alternative clinically based and empirically derived LSMs were determined via model validation assessment including bootstrap simulation testing. *Results*: The best LSMs for CPT-11 AUC included concentrations recorded at the end of infusion and 4 h later with an option to include a blood draw at 7.5 h from infusion start. For SN-38 and SN-38G AUC, optimal LSMs included the additional metabolite concentration at 48 h after infusion. The LSMs were able to predict most patient AUC values to within 10% of the true value. *Conclusion*: CPT-11 AUC can be modeled with acceptable accuracy using only two or three plasma concentration time-points. A variety of LSM alternatives provided comparable accuracy in predicting AUC. Given the wide variety of LSM alternatives, clinical considerations and patient burden become more important performance parameters than statistical considerations for the choice of time-points in constructing LSMs.

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Introduction

The plant alkaloid camptothecin was found to have potent antiproliferative activity, but its clinical evaluation was discontinued due to severe and unpredictable toxicity [24]. Irinotecan (7-ethyl-10-{4-[1-piperidino]-1-piperidino}carbonyloxy-camptothecin; CPT-11) is an analog of camptothecin [35] possessing greater aqueous solubility and greater antiproliferative activity, and is associated with less severe and more predictable toxicity [21, 22, 44]. CPT-11 and camptothecin potently inhibit topoisomerase I, a nuclear enzyme that plays a critical role in DNA replication and transcription, by binding to the DNA-topoisomerase I complex. This inhibits religation of the DNA halting nucleic acid synthesis resulting in cell death [23].

The activity of CPT-11 has been attributed to SN-38, which is produced by carboxylesterase-catalyzed cleavage of the dipiperidinyl moiety [3, 42]. SN-38 is approximately 1000-fold more potent than CPT-11 in inhibiting topoisomerase I. SN-38 is conjugated by uridine diphosphate glucuronosyl transferases (UGT1A1) to form the metabolite, SN-38 glucuronide (SN-38G) [16, 41]. Neither SN-38G nor the newly discovered metabolite 7-ethyl-10-[4-*N*-(5-aminopentatonic acid)-1-piperidino] carbonyloxycamptothecin (APC) [42] contribute directly to the activity and toxicity profile of CPT-11 in vivo [6, 16, 18]. However, different SN-38 glucuronidation rates among patients may explain interindividual variation in SN-38 pharmacokinetic parameter estimates and different toxicities observed after administration of CPT-11 [16, 23, 26, 41].

The pharmacokinetics of CPT-11 have been examined in a number of patients and it has been suggested that therapeutic drug monitoring may optimize CPT-11 treatment by taking into consideration interpatient

variability and the potential relationship between concentrations of CPT-11 and adverse events [3, 7, 8, 11, 14, 17, 23, 42, 43, 44]. Statistical modeling of these data has produced limited sampling models (LSMs) to represent area under the curve (AUC) [29, 30, 36, 37, 50]. The rationale for the development of yet another LSM is both statistical and pragmatic. Previously developed LSMs predicting CPT-11, SN-38, and SN-38G AUC may not be applicable to every 3-week dosing [1, 2, 25, 39, 40]. The performance and generalizability of these models has also been variable. Further, the practicality of collecting multiple blood specimens from patients represents an unacceptable burden. Thus, we explored new LSMs to estimate the AUC of the parent drug and its metabolites [47].

Materials and methods

Study population and treatment plan

Pharmacokinetic data were obtained from a phase I trial involving 34 patients with advanced solid tumors carried out at the Mayo Clinic Cancer Center [34]. Patients received 240 to 340 mg/m^2 CPT-11 via a 90-min intravenous infusion every 3 weeks until disease progression. Patient demographics are summarized in Table 1. The trial concluded with a maximum tolerated dose of 320 mg/m^2 and dose-limiting toxicity was leukopenia, neutropenia and diarrhea.

Pharmacokinetic studies

Plasma specimens were collected during drug administration and for 48 h after infusion (at 0.75, 1.5, 1.58, 1.67, 1.75, 2.0, 2.5, 3.5, 5.5, 7.5, 9.5, 11.5, 13.5, 25.5, 33.5, and 49.5 h). CPT-11, SN-38 and SN-38G plasma concentrations were determined as described previously [34]. The plasma concentration-time data were analyzed by noncompartmental analysis using the program WINNONLIN (version 1.5). The AUC from time zero to the last measurable concentration was determined by linear trapezoidal approximation. The AUC to time infinity was determined by dividing the last measurable concentration by the terminal elimination rate constant estimated by a log-linear regression of the terminal phase of the plasma profile. The total AUC was calculated as the sum of these two AUCs.

Table 1 Dose levels and demographics ($n = 34$)

	No. of patients
CPT-11 dose (mg/m^2)	
240	3
290	12
320	13
340	6
Tumor site	
Colorectal	32
Esophageal	1
Gallbladder	1
Gender	
Male	21
Female	13
ECOG performance status	
0	20
1	11
2	3
Radiotherapy	
Yes	13
No	21

Statistical methods

Dataset processing

CPT-11 pharmacokinetics were linear over the dose range studied in this trial, thus dose-normalization was performed so that all concentration and AUC data were in terms of the 320 mg/m^2 dose level [29, 38]. Concentration values for missing data were estimated via nearest neighbor value imputation methods [15] and were used for 15 individual data points on three patients out of 1632 possible data points (0.9%). Modeling was performed on data that were transformed logarithmically, the complete dataset of 30 patients, and the imputed full dataset of 34 patients. The logarithmically transformed data produced inferior modeling performance statistics relative to the untransformed data, and there were no noticeable differences between the complete or dose-normalized imputed data sets, so only models using the imputed data set are reported.

Basic statistical methods

Basic summary statistics were used to inspect the distributions of the CPT-11, SN-38 and SN-38G AUCs as well as each plasma concentration. Normality testing for each variable was done via Shapiro-Wilk procedures [45]. Initial relationships between CPT-11 AUC and the plasma concentration were examined via Pearson and Spearman correlation coefficients [10, 12, 19].

Model selection and model validation procedures

Multiple regression models ideally should have no more than one variable for every ten observations in the dataset to avoid the problems of collinearity and parameter estimate instability [48]. Our sample size of 34 patients indicated that no more than three time-points should be used to produce a LSM. Standard stepwise regression on plasma concentration variables was used to determine the initial time-points to investigate [9, 27, 29, 31, 32]. Collinearity diagnostics including variance inflation factors (VIF) were used as screening statistics [4].

The comparative performance characteristics for model assessment included: the standard R^2, Mallows' Cp, mean prediction error (MPE), root mean square error (RMSE), mean square prediction error (MSPR), and predicted residual sum of squares (PRESS) statistics [28, 32, 36, 46, 48]. We also investigated the percentage of patients whose AUC was predicted within varying absolute and relative ranges. The stability of the model results was evaluated by splits of the dataset to produce a model equation from one half of the data and to test the model's performance with the other half of the data [33, 48]. Bootstrapping of 10,000 simulated samples drawn with replacement from the original sample of 34 patients was undertaken to assess the sensitivity of the modeling results to changes in sample structure [5].

Results

Initial results

Summary statistics of the CPT-11, SN-38 and SN-38G AUCs indicated that all three variables were positively skewed (Table 2). The CPT-11, SN-38, and SN-38G semilogarithmic plasma profiles for all 34 patients on

study indicated a biphasic elimination after completion of the 90-min infusion (Fig. 1). Substantial variability was observed for the dose-normalized plasma concentrations and AUCs of CPT-11 and its metabolites. The variability of CPT-11 AUC as represented by the coefficient of variation was notably lower than that of the metabolites.

Weak to moderate Pearson coefficients (0.43, 0.58) were observed for correlation of CPT-11 with SN-38 and SN-38G AUC. This suggests that the three AUC variables are related but measure distinguishably different aspects of CPT-11 pharmacokinetics and therefore should be modeled individually [33].

Regression modeling results

We present results for clinically based time-point selection for all AUC endpoints followed by empirically based time-point selection. Four clinically based models

Table 2 Dose-normalized AUC (ng·h/ml) distributions

	Range	Mean	Median	SD	Coefficient of variation (%)
CPT-11	11,837–40,589	21,313	19,869	7,332.0	34.4
SN-38	287–1,882	744	625	392.0	52.8
SN-38G	799–5,952	2,106	1,275	51.9	51.9

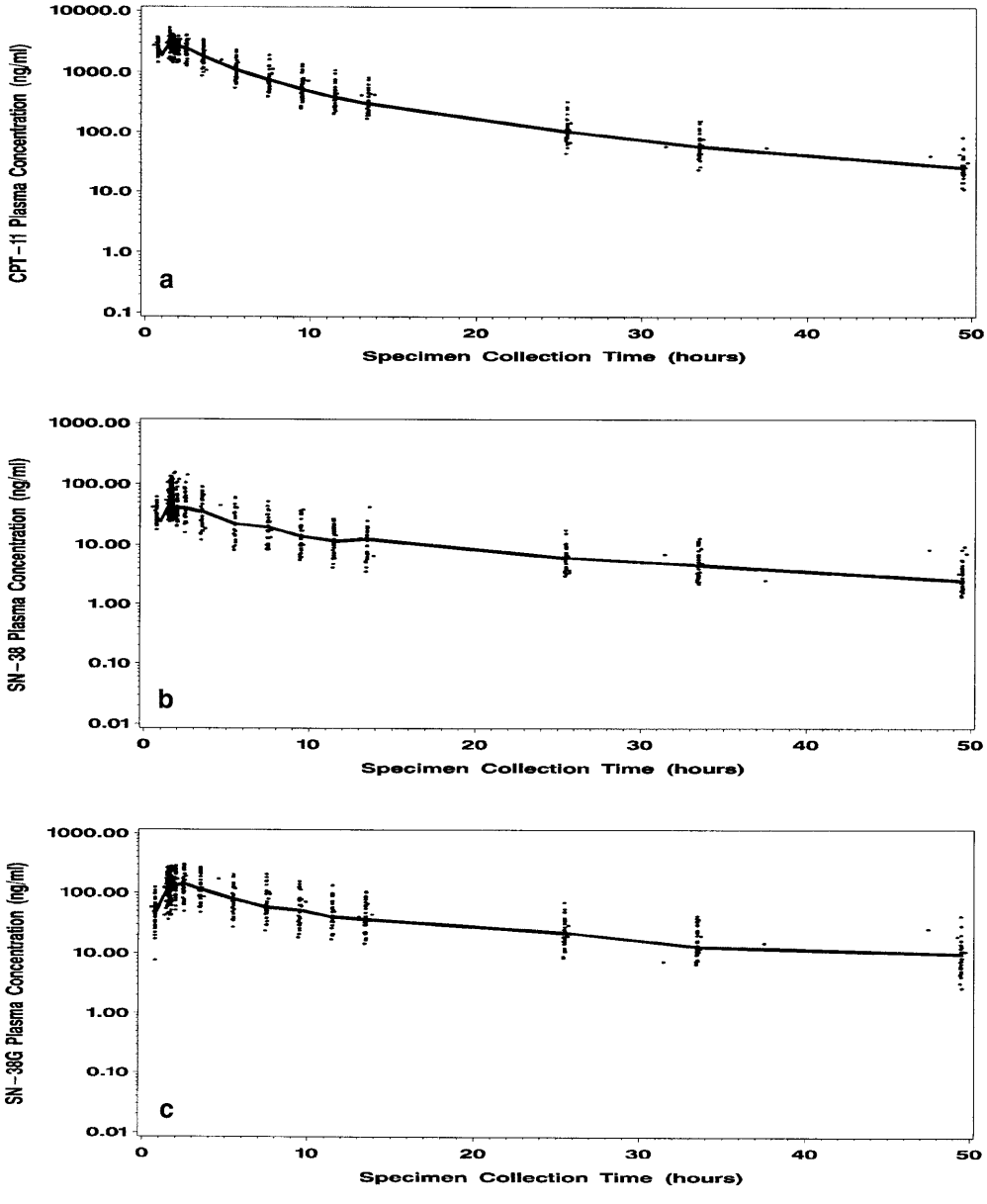

Fig. 1a–c Semilogarithmic plots of individual CPT-11 (**a**), SN-38 (**b**) and SN-38G (**c**) plasma concentrations and median plasma concentrations versus specimen collection time-points for 34 patients

and three empirically based models were potential credible alternatives for CPT-11 AUC after validation and selection procedures [20, 48]. SN-38 and SN-38G data produced no credible clinically based model, but suggested three potential alternative empirically based models each.

Criteria for clinically based plasma concentration time-point selection

Four clinically based models were investigated for determining the AUC of CPT-11 and metabolites. The end of infusion (1.5 h), alpha half-life (5.5 h) and beta half-life (25.5 h) were thought to be relatively important and formed the basis for one model. A second set of time-points was proposed to include sampling times around the peak concentration time, which had the highest variability and held the greatest potential impact on AUC. This set included the 0.75, 2.0, 3.5 and 25.5-h time-points. A third model, convenient for the patient and clinical practice scheduling, was based on the assumption that AUC could be predicted reasonably well by sampling at the end of infusion and 4 h thereafter (1.5 and 5.5 h). Adding a sample drawn 24 h after infusion to this model would require an overnight stay for the patient but if it provided additional predictive power to the LSM, could be worth the inconvenience. The fourth model comprised a single time-point at 1.5 h.

Comparisons were made among the clinically based models. For predicting CPT-11 AUC, the single variable model using the 1.5-h time-point was inferior using all criteria. Adding the 5.5-h blood draw to the 1.5-h variable substantially increased model performance and predicted 24 of 34 patients' AUC within 5% and all but three patients within 10%. The results for this two-variable model were comparable and were found to be no different from those of the three-variable and four-variable models. Thus the 1.5-h and 5.5-h time-points model was determined to be the best in predicting CPT-11 AUC.

The clinically based models were all substantially inferior and displayed poor performance characteristics when applied to the prediction of SN-38 and SN-38G AUC. None of the models achieved a reasonable R^2 value or success in predicting more than 20 of the 34 patients SN-38 AUC nor in predicting more than 23 of the 34 patients' SN-38G AUC to within 15%. As such, no clinically based model for SN-38 was carried forward into the validation process.

Criteria for empirically based plasma concentration time-point selection

Statistical criteria (R^2, Mallows' Cp, PRESS, MPE, and RMSE) were used to build alternative, empirically based LSMs. Initial time-point options were determined by examining the Pearson correlation (Table 3). Correlation between the latter time-points and CPT-11 AUC was strong, although partially due to the increased length of time for these latter points. These high correlation values indicate interchangeability in the time-points. Some were eliminated from consideration if there was substantial collinearity, i.e. VIF values in excess of 10 [31].

For CPT-11 AUC, stepwise linear regression showed that the most predictive power of any individual time-point (R^2 = 97%) was at 7.5 h, but other time-points provided similarly high R^2 values. A regression analysis exploring all possible subsets and a three time-point stepwise procedure confirmed that any combination including at least one of the 5.5-h, 7.5-h, 9.5-h or 13.5-h time-points produced similar accuracy. Therefore a model with the best performance characteristics (0.75-h, 7.5-h and 13.5-h time-points) was compared with two alternative models that had practical advantages over the optimal model. These two options were the set of the 1.58-h, 5.5-h and 7.5-h time-points and the set of only the 0.75-h and 7.5-h time-points.

Performance characteristics for these three models were relatively consistent. The RMSE was substantially larger for the two time-points model, while the 1.58-h, 5.5-h and 7.5-h model had the lowest MPE%. The PRESS statistic, expressed as a ratio of the SSE had a small value for all three models. The three time-point models allowed seven more patients' AUC to be predicted within 5% as compared to the two time-point model, and all AUC values were predicted to within 10% of the observed CPT-11 AUC. Both three-variable models had equal performance. Thus the 1.58-h, 5.5-h and 7.5-h model was chosen for validation.

A parallel process was performed for determining empirically based time-points for predicting AUCs for the metabolites. Results were markedly different from those seen for CPT-11 AUC both in terms of the time-points selected and the predictive power of the models. In general, empirically based models on the metabolites required the use of later time-points. In particular, the 49.5-h time-point had the highest correlation for SN-38 and the second highest correlation for SN-38G. It was

Table 3 CPT-11 concentration time-point distribution, coefficient of variation, and Pearson correlation coefficients with CPT-11 AUC

	Time (h)															
	0.75	1.5	1.58	1.67	1.75	2.0	2.5	3.5	5.5	7.5	9.5	11.5	13.5	25.5	33.5	49.5
CV	21.6	26.8	25.1	25.6	25.6	26.0	31.5	35.3	41.3	44.3	47.0	47.3	45.9	51.7	54.5	48.3
Correlation	0.63	0.83	0.80	0.81	0.82	0.69	0.88	0.92	0.98	0.99	0.97	0.95	0.96	0.93	0.84	0.79

the most prevalent variable in terms of the all possible subsets regression modeling process.

The stepwise selection process indicated that for SN-38, the three-variable 1.5, 9.5 and 49.5-h model was optimal with additional models being the two-variable 1.75 and 49.5-h and the three-variable 1.75, 9.5 and 49.5-h time-point concentrations. SN-38G had an optimal combination of 5.5, 13.5 and 49.5-h time-points with additional two-variable models of 5.5 and 49.5-h time-points and the combination of the 13.5 and 49.5-h concentrations.

SN-38 AUC was easier to predict than SN-38G AUC. Again, the R^2, Mallows' Cp and RMSE were consistent across all three models. The PRESS statistic was also similar with a score of around 1.5. The minimal predictive power of the two-variable model resulted in its removal from further consideration. The two alternative three-variable models showed little difference in predicting AUC, which suggests that the 1.5 and 1.75-h time-points are interchangeable. Thus, for consistency with the CPT-11 models, it was decided to choose the three-variable 1.5, 9.5 and 49.5-h time-points as the best empirically based model for predicting SN-38 AUC to carry forward into the validation process.

Models for SN-38G AUC also had consistent R^2 and Mallows' criteria as well as consistent RMSE. The MPE% was higher for the 13.5 and 49.5-h time-point model than for the other two. All models had approximately equal predictive power. Given the practical advantages of using the 5.5-h time-point versus the 13.5-h time-point, the best model for predicting SN-38G contained the 5.5 and 49.5-h time-points.

The final models

Table 4 summarizes the four alternative regression models for predicting CPT-11 AUC, SN-38 AUC, and SN-38G AUC. There was little practical difference between the empirically based and clinically based models for predicting CPT-11 AUC. The empirically based models for the metabolites performed less accurately than the CPT-11 models in terms of percentage of the sample predicted within specified amounts.

Model validation results

Table 5 shows the results of the validation of the four models identified in the previous section. Results for CPT-11 AUC indicate that the empirically based model performed slightly better than the clinically based one even though both predicted the AUC of 14 of the 17 patients within 5% and all of the patients within 10%. The empirically based models for predicting SN-38 and SN-38G AUC were less successful, and had higher variability, than those for predicting CPT-11 AUC. The MPE was higher and the number of predicted values within 15% was lower. The observed versus predicted AUC values for each of the four is plotted in Fig. 2. Figure 3 presents the residual plots, which show very few outlying values.

To further assess the stability of the limited sampling regression model coefficients, we bootstrapped 10,000 samples from the original data [13] and applied our models to the subsequent data sets (Table 6). The results

Table 4 Regression summary predicting AUCs (equations calculated for all of 34 patients). Clinically based models involved time-points determined from a strictly pragmatic approach, taking into consideration the realities of the clinical environment. Empirically based models were determined strictly through statistical criteria only

	CPT-11	SN-38		SN-38G
	Empirically based (1.58, 5.5, 7.5 h)	Clinically based (1.5, 5.5 h)	Empirically based (1.5, 9.5, 49.5 h)	Empirically based (5.5, 49.5 h)
Coefficients				
Intercept	1692.75*	1172.79	–53.27	262.54*
1.5 h		1.69*	3.95*	
1.58 h	1.70*			
5.5 h	4.96*	12.15*		11.12*
7.5 h	10.54*			
9.5 h			10.66*	
49.5 h			118.88*	94.71*
R^2	0.990	0.978	0.975	0.965
Adjusted R^2	0.989	0.977	0.973	0.963
Cp[a]	4	3	4	3
RMSE	783.87	1109.72	64.58	245.23
PRESS/SSE	1.22	1.19	1.52	1.78
Mean percent error	−0.17	–0.25	−0.12	−1.21
AUC within n% (number (%) of patients)				
Within 5%	29 (85)	24 (71)	18 (53)	10 (29)
Within 10%	34 (100)	31 (91)	25 (74)	20 (59)
Within 15%	34 (100)	33 (97)	32 (94)	30 (88)

*Significant

[a]Mallows' Cp is an estimate of the expected value of the scaled sum of squared errors

Table 5 Regression summary predicting AUCs with half of the data (equations calculated for half of the 34 patients, and predicting the other half). Clinically based models involved time-points determined from a strictly pragmatic approach, taking into consideration the realities of the clinical environment. Empirically based models were determined strictly through statistical criteria only

	CPT-11	SN-38		SN-38G
	Empirically based (1.58, 5.5, 7.5 h)	Clinically based (1.5, 5.5 h)	Empirically based (1.5, 9.5, 49.5 h)	Empirically based (5.5, 49.5 h)
R^2	0.989	0.974	0.963	0.948
Adjusted R^2	0.986	0.970	0.955	0.940
Cp[a]	4	3	4	3
RMSE	997.17	1448.62	54.50	257.53
PRESS/SSE	1.40	1.36	1.45	1.42
Mean percent error (%)	1.47	0.99	−4.48	−3.81
P-value	0.13	0.42	0.08	0.13
AUC within *n*% (number (%) of patients)				
Within 5%	14 (82)	14 (82)	6 (35)	6 (35)
Within 10%	17 (100)	17 (100)	10 (59)	10 (59)
Within 15%	17 (100)	17 (100)	14 (82)	15 (88)

[a]Mallows' Cp is an estimate of the expected value of the scaled sum of squared errors

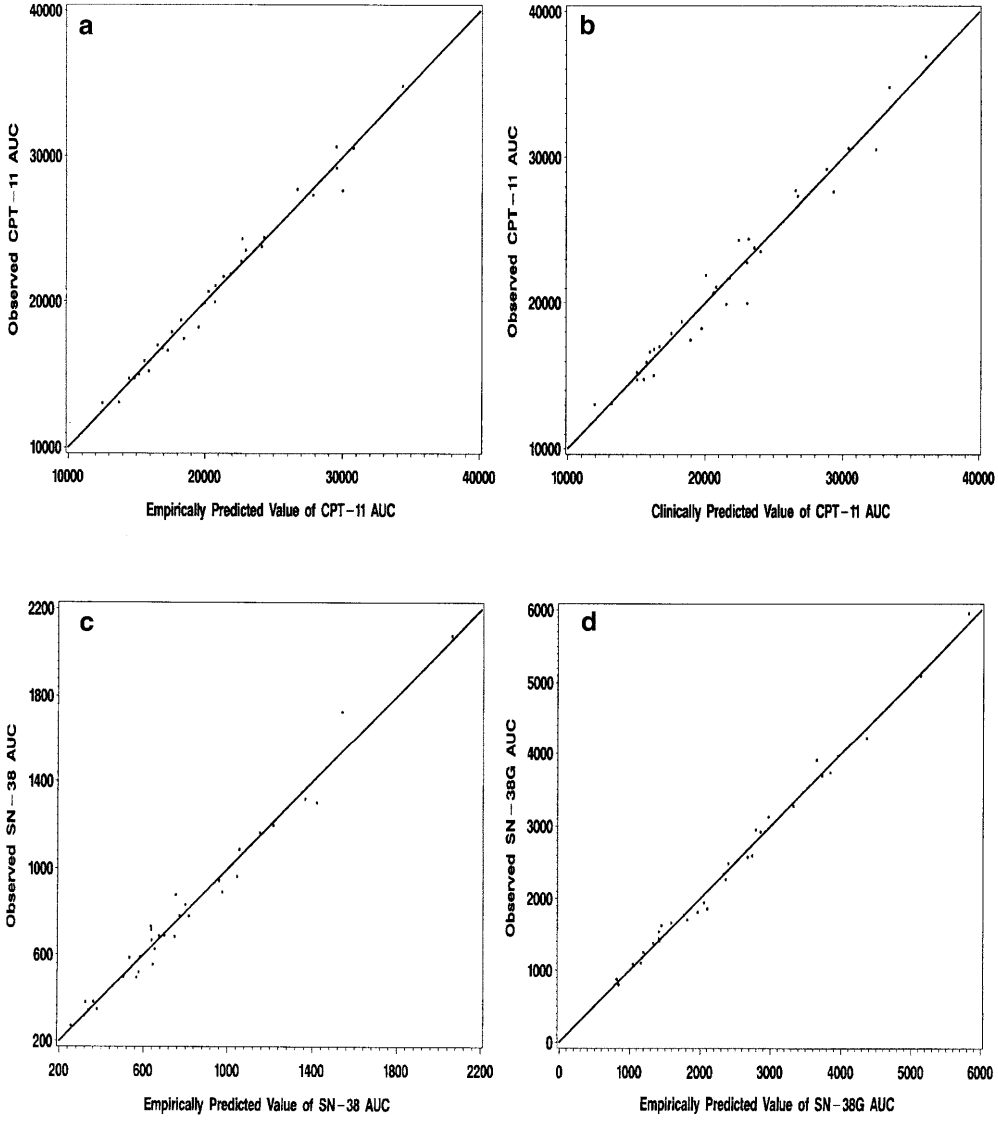

Fig. 2a–d Scatter plots of observed versus predicted values for AUC variables by the selected multiple regression models. **a**, **b** Results for the empirically based (1.58, 5.5 and 7.5 h) and clinically based (1.5 and 5.5 h) models predicting CPT-11 AUC. **c**, **d** Results for the empirically based models (1.5, 9.5 and 49.5 h and 5.5 and 49.5 h) predicting SN-38 AUC and SN-38G AUC, respectively

indicate coefficients of variation of less than 22% and consistently high R^2 values (>0.9). The addition of the 7.5-h time-point in the CPT-11 AUC model added substantially to the predictive capabilities of the regression model by correctly predicting 17% more patients within 5%.

The stability of our selected models was assessed by carrying out a stepwise procedure to a maximum of four variables on each of the created samples. For CPT-11, the three most often selected variables were the 0.75-h, 7.5-h, and 13.5-h time-point plasma concentrations. They appeared in 48%, 69% and 53% of the 10,000 models. The 5.5-h time-point was fourth, selected in 44% and the 1.5-h time-point was in only 17% of the models. These results confirm that there are a number of competing models for predicting CPT-11 AUC, all of which perform well. Results for predicting SN-38 AUC were reasonably accurate. The three variables most often seen were the three variables involved in our selected model, the 1.5, 9.5 and 49.5-h time-points, which appeared 44%, 85%, and 99.9% of the time. For SN-38G, the 49-h time-point appeared in 96% of the models produced from the stepwise process. The 13.5-h time-point appeared in 65%, while the 5.5-h time-point appeared in 55% of the models. None of the other time-points appeared in more than 25% of the models produced for SN-38 and SN-38G.

Further model validation was provided by other models proposed in the literature. Mick et al. [30] presented LSMs for CPT-11 AUC and its metabolites involving time-points at 3.0, 9.5 and 11.5 h for a study involving a dose level of 145 mg/m^2. We used the 3.5-h time-point from our data for the regression modeling in place of their 3.0-h time-point as it was the closest of our available time-points. These models used on our data indicated substantially poorer performance characteristics than our suggested models.

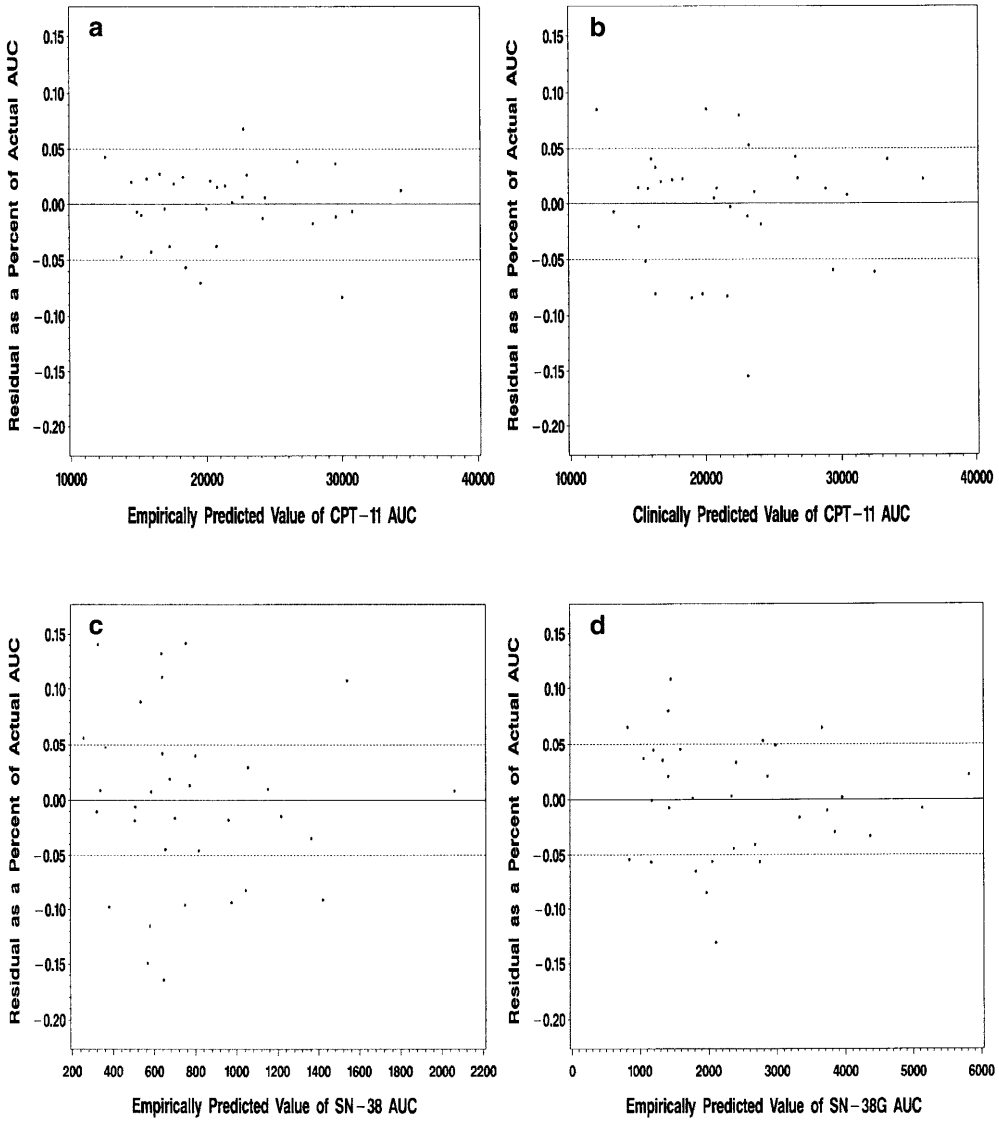

Fig. 3a–d Scatter plots of residuals versus predicted values for AUC variables by the selected multiple regression models. **a**, **b** Results for the empirically based (1.58, 5.5 and 7.5 h) and clinically based (1.5 and 5.5 h) models predicting CPT-11 AUC. **c**, **d** Results for the empirically based (1.5, 9.5 and 49.5 h and 5.5 and 49.5 h) models predicting SN-38 AUC and SN-38G AUC, respectively

Table 6 Results of regression modeling on 10,000 bootstrapped samples for predicting CPT-11, SN-38, and SN-38G AUC

	CPT-11		SN-38	SN-38G
Time-points (h)	1.5, 5.5	1.5, 5.5, 7.5	1.5, 9.5, 49.5	5.5, 49.5
Estimated CV (%)	20, 4	15, 22, 16	19, 20, 8	14, 17
Percent	–0.002	–0.002	0.0014	–0.0120
RMSE	1060	745	58	224
R^2 (%)	97.8	98.9	97.8	96.8
AUC within *n*% (% of patients)				
Within 1%	18	26	12	7
Within 5%	68	85	53	34
Within 10%	94	99	77	64
Within 15% +	2	0.1	7	12

Discussion

The blood concentration time-points for the optimal CPT-11 AUC model were 1.58, 5.5 and 7.5 h based upon statistical criteria alone. However, the 1.5 and 5.5-h time-points model was more clinically feasible and statistically comparable to the model including the 7.5 h time-point. The ultimate choice between these two models would likely be case-specific. Results for the metabolites are substantively different from those for CPT-11 AUC. Due to the long half-life of the metabolites, there was no clinically convenient model that was a successful predictor. For SN-38, blood concentrations at 1.5, 9.5 and 49.5 h were used for the best model. The foremost model for SN-38G used blood concentrations at 5.5 and 49.5 h. The 48-h post-infusion sample is impractical in typical clinical settings but it is critical to ensure an accurate prediction.

Recent work on LSMs for CPT-11 using 145 mg/m^2 produced models using 3.0-h, 9.5-h and 11.5-h time-points which did not perform well for our data [30]. The dose and schedule (weekly administration) used in that study, however, were substantially different from those used in our study. This result indicates the need for exploring alternative models for other schedules. It is reasonable to hypothesize that the application of LSMs may differ depending upon the range of doses under consideration at the sampling times at which specimens were collected.

There are many feasible alternative LSMs of drug disposition. The small sample sizes, multiple sources of collinearity and complex underlying relationships make the task of developing models that will generalize across sampling environments difficult. The various modeling processes we employed confirmed that there were several alternative LSMs with comparable performance characteristics that may be chosen to model AUC. The decreasing values of AUC over the various time-points allows the requisite information for accurate prediction from any of the potential predictor variables to be obtained. The ultimate choice among the alternatives is therefore left to the specifics of the clinical environment and logistics of blood draw timing [38, 49]. Using even the "worst" of the models, there is a reasonable level of accuracy in predicting AUC.

Ultimately, the potential importance of these sampling models lies in their predictive ability. Predicting a patient's AUC clinically could lead to identifying AUC levels which have been seen to be correlated with toxicity. We have taken the first step by systematically examining alternative LSMs to predict AUC for CPT-11, SN-38, and SN-38G. Since the three AUC variables seem to be measuring different entities, it is important to develop separate models for all three variables until the AUC ultimately linked most closely with toxicity incidence or clinical benefit is determined. Further studies are necessary, however, to forge this link between the LSMs and toxicity prediction. Some of these data may come from an ongoing North Central Cancer Treatment Group phase II trial involving gastric patients wherein blood is drawn at sampling points of 1.5, 5.5 and 49.5 h for SN-38 prediction rather than at the sampling points of 1.5, 9.5 and 49.5 h suggested here. This model's coefficients and performance parameters are comparable to our optimal model which contains the 9.5-h rather than the 5.5-h time-point, but the predictive performance of our model was superior.

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