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ORIGINAL ARTICLE

# Pharmacokinetics of irinotecan and its metabolites in pediatric cancer patients: a report from the children's oncology group

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**Abstract**
*Objective* To develop a population pharmacokinetic model of irinotecan and its major metabolites in children with cancer and to identify covariates that predict variability in disposition.
*Methods* A population pharmacokinetic model was developed using plasma concentration data from 82 patients participating in a multicenter Pediatric Oncology Group (POG) single agent phase II clinical trial. Patients between 1 and 21 years of age with solid tumors refractory to standard therapy received irinotecan, 50 mg/m$^2$, as a 60-min intravenous infusion for 5 consecutive days every 3 weeks. Blood samples were collected and analyzed for irinotecan and three metabolites (SN-38, SN-38G, and APC). The population model was developed with NONMEM. Clearance and volume were scaled allometrically using corrected body weight. Exponential error models were used to describe the interindividual variance in pharmacokinetic parameters, and the residual error was described with a proportional model. Significant covariate effects were identified graphically using S-PLUS and were added to the base-model. The final model was evaluated by simulating data from two other POG trials.
*Results* The best structural model for irinotecan and its metabolites consisted of six-compartments: two compartments for irinotecan and SN-38, and one each for APC and SN-38G. Age and bilirubin were found to be significant covariates affecting SN-38 clearance. SN-38 clearance was greater in patients less than 10 years of age and lower in patients with a total serum bilirubin >0.6 mg/dL. Simulations revealed that the model was able to predict drug and metabolite exposure (AUC) for patients receiving the same or similar doses (30–65 mg/m$^2$) of irinotecan.
*Conclusions* This population model accurately describes the pharmacokinetics of irinotecan and its primary metabolites. The model, which includes age and bilirubin as covariate effects on SN-38 clearance, is the first population model to describe the pharmacokinetics of irinotecan and its major metabolites in children.

**Keywords** Irinotecan · CPT-11 · Pediatrics · Pharmacokinetics · Population modeling

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## Introduction

Irinotecan (also known as CPT-11) is a semisynthetic water-soluble analog of camptothecin that differs from other

camptothecin analogs in that it is a prodrug that undergoes deesterification to a much more potent topoisomerase-I inhibitor, 7-ethyl-10-hydroxycamptothecin (SN-38). Irinotecan itself possesses a marginal antiproliferative effect, while its metabolite SN-38 is 100–1,000-fold more active in vitro [19]. SN-38 is glucuronidated by the hepatic uridine diphosphate glucuronosyltransferase UGT1A1 to 10-*O*-glucuronyl-SN-38 (SN38-G), an inactive metabolite that is excreted into the bile and urine. Irinotecan also undergoes P450 CYP3A4-mediated metabolism to form two additional minor metabolites 7-ethyl-10-[4-*N*-(5-aminopentanoic acid)-1-piperidino]-carbonyloxycamptothecin (APC) and 7-ethyl-10-[4-amino-1-piperidino]-carbonyloxycamptothecin (NPC). Neither APC nor NPC have anti-tumor effects.

Irinotecan is approved for use in the treatment of colon cancer and its pharmacokinetics and pharmacogenetics have been described in adults [1, 8, 13–15, 25, 26, 28, 30, 31, 36–38, 40]. Irinotecan has also shown some promise in the treatment of difficult to cure pediatric solid tumors with objective anti-tumor responses observed in the phase I and II setting in a variety of tumor types including neuroblastoma, hepatocellular carcinoma, rhabdomyosarcoma and medulloblastoma [3, 5, 11, 45].

Pharmacokinetic studies have shown that there is marked interpatient variability in the pharmacokinetic disposition of irinotecan and its metabolites [6, 7, 21, 34]. Dose-limiting side effects include diarrhea and neutropenia. In adult cancer patients significant relationships among drug metabolizing genotype, clinical factors (age, sex, and organ function), and pharmacokinetic and toxicity parameters have been reported [2, 15, 16, 22, 27, 28, 32, 48]. Impaired glucuronidation activity of the UGT1A1 enzyme has been linked with elevated levels of SN-38, leading to toxicities. UGT1A1*28 involves an extra TA repeat in the UGT1A1 promoter region and is the variant most frequently contributing to interpatient variability in irinotecan pharmacokinetics and toxicities. This information led to the revision of the irinotecan label by the US Food and Drug Administration. The text added to the label states that individuals who are homozygous for the UGT1A1*28 allele are at increased risk for neutropenia and that a reduced initial dose of irinotecan should be considered for patients known to be homozygous for the UGT1A1*28 allele. In children, however, the number of clinical pharmacology studies of irinotecan is relatively limited and the factors contributing to variability in pharmacokinetics and toxicity are less well understood [10, 23, 35, 45]. Furthermore, the dose schedules used in pediatric oncology are frequently different. In adult cancer trials irinotecan has demonstrated efficacy when dosed every 3 weeks or alternatively, weekly 4 times, every 6 weeks. Pediatric trials have primarily utilized a daily schedule for 5 consecutive days every 21 days or daily for 5 days per week for 2 weeks every 21 days (daily ×5 for 2 weeks q 21 days) [11, 17, 33, 41]. Alternative schedules similar to those used for adults have also been evaluated [5, 35, 44, 45]. A recent study by Stewart et al. [42] suggests that drug metabolizing genotype may affect the pharmacokinetics of irinotecan when it is given to children on a protracted schedule (daily for 5 days per week for 2 weeks every 21 days), but not toxicity. Bomgaars et al. [4] also found that genotype did not affect toxicity on a daily ×5 schedule every 21 days, and they did not see any difference in non-compartmental pharmacokinetics as a result of genotype.

This analysis focuses on developing a thorough understanding of irinotecan pharmacokinetics in children. We present the first pediatric population pharmacokinetic model for irinotecan and its metabolites and provide an analysis of the demographic and clinical factors that contribute to the variability of the pharmacokinetics of irinotecan in children.

## Patients and methods

### Patients

We used pharmacokinetic data from a multicenter single agent phase II Pediatric Oncology Group (POG) Trial, POG 9761, of irinotecan to develop the population analysis. We subsequently evaluated the resultant model using data from two smaller POG trials, POG 9571 and POG 9971. A brief description of each study follows.

#### *POG 9761*

Pediatric patients between 1 and 22 years of age with refractory solid or CNS tumors received irinotecan at a dose of 50 mg/m$^2$ IV over 1 h daily for 5 consecutive days. Patients with brain tumors could not be receiving concomitant anticonvulsants and if receiving dexamethasone had to be on a stable or decreasing dose. Other eligibility requirements were standard and included: an adequate performance status (Karnofsky or Lansky ≥50%), serum albumin >3 g/dL, adequate bone marrow function [absolute neutrophil count (ANC) >1,000/mm$^3$; a platelet count >100,000/mm$^3$; a hemoglobin (Hgb) >8.0 g/dL], and adequate organ function (creatinine normal for age or glomerular filtration rate >70 mL/min/1.73 m$^2$, total bilirubin <1.5 mg/dL, and ALT <5× normal). Pharmacokinetic data with clinical covariates were available from 82 patients, complete data for 79 patients and partial data for 3 patients.

#### *POG 9571*

Specific eligibility requirements for POG 9571, a phase I study of irinotecan given as a single agent over 1 h daily for

5 consecutive days, were similar to POG 9761 except that the study required a hemoglobin >9.0 g/L and ALT <2× normal. The starting dose for this trial was 30 mg/m$^2$/dose (daily ×5 days). Dose escalations were in increments of 30% up to a maximum tested dose of 65 mg/m$^2$/dose. Pharmacokinetic data with clinical covariates were available from 25 patients enrolled on this study.

*POG 9971*

Pediatric patients with solid tumors refractory to conventional therapeutic modalities were treated on this phase I protocol which used irinotecan in combination with weekly vincristine. Patients with brain tumors were also eligible if they were not receiving anticonvulsants. Specific eligibility requirements for this study were similar to POG 9761. Patients received irinotecan at a dose of 50 mg/m$^2$ IV over 1 h daily for 5 consecutive days every 3 weeks. Pharmacokinetic data with clinical covariates were available from 14 patients.

Pharmacokinetic data collection

Pharmacokinetic data collection varied among the three studies as described below.

*POG 9761*

Two different sampling schedules were used on this protocol. Initially a serial sampling schedule in which samples were collected in heparinized tubes on day 1, cycle 1 prior to drug administration, at the end of the infusion, and at 5, 15, 30, and 45 min and 1, 2, 4, 6, and 8 h following the completion of the infusion. Sixteen patients had complete pharmacokinetic sampling on this schedule. A "limited" sampling schedule in which blood was collected prior to drug administration, at the end of the infusion, and at 1.5, 3.5, 6, and 24 h following the completion of the infusion was used for the remaining 66 patients.

*POG 9571*

Blood samples for pharmacokinetic (PK) analysis were collected in heparinized tubes prior to drug administration, at the end of the infusion, and at 5, 15, and 30 min, and 1, 2, 4, 6, 8 h following the completion of the infusion.

*POG 9971*

Blood samples for PK analysis were collected in heparinized tubes on day 1, cycle 1 prior to drug administration, at the end of the infusion, and at 3.5, 6.5, 8, and 24 h following the completion of the infusion.

Analytical method

Blood samples were immediately centrifuged at 3,000 rpm for 10–15 min at 4°C to separate the plasma. Plasma was then frozen at −20 to −70°C until analysis. The plasma specimens were assayed using a validated, sensitive, and specific isocratic high-performance liquid chromatography (HPLC) method with fluorescence detection as previously reported [5]. Concentration determinations were made for the total analyte (lactone plus carboxylate) for CPT-11 and SN-38.

Population pharmacokinetic modeling

We used NONMEM VI (GloboMax LLC, Hanover, MD) to perform the model fitting on a personal computer using a DIGITAL Visual FORTRAN compiler (Version 6.1). The ADVAN5 subroutine and the first-order conditional estimation (FOCE) method with $\eta$–$\varepsilon$ interaction were used throughout the model building process.

In specifying our model, we chose to a priori fix the fractional conversion of the irinotecan to its metabolites (APC, SN-38, and SN-38G) based on their respective AUCs (calculated on a molar basis) since the PK parameters are not uniquely identifiable. For example, the mean AUC of APC in the POG data sets was approximately 15% of the mean AUC of CPT-11 (on a molar basis), therefore we fixed the fractional conversion of CPT-11 to APC at 15%. The fraction conversion to SN-38 was based on the ratio of the sum of the AUCs of SN-38 and SN-38G to the AUC of CPT-11, and, based on all the POG data sets, this was also approximately 15%. The fraction of SN-38 converted to SN-38G was fixed at 65%. This was based on previously reported data from a cancer patient with a biliary drain in whom feces, urine, and bile samples were collected for irinotecan and its metabolites [8]. The assumption of a fractional conversion is somewhat arbitrary and different assumptions could be made. In one pharmacokinetic model for adult patients, the fractional conversion of CPT-11 to SN-38 and SN-38G was assumed to be 12% based on knowledge of excretion characteristics gained from prior mass balance studies [47]. An alternative, used in other pharmacokinetic models for irinotecan, is to not define the fractional conversion and instead lump it into an "apparent PK parameter" (e.g. apparent clearance equals clearance divided by fractional conversion) [22]. We chose our approach because we felt that given the complexity of our model it was more explicit and straightforward.

We initially formed a structural model without any covariates. However, it was apparent that patient size was an essential covariate for all pharmacokinetic parameters based on plots against different body size measures (weight, body surface area, and corrected body weight). Ultimately,

allometric scaling based on corrected body weight (CBW) was used to account for patient size. For patients who have an actual body weight that is greater than their ideal body weight (IBW), CBW is equal to IBW. For patients who have an actual body weight that is less than their IBW, CBW is equal to actual body weight. IBW was calculated using the method of Traub [43]. We used exponent values of 0.75 and 1.00 to describe the change in clearance and volume parameters over the range of patient weights. This approach was based on the expectation that organ size and function (and hence clearance) would correlate more closely with CBW than IBW.

Potentially significant covariate effects were identified graphically using S-PLUS and LOESS curve-fitting [24]. Plots of each pharmacokinetic parameter as a function of the available covariates were generated including age, gender, and total bilirubin. Along with typical goodness-of-fit diagnostic plots, we used the likelihood ratio test to evaluate nested alternative models including covariates effects. When using this approach to compare alternative models, the difference in the value of the objective function is approximately chi-square distributed with $n$ degrees of freedom (where $n$ is the difference in the number of parameters between the full and the reduced model). This approach has been shown to be reliable for the FOCE-INTERACTION estimation method. According to the chi-squared distribution under the null hypothesis, the $p$ value of <0.001 required in this study corresponds to a decrease in the value of the objective function of at least 10.88 for 1 degree of freedom.

Exponential error models were used to describe the interindividual variance in pharmacokinetic parameters. The residual error was described with proportional error models.

### Model evaluation

We evaluated the robustness of the final model constructed from the POG 9761 data using the pharmacokinetic data collected in the other two clinical trials. We chose to evaluate the model by examining its ability to predict area under the curve (AUC) for irinotecan and its metabolites in two groups of patients: (1) patients enrolled on POG 9571 or POG 9971 who received 50 mg/m$^2$ of irinotecan daily ×5 days, and (2) patients enrolled on POG 9571 who received irinotecan at doses ranging from 30 to 65 mg/m$^2$ on a daily ×5 schedule.

We first tested the accuracy of the model in predicting irinotecan and metabolite AUCs for patients receiving 50 mg/m$^2$, which was the same dose used for model building. Data from patients receiving this dose (enrolled in either the POG 9571 or POG 9971 trial) were combined into one evaluation data set consisting of 25 patients. The NOMEM model developed from the POG 9761 trial was then used to run 500 Monte-Carlo simulation replicates with this evaluation data set. A PERL script was used to calculate AUCs for CPT-11, APC, SN-38, and SN-38G using the trapezoidal rule from the simulated concentration–time curves. We then compared the observed AUCs to the AUCs estimated from the 500 simulation runs. A predictive check $p$ value was calculated for the median observed AUC compared to the range of predicted median AUCs from the simulations. This $p$ value was calculated as the proportion of simulated values that were less than the observed value of the median AUC. This $p$ value defined the probability that the simulated data (under the model and parameter point estimates) could be more extreme than the observed data [12]. We used this approach for both groups of patients for irinotecan and each metabolite.

## Results

### Population pharmacokinetic model

Table 1 summarizes patient specific characteristics for the study used for model building (POG 9761) as well as the studies used for model evaluation (POG 9571 and POG 9971). As shown in the table, the range of patient age and size (BSA and weight) and bilirubin levels were similar for each of the three trials.

Based on both the objective function and graphical inspection of the diagnostic plots, the best structural model for irinotecan and its metabolites consisted of a total of six-compartments. Two compartments were used for irinotecan and SN-38, and one each for APC and SN-38G. A schematic of the structural model is shown in Fig. 1. The best approach to scaling the pharmacokinetic parameters in the base model was allometric scaling based on corrected body weight. This approach minimized interindividual variance compared to other scaling approaches including BSA-based scaling, weight-based scaling, and allometric scaling based on body weight. The model structure in terms of covariate effects, interindividual variability, and residual error is summarized in Fig. 2.

The effect of age on SN-38 clearance was the first covariate effect added to the base model. Based on inspection of our diagnostic plots (such as the one shown in Fig. 3a), we empirically chose to include the effect of age as an exponential effect for patients less than 10 years of age (Fig. 2 shows the equations used). Inclusion of age as a covariate effect on SN-38 clearance significantly lowered the objective function (−21.8). This also resulted in a decrease in the estimate of the interindividual coefficient of variation of SN-38 CL from 57 to 48%. This model was then carried

**Table 1** Comparison of irinotecan pediatric clinical trials

| Study | POG 9761 | POG 9971 | POG 9571 |
|---|---|---|---|
| Irinotecan administration | Daily x5 | Daily ×5 | Daily ×5 |
| Dose levels (mg/m$^2$) | 50 | 50 | 30, 39, 50, 65 |
| Analytes measured | Irinotecan, APC, SN-38, and SN-38G | Irinotecan, APC, SN-38, and SN-38G | Irinotecan, APC, SN-38, and SN-38G |
| Number of patients | 82 | 14 | 25 |
| Male/female | 47/35 | 3/11 | 17/8 |
| Age (years) | | | |
| Range | 1–23 | 1–18 | 1–20 |
| Median | 10 | 7 | 9 |
| Weight (kg) | | | |
| Range | 9.3–112 | 9.0–68.7 | 8.3–82.3 |
| Mean ± SD | 39.3 ± 24.8 | 30.7 ± 18.6 | 37.6 ± 22.5 |
| BSA (m$^2$) | | | |
| Range | 0.46–2.33 | 0.41–1.87 | 0.41–2.01 |
| Mean ± SD | 1.19 ± 0.49 | 1.02 ± 0.43 | 1.17 ± 0.49 |
| Bilirubin (mg/dL) | | | |
| Range | 0.0–1.5 | 0.1–1.4 | 0.2–1.2 |
| Mean ± SD | 0.42 ± 0.27 | 0.56 ± 0.35 | 0.44 ± 0.28 |

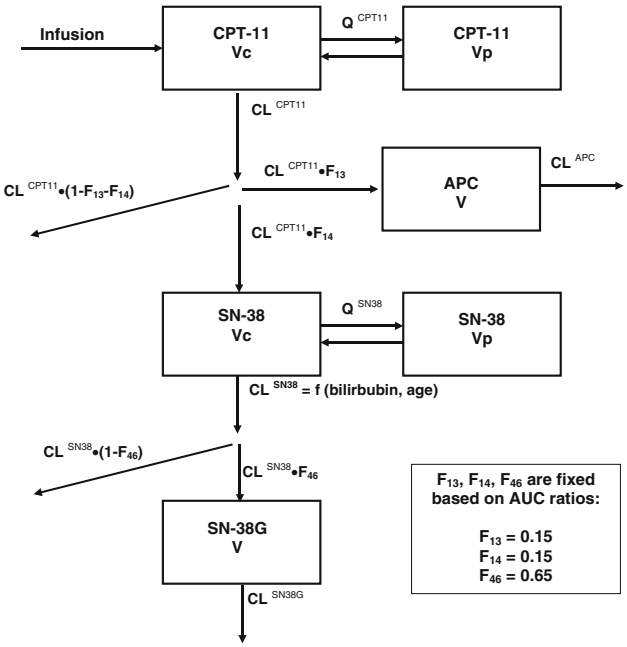


**Fig. 1** Schematic of pediatric population pharmacokinetic model for irinotecan and its metabolites. The model includes two compartments for irinotecan (CPT-11), one for APC, two for SN-38, and one for SN-38G

forward as the reference model for the remainder of the covariate analysis.

Based on further inspection of the diagnostic plots (such as the one shown in Fig. 3b) we then added the effect of bilirubin on SN-38 clearance to the base model. We empirically chose to use a total bilirubin level of 0.6 mg/dL as a cut point to divide the patients into two groups, one group characterized by lower bilirubin levels and higher SN-38 clearance and the other group with higher bilirubin and lower SN-38 clearance. We chose to use bilirubin as a discrete rather than continuous covariate, since the bilirubin level may serve as a biomarker that distinguishes discrete populations having different UGT1A1genotypes. Inclusion of bilirubin as a covariate in this way resulted in a further

**Pharmacokinetic Model for Irinotecan (CPT-11)**

$$CL^{CPT11}_i = \theta_{CL\text{-}CPT11} \bullet (CBWi/40)^{0.75} \bullet \exp(\eta_{CL\text{-}CPT11i})$$
$$Vc^{CPT11}_i = \theta_{Vc\text{-}CPT\text{-}11} \bullet (CBWi/40) \bullet \exp(\eta_{Vc\text{-}CPT11i})$$
$$Vp^{CPT11}_i = \theta_{Vp\text{-}CPT11} \bullet (CBW_i/40) \bullet \exp(\eta_{Vp\text{-}CPT11i})$$
$$Q^{CPT11}_i = \theta_{Q\text{-}CPT11} \bullet (CBWi/40)^{0.75} \bullet \exp(\eta_{Q\text{-}CPT11i})$$

**Pharmacokinetic Model for APC**

$$CL^{APC}_i = \theta_{CL\text{-}APC} \bullet (CBWi/40)^{0.75} \bullet \exp(\eta_{CL\text{-}APCi})$$
$$V^{APC}_i = \theta_{Vc\text{-}APC} \bullet (CBWi/40) \bullet \exp(\eta_{V\text{-}APCi})$$

**Pharmacokinetic Model for SN-38**

$$CL^{SN38}_i = BILIEFF \bullet (CBWi/40)^{0.75} \bullet \exp(\eta_{CL\text{-}SN38i}) \bullet AGEFF$$

- BILIEFF= $\theta_{CL\text{-}SN38}$ for patients with a bilirubin < 0.6 mg/dl and $\theta_{CL\text{-}SN38\text{-}BILI}$ for patients with a bilirubin > 0.6 mg/dl
- AGEFF = $\exp[\theta_{CL\text{-}SN38\text{-}AGEFF} \bullet (AGE\text{-}10)]$ for patients <10 yr and AGEFF=1 for patients >10 yr

$$Vc^{SN38}_i = \theta_{Vc\text{-}CPT\text{-}11} \bullet (CBWi/40) \bullet \exp(\eta_{Vc\text{-}SN38i})$$
$$Vp^{SN38}_i = \theta_{Vp\text{-}SN38} \bullet (CBW_i/40)$$
$$Q^{SN38}_i = \theta_{Q\text{-}SN38} \bullet (CBWi/40)^{0.75}$$

**Pharmacokinetic Model for SN38G**

$$CL^{SN38G}_i = \theta_{CL\text{-}SN38G} \bullet (CBWi/40)^{0.75} \bullet \exp(\eta_{CL\text{-}SN38Gi})$$
$$V^{SN38G}_i = \theta_{Vc\text{-}SN38G} \bullet (CBWi/40) \bullet \exp(\eta_{V\text{-}SN38Gi})$$

**Residual Error Model**

$$C^{CPT11}_{ij} = C^{P\text{-}CPT11}_{ij} \bullet (1+\varepsilon_{P1ij})$$
$$C^{APC}_{ij} = C^{P\text{-}APC}_{ij} \bullet (1+\varepsilon_{P2ij})$$
$$C^{SN38}_{ij} = C^{P\text{-}SN38}_{ij} \bullet (1+\varepsilon_{P3ij})$$
$$C^{SN38G}_{ij} = C^{P\text{-}SN38G}_{ij} \bullet (1+\varepsilon_{P4ij})$$

**Fig. 2** Pediatric population pharmacokinetic model for irinotecan and its metabolites. Pharmacokinetic parameters are as follows: $CL^{CPT11}$ Clearance of CPT-11; $Vc^{CPT11}$ volume of distribution of central CPT-11 compartment; $Vp^{CPT11}$ volume of distribution of peripheral CPT-11 compartment; $Q^{CPT11}$ intercompartmental CPT-11 clearance; $CL^{APC}$ clearance of APC; $V^{APC}$ volume of distribution of APC; $CL^{SN38}$ clearance of SN-38; $Vc^{SN38}$ volume of distribution of central SN-38 compartment; $Vp^{SN38}$ volume of distribution of peripheral SN-38 compartment; $Q^{SN38}$ intercompartmental SN-38 clearance; $CL^{SN38G}$ clearance of SN-38G; $V^{SN38G}$ volume of distribution of SN-38G. The *subscript* i indicates an individual-specific parameter or variable. The $\theta$ are population parameters and the $\eta$ are interindividual random effects. Each of the $\eta$'s have a normal distribution around zero with a coefficient of variance equal to $\omega$. $C^{CPT11}_{ij}$, $C^{APC}_{ij}$, $C^{SN\text{-}38}_{ij}$, and $C^{SN38G}_{ij}$, are the jth measured plasma concentrations in the ith individual for CPT-11, APC, SN-38, and SN-38G, respectively. $C^{P\text{-}CPT11}_{ij}$, $C^{P\text{-}APC}_{ij}$, $C^{P\text{-}SN38}_{ij}$, and $C^{P\text{-}SN38G}_{ij}$, are the jth predicted plasma concentrations in the ith individual for CPT-11, APC, SN-38, and SN-38G, respectively. $\varepsilon_{P1ij}$, $\varepsilon_{P2ij}$, $\varepsilon_{P3ij}$, and $\varepsilon_{P4ij}$, are the proportional residual random error terms associated with CPT-11, APC, SN-38, and SN-38G

decrease (−11.7) in the value of the objective function and also reduced the estimate of interindividual coefficient of variation for SN-38 clearance from 48 to 46%.

Table 2 summarizes the final model and presents the point estimates, standard errors, relative standard errors, and coefficients of variation (for interindividual and residual error terms). For the final model, predicted versus observed concentrations are shown for CPT-11, APC, SN-38, and SN-38G in Fig. 4a–d.

## Model evaluation

Table 3 summarizes the results of the model evaluation. As the table shows, the measured median AUCs for irinotecan and its metabolites fall within the range for the predicted median AUCs for patients dosed at 50 mg/m$^2$. The predictive-check $p$ values are between 0.43 and 0.89. This indicates that none of the simulation results differ significantly (at a 95% confidence level) from the observed data. As the

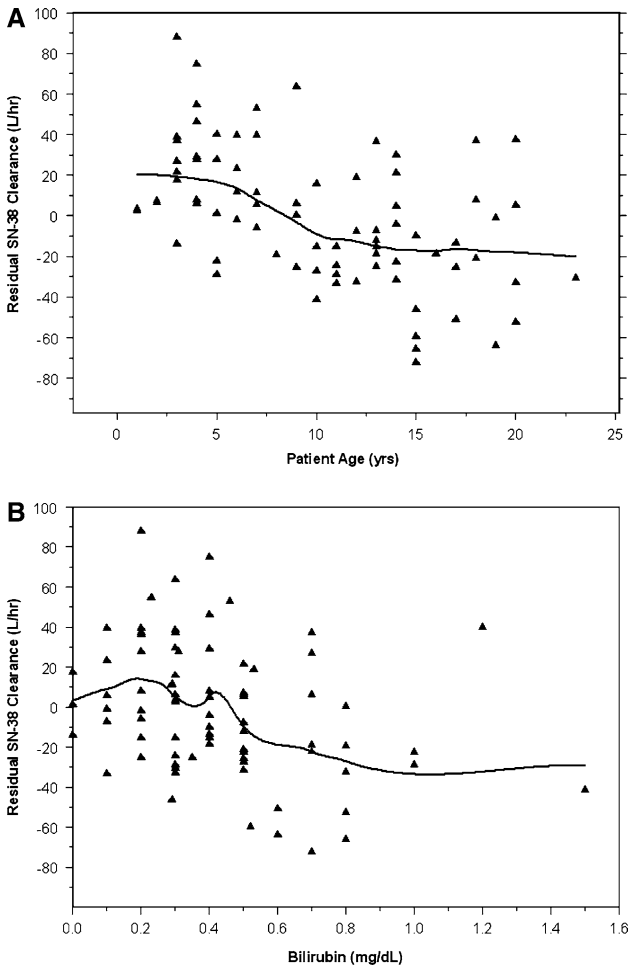


**Fig. 3** Plots of residual SN-38 clearance versus significant covariates. **a** Residual clearance plotted against age. **b** Residual clearance against bilirubin. Residual clearance is defined as the individual predicted clearance for a patient minus the population estimate. **a** Patients less than 10 years of age generally have SN-38 clearances greater than expected based on the population estimate. **b** Patients with a bilirubin greater than 0.6 mg/dL generally have SN-38 clearances less than expected based on the population estimate. The *solid lines* in both figures represent the LOESS fit of residual clearance

table also shows, similar results are seen for the group of patients who received irinotecan at other doses (30, 39, and 65 mg/m$^2$). The predictive check $p$ values for irinotecan and its metabolites are between 0.06 and 0.68 for this group. Overall, the model does an adequate job of predicting the median AUCs of irinotecan and its metabolites for the two populations of patients used in model evaluation.

## Discussion

The results of the first pediatric population pharmacokinetic model for irinotecan are reported here. A six-compartment model with allometric scaling based on corrected body weight was found to provide the best fit to the plasma concentration data for irinotecan and its metabolites APC, SN-38, and SN-38G. Bilirubin and patient age were found to be covariates that influenced the clearance of irinotecan's active metabolite SN-38.

Our pediatric population model has several similarities to what has been reported for irinotecan pharmacokinetics in adults. Klein et al. [22] developed a population model for irinotecan in adult patients that included three compartments for irinotecan, two for SN-38, and one for SN38-G. Although, our model has a slightly different structure for irinotecan (only two compartments were needed to fit our data), the estimated irinotecan clearance is similar [22]. Klein et al. [22] determined for their population that irinotecan clearance was 25.2 L/h and that it increased 2.1 L/h for every 10 years younger than 60 years. Extrapolating these results to a 40 kg 10-year old, Klein et al. would estimate irinotecan clearance to be 35.7 L/h, while our model would estimate 34.2 L/h. Additionally, Klein et al. observed that patients with higher total serum bilirubin (>0.9 mg/dL) had increased SN-38 exposure. In a phase I study of patients with hepatic or renal dysfunction Venook et al. [46] also found that elevated bilirubin levels had the most significant impact on SN-38 exposure and were associated with increased toxicity. In our pediatric analysis, we also saw a relationship between bilirubin and SN-38 exposure even though all the patients had normal bilirubin (total bilirubin <1.5 mg/dL). The fact that within the range of normal bilirubin we observed two populations (one with lower SN-38 clearance and one with higher SN-38 clearance) suggests that bilirubin may be a weak marker for genetic variation in conjugation since the genetic basis for differences in SN-38 clearance has been related to genetic polymorphisms in conjugation enzymes. This observation has been reported in prior studies of both adults and children [22, 42]. The results of our study, taken together with adult studies [39, 46] also suggest that elevated bilirubin may be a predictor of increased SN-38 exposure and that pediatric patients with elevated bilirubin levels may be at increased risk of irinotecan toxicity and further study should be considered.

The inclusion of age in the population model as a covariate is largely empiric. However a frequent observation in studies of drugs metabolized in the liver is an age-dependent increase in plasma clearance in children younger than 10 years of age [20]. Part of this age-related increase is due to liver size. Liver mass as a percentage of total body mass reaches a maximum between 1 and 3 years of age and declines to adult values by adolescence. However, for some drugs the clearance is increased in younger children even after correction for liver weight [20].

The identification of covariate effects in small and moderately sized studies can be challenging. Covariate relationships can be hidden or falsely induced due to "shrinkage"

**Table 2** Population pharmacokinetic parameter estimates

| Parameter | Point estimate | Units | SE | RSE (%) | Coefficient of variation[3] (%) |
|---|---|---|---|---|---|
| $\theta_{\text{CL-CPT11}}$ | 34.2 | L/h | 3.17 | 9.3 | NA |
| $\theta_{\text{Vc-CPT11}}$ | 95.5 | L | 11.7 | 12.3 | NA |
| $\theta_{\text{Vp-CPT11}}$ | 101 | L | 13.7 | 13.6 | NA |
| $\theta_{\text{Q-CPT11}}$ | 23.1 | L/h | 1.13 | 4.9 | NA |
| $\theta_{\text{V-APC}}$ | 56.8 | L | 9.43 | 16.6 | NA |
| $\theta_{\text{CL-APC}}$ | 30.5 | L/h | 4.17 | 13.7 | NA |
| $\theta_{\text{Vc-SN38}}$ | 19.9 | L | 4.32 | 21.7 | NA |
| $\theta_{\text{CL-SN38}}$ (total bilirubin < 0.6 mg/dL) | 72.7 | L/h | 8.30 | 11.4 | NA |
| $\theta_{\text{CL-SN38-BILI}}$ (total bilirubin > 0.6 mg/dL) | 45.4 | L/h | 8.96 | 19.7 | NA |
| $\theta_{\text{CL-SN38-AGEFF}}$ | 0.091 | $\text{Year}^{-1}$ | 0.025 | 27.5 | NA |
| $\theta_{\text{Vp-SN38}}$ | 737 | L | 130 | 17.6 | NA |
| $\theta_{\text{Q-SN38}}$ | 42.8 | L/h | 1.63 | 3.8 | NA |
| $\theta_{\text{V-SN38G}}$ | 10.4 | L | 1.66 | 16.0 | NA |
| $\theta_{\text{CL-SN38G}}$ | 26.7 | L/h | 3.20 | 12.0 | NA |
| $\omega^2{}_{\text{CL-CPT11}}{}^{1}$ | 0.118 | NA | 0.0301 | 25.5 | 34.4% |
| $\omega^2{}_{\text{Vc-CPT11}}$ | 0.191 | NA | 0.0784 | 41.0 | 43.7% |
| $\omega^2{}_{\text{Vp1-DOX}}$ | 0.326 | NA | 0.000373 | 0.1 | 57.1% |
| $\omega^2{}_{\text{V-APC}}$ | 0.344 | NA | 0.0997 | 29.0 | 58.7% |
| $\omega^2{}_{\text{CL-APC}}$ | 0.308 | NA | 0.0941 | 30.6 | 55.5% |
| $\omega^2{}_{\text{Vc-SN38}}$ | 0.220 | NA | 0.277 | 125.9 | 46.9% |
| $\omega^2{}_{\text{CL-SN38}}$ | 0.214 | NA | 0.0540 | 25.2 | 46.3% |
| $\omega^2{}_{\text{V-SN38G}}$ | 0.134 | NA | 0.0975 | 72.8 | 36.6% |
| $\omega^2{}_{\text{CL-SN38G}}$ | 0.357 | NA | 0.0961 | 26.9 | 59.7% |
| $\sigma^2{}_{\text{Proportional, CPT11}}{}^{2}$ | 0.0705 | NA | 0.00718 | 10.2 | 26.6% |
| $\sigma^2{}_{\text{Proportional, APC}}$ | 0.0203 | NA | 0.00213 | 10.5 | 14.2% |
| $\sigma^2{}_{\text{Proportional, SN38}}$ | 0.0560 | NA | 0.00425 | 7.6 | 23.7% |
| $\sigma^2{}_{\text{Proportional, SN38G}}$ | 0.0530 | NA | 0.00445 | 8.4 | 23.0% |

$\omega^2$ Random-effect parameter that represents interpatient variance; $\sigma^2$ random-effect parameter that represents residual (intrapatient) variance; % CV calculated as the square root of interpatient variance ($\omega^2$) or the square root of proportional residual (intrapatient) variance ($\sigma^2$)

of the post-hoc parameter estimates toward the population mean [18]. However, our analysis (82 patients) should have data sufficiently rich to characterize interpatient variation. Consequently, we do not expect shrinkage to be a significant issue. In addition, the interpatient variability we observed is of similar magnitude to what has been reported in other studies [22, 49]. Our analysis was also aimed primarily at generating hypotheses regarding covariate parameter relationships. The covariate parameter relationships identified in our study need to be further evaluated before dosing adjustments are considered. The patients that were enrolled on the COG studies we used for model building tolerated irinotecan well regardless of age or bilirubin. However, these studies did not include infants or patients with liver dysfunction where dose adjustment could be required. Additional studies in patients from these populations should be considered.

Our model includes allometric scaling of pharmacokinetic parameters based on weight. We chose this approach because it is generally accepted that clearance correlates with body size in an allometric relationship. In the process of model development we found that the pharmacokinetic parameters correlated best when scaled allometrically on corrected body weight (CBW). However, we do not expect the difference between allometric scaling based on corrected body weight and linear scaling on body surface area to be clinically relevant in most children (patients age 1–18). Body surface area based dosing is well-established historically in this population and should be adequate. However, for infants (patients age <1 year), scaling dosage based on body surface area has proven problematic with some chemotherapy agents [9, 29], and may need to be evaluated for irinotecan.

The validity of the final model was evaluated by simulating studies that were not used in the model building process. This method was chosen because it is the most robust approach for model evaluation. AUC (rather than peak concentration or average concentration) was chosen as the metric for comparing the model simulations to the observed data because toxicity has been most closely linked to exposure.

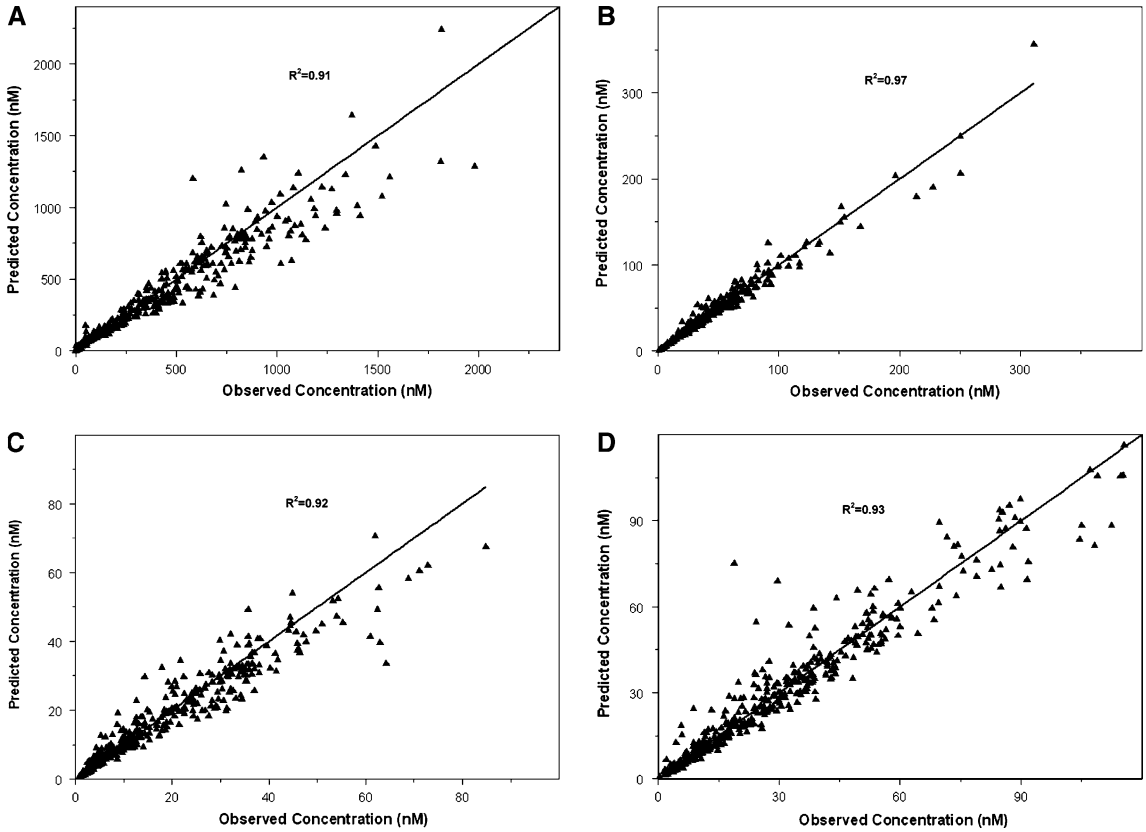


**Fig. 4** Scatterplots of predicted concentrations versus observed concentrations. **a** Results for CPT-11, **b** results for APC, **c** results for SN-38, **d** results for SN-38G. The line of identity is included for comparison

**Table 3** Model evaluation

| Category | Observed median AUC (nM-h) | Simulated median AUC range (nM-h) | *p* Value |
|---|---|---|---|
| Group 1 | | | |
| Daily dosing at 50 mg/m$^2$ ($N$ = 25 patients) | | | |
| CPT-11 | 2,827 | 2,244–3,725 | 0.56 |
| APC | 415 | 263–766 | 0.43 |
| SN-38 | 148 | 95–176 | 0.89 |
| SN-38G | 294 | 168–445 | 0.77 |
| Group 2 | | | |
| Daily dosing at 30–65 mg/m$^2$ ($N$ = 14 patients) | | | |
| CPT-11 | 2,032 | 1,507–2,802 | 0.41 |
| APC | 303 | 230–742 | 0.06 |
| SN-38 | 101 | 58–142 | 0.68 |
| SN-38G | 206 | 121–340 | 0.55 |

The evaluation process showed that the model was predictive for the dose most commonly used in Children's Oncology Group trials (50 mg/m$^2$), as well as for other doses used on a daily schedule (30, 39, and 65 mg/m$^2$).

In conclusion, a population pharmacokinetic model was developed for irinotecan and its metabolites in pediatric patients. Age and bilirubin were found to be significant covariates that influenced the clearance of irinotecan's active metabolite SN-38. As demonstrated by the model evaluation, the final population pharmacokinetic model has good predictive performance for the dosing schedule used in the model building data set (50 mg/m$^2$ daily) and similar daily dosing schedules (30, 39, and 65 mg/m$^2$).

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