Received: 4 October 2023 | Revised: 17 January 2024 | Accepted: 13 March 2024

DOI: 10.1002/psp4.13136

ARTICLE

Population pharmacokinetics of intraperitoneal irinotecan and SN-38 in patients with peritoneal metastases from colorectal origin

Pascale C. S. Rietveld[1,2,3] | **Sebastiaan D. T. Sassen**[1,3] | **Niels A. D. Guchelaar**[2] | **Ruben A. G. van Eerden**[2] | **Nadine L. de Boer**[4] | **Teun B. M. van den Heuvel**[5] | **Jacobus W. A. Burger**[5] | **Ron H. J. Mathijssen**[2] | **Birgit C. P. Koch**[1,3] | **Stijn L. W. Koolen**[1,2]

[1]Department of Clinical Pharmacy, Erasmus MC, Rotterdam, The Netherlands

[2]Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands

[3]Rotterdam Clinical Pharmacometrics Group, Rotterdam, The Netherlands

[4]Department of Surgical Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands

[5]Department of Surgery, Catharina Hospital, Eindhoven, The Netherlands

Correspondence
Pascale C. S. Rietveld, Department of Medical Oncology and Department of Clinical Pharmacy, Erasmus MC, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands.
Email: p.rietveld@erasmusmc.nl

Abstract

Peritoneal metastases (PM) are common in patients with colorectal cancer. Patients with PM have a poor prognosis, and for those who are not eligible for cytoreductive surgery (CRS) with or without hyperthermic intraperitoneal chemotherapy (HIPEC), palliative chemotherapy is currently the only option. Recently, we conducted a phase I trial (INTERACT) in which irinotecan was administered intraperitoneally (IP) to 18 patients ineligible for CRS-HIPEC. The primary objective was to evaluate covariates influencing the PK profile of irinotecan and SN-38 after IP administration. Secondly, a population PK model was developed to support the further development of IP irinotecan by improving dosing in patients with PM. Patients were treated with IP irinotecan every 2 weeks in combination with systemic FOLFOX-bevacizumab. Irinotecan and SN-38 were measured in plasma (588 samples) and SN-38 was measured in peritoneal fluid (267 samples). Concentration-Time data were log-transformed and analyzed using NONMEM version 7.5 using FOCE+I estimation. An additive error model described the residual error, with inter-individual variability in PK parameters modeled exponentially. The final structural model consisted of five compartments. Weight was identified as a covariate influencing the SN-38 plasma volume of distribution and GGT was found to influence the SN-38 plasma clearance. This population PK model adequately described the irinotecan and SN-38 in plasma after IP administration, with weight and GGT as predictive factors. Irinotecan is converted intraperitoneal to SN-38 by carboxylesterases and the plasma bioavailability of irinotecan is low. This model will be used for the further clinical development of IP irinotecan by providing dosing strategies.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Colorectal cancer patients with peritoneal metastases (PM) have a poor prognosis and limited treatment options. Intraperitoneal (IP) chemotherapy with irinotecan may be a promising treatment against PM. There is limited knowledge on the PK of IP irinotecan and active metabolite SN-38 following IP administration.

WHAT QUESTION DID THIS STUDY ADDRESS?

What is the irinotecan and SN-38 exposure after IP administration and can we identify covariates influencing the PK.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Our developed five-compartment population PK model adequately described the irinotecan and SN-38 plasma concentrations after IP administration, with weight and GGT as predictive factors. Irinotecan converted IP to SN-38 and the plasma bioavailability of irinotecan is low.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

This model will be used as a tool for the further clinical development of IP irinotecan and support our gastric cancer clinical trial and phase II colorectal cancer trial. Model-informed dose escalation strategies will be used to advance intraperitoneal chemotherapy treatment strategies.

INTRODUCTION

Colorectal cancer (CRC) is a highly prevalent malignancy, accounting for approximately 10% of all cancer diagnoses worldwide.[1] At diagnosis, peritoneal metastases (PM) are present in about 5% of patients with CRC (called synchronous PM).[2] Moreover, 20% of the patients develop PM during the disease course after an initial curative treatment (called metachronous PM).[3,4] The current standard of care for patients with peritoneal disease comprises of cytoreductive surgery (CRS) with or without heated intraperitoneal chemotherapy (HIPEC).[5] Unfortunately, only the subgroup of patients with limited peritoneal disease (with a Peritoneal Cancer Index (PCI) < 20) are eligible for this treatment.[6] The PCI can be determined by the sum of the scores of 13 abdominal regions. Each area is given a rating between 0 and 3, depending on the size of the biggest tumor found in the region. The total score can range from 0 to 39, with higher scores indicating a more extensive peritoneal spread.[7] Most patients with PM have a PCI >20 and are therefore not eligible for this treatment (only 10%–15% of the patients undergo CRS-HIPEC treatment).[8] For the ineligible patients, palliative systemic chemotherapy or best supportive care are the only available treatment options. These are associated with low survival rates, with a median overall survival of 10–14 months for palliative systemic chemotherapy and 6–8 months for best supportive care.[8,9]

This unfavorable prognosis could arise from the inability of palliative systemic chemotherapy to penetrate the peritoneal plasma barrier. This has led to the exploration of novel therapeutic strategies, such as catheter-based repeated intraperitoneal chemotherapy.[7] Recently, we conducted a phase I trial (INTERACT) in which irinotecan was administered intraperitoneally (IP) to patients ineligible for CRS-HIPEC treatment due to too extensive peritoneal disease or an unresectable primary tumor.[10,11] Through this local administration, a slow IP clearance is anticipated, resulting in a high cumulative local exposure to the peritoneal lesions and a low systemic exposure.[12–14]

Irinotecan is a widely used chemotherapeutic agent that is converted in the blood, liver, and intestines into the active metabolite SN-38, a Topoisomerase-I (TOP-I) inhibitor that is up to 1000 times more cytotoxic than its parent and primarily responsible for the anticancer effect of irinotecan.[15,16] The metabolization of irinotecan to SN-38 is initiated by carboxylesterases (CES) through hydrolysis.[17] The mechanism of action of irinotecan, and the highly potent SN-38, is through inhibition of TOP-I, an enzyme with a crucial role in the DNA replicating process.[18] Colorectal cancer cells are more likely to respond to irinotecan treatment as they tend to have a higher expression of TOP-I compared to normal mucosa.[19] SN-38 is inactivated through glucuronidation by UGT1A enzymes in the liver and gut, followed by renal

secretion. Irinotecan is also broken down into inactive metabolites by hepatic CYP3A4 conversion and subsequently excreted in the bile.

In the INTERACT trial, the maximum tolerated dose (MTD) for IP irinotecan was established at 75 mg two-weekly in combination with standard systemic treatment consisting of 5-fluorouracil/leucovorin with oxaliplatin (FOLFOX) and the targeted agent bevacizumab. This MTD was generally well tolerated and out of the total patients, 13 exhibited a partial radiologic response, five experienced stable disease, and four achieved a complete peritoneal tumor response.[11] Intraperitoneal exposure of SN-38 was highly variable and not dose-proportional.

The intraperitoneal administration of irinotecan in patients with PM may be a favorable method to achieve a high concentration in the local area. Yet, there is limited data about the pharmacokinetics (PK) of irinotecan and SN-38 following intraperitoneal administration. The primary objective of this study was to get a better understanding of the irinotecan PK and to identify covariates that influence the PK profile of irinotecan and SN-38 after IP administration. Secondly, a population PK model was developed to support the further development of IP irinotecan for patients with PM from colorectal origin.

METHODS

Study design and study population

Data for the population PK study were obtained from a phase I study (INTERACT) of two-weekly irinotecan in combination with FOLFOX-bevacizumab in patients with PM from colorectal origin.[10,11] The protocol received approval from the Central Committee on Research Involving Human Subjects, the Erasmus MC Medical Research and Ethics Committee, and the board of directors of Erasmus MC and Catharina Hospital. The trial adhered to Good Clinical Practice guidelines and the Declaration of Helsinki, with all patients providing written informed consent before study-related procedures.[11] In total, 18 patients were treated with intraperitoneal irinotecan in this phase I study. Patients were aged ≥18 years, had a diagnosis of histologically proven CRC, and had extensive peritoneal disease (i.e. PCI > 20) without other extra-abdominal metastases. The administered doses of IP irinotecan ranged from 50 to 100 mg and dose escalation was performed according to a classic 3 + 3 dose escalation design.[10] Irinotecan was prewarmed to 37°C and administered simultaneously with systemic chemotherapy in 1.5 h.

Pharmacokinetic sample collection

Peritoneal fluid samples were collected through a peritoneal access port that was connected to a catheter with a multi-fenestrated tip positioned within the pouch of Douglas. This port served a dual purpose as both the entry point for administering the treatment and for pharmacokinetic sample collection. IP samples were taken predose, 30 min, 1, 1.5, 2, 3, 4, 6, 22.5, and 46.5 h after infusion. Additionally, after collecting each sample, the catheter was flushed with NaCl. Plasma samples were taken at the same intervals, plus one additional sample at 45 min after the start of infusion. Irinotecan and SN-38 were measured in plasma and SN-38 was measured in peritoneal fluid. Samples were taken in a lithium-heparin tube and stored at ≤70°C until analysis.

Determination of irinotecan and SN-38

Plasma samples were centrifuged (10 min at 2500 g, 4°C) following analysis of both plasma and peritoneal samples using a validated Liquid chromatography-mass spectrometry (LC–MS/MS) method. Irinotecan and SN-38 were measured in plasma and SN-38 was measured in peritoneal fluid. The Lower Limit of Quantification (LLQ) for irinotecan and SN-38 in plasma was 1 ng/mL, and for SN-38 IP it was 2 ng/mL.[11]

Population pharmacokinetic modeling

Concentration-time data were natural log-transformed and analyzed using Non-Linear Mixed Effects Modeling (NONMEM) (version 7.5, ICON, Development Solutions, Ellicott City, MD, USA), using First-Order Conditional Estimation with Interaction. For the model development, Pirana software version 2.9.9 (Certara, NJ, USA), R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria), and Xpose4 version 4.7.2 were used. Initially, a one-compartment model with first-order absorption was tested. Then multi-compartmental models for irinotecan and SN-38 were constructed, up to 3-compartments for irinotecan and 2-compartments for SN-38. An additive error model was used to describe the residual error. Inter-individual variability (IIV) of PK parameters was modeled exponentially.

After the structural model, different covariate models were evaluated. The following covariates were tested on the model: UGT1A1 genotypes, PCI scores, BSA, WT, BMI, sex, age, hepatic function, and smoking status. Continuous variables were centered at their median and modeled as exponential and power functions. Categorical variables

were modeled as proportional functions. Stepwise forward inclusion ($p < 0.05$) and backward elimination ($p < 0.01$) were used for the establishment of parameter-covariate relationships.

Model evaluation

Models were evaluated based on the drop in Objective Function Value (OFV) and graphical representations of goodness of fit. A drop in OFV greater than 3.84 for a change of one degree of freedom between two nested models was considered significant ($p < 0.05$). Visual predictive checks, ETA distributions, estimate precision (<50%), shrinkage (<25%), conditional number (<1000), check for high correlation/covariance, and successful minimizations were used to assess model fit and a non-parametric bootstrap procedure ($n = 1000$) was used for model validation.

Calculation of the bioavailability of irinotecan and SN-38

Using Equation 1, we computed the bioavailability of IP irinotecan. The plasma AUCs were normalized to the administered irinotecan dose. As the INTERACT study did not involve the administration of IV irinotecan, we utilized the calculated plasma AUCs from our previous IV irinotecan study.[15] In the DIRINO study, where the influence of protein and calorie restriction on irinotecan PK was studied, a plasma AUC_{0-24h} of 22.37 μg h/mL (irinotecan) was calculated after infusion of 600 mg IV irinotecan to patients without diet restrictions.[15] The INTERACT study estimated plasma AUCs for irinotecan between 892.8 ng h/mL (50 mg IP) and 2391.7 ng h/mL (100 mg IP).[11]

$$F = \left(AUC_{IP} / Dose\right) / \left(AUC_{IV} / Dose\right) \quad (1)$$

The SN-38 AUC_{0-48h} were computed using our developed population PK model and used to calculate the $AUC_{IP/IV}$ ratio in our population.

RESULTS

Patients and samples

Table 1 presents the baseline patient characteristics. Drug concentrations from 11 time points of irinotecan (334 samples) and SN-38 (258 samples) in plasma and concentrations of SN-38 in peritoneal fluid (263 samples) were quantified (Figures S1–S3). A total of 855 PK samples were collected in blood (592 samples) and peritoneal fluid (263 samples), and used to construct a population PK model. One measured concentration of SN-38 in plasma at time point 48 h was censored as it was the only value among 18 samples collected at this time point to exceed the lower limit of quantification (LLOQ). There were no noticeable differences between the first and second treatment cycles. Furthermore, Inter Occasion Variability (IOV) was tested but led to no significant model improvement. As there was no accumulation, data from the first two treatment cycles were combined, and reported as concentrations at time after dose (TAD). The M3 method has been identified as the most effective for handling BLOQ data in NONMEM.[20,21] Using the M3 method resulted in equal parameter estimates and did not result in model improvement. This was not further pursued to maintain model simplicity.

TABLE 1 Baseline patient characteristics of study population.

	Overall ($n = 18$)
Sex	
Female	6
Male	12
Age (years), median (min, max)	64 (42, 77)
PCI score, median (min, max)	29 (17, 39)
BMI (kg/m^2), median (min, max)	26.9 (20.9, 31.8)
Weight (kg), median (min, max)	79.7 (59, 105)
Height (cm), median (min, max)	177 (163, 192)
BSA (m^2), median (min, max)	1.97 (1.65, 2.33)
Smoking status	
Smoker	4
Ex-smoker	6
Non-smoker	6
Unknown	2
ECOG performance score	
0	12
1	6

Abbreviations: BMI, body mass index; BSA, body surface area; ECOG, Eastern Cooperative Oncology Group; PCI, Peritoneal Cancer Index.

Compartmental population PK model

The optimal structural model (Figure 1) consisted of an integral model combining a two compartments model for irinotecan (plasma and peripheral) with single compartments for SN-38 (plasma and IP) and inter-individual variability (IIV) was included in the model for SN-38 plasma CL and the volume of distribution (V_d) of the central SN-38 compartment. Incorporating IIV to the IP compartment

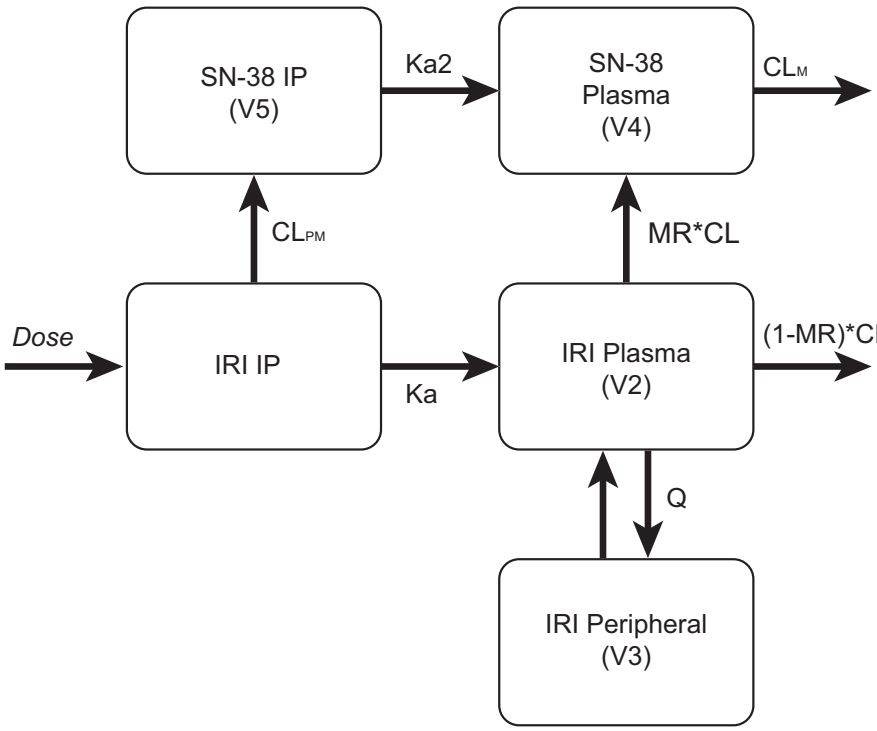

FIGURE 1 Final structural model for irinotecan and SN-38.

to explain some of the variability improved its numerical performance, but not its visual representation. The final parameter estimates are summarized in Table 2. The percentage of central irinotecan converted to SN-38 was fixed at 3%, based on the literature, which resulted in the best model fit and stability.[22] High covariance was identified between the SN-38 IP volume of distribution (V5) and the IP conversion rate to SN-38 (CL_{PM}). As a result, although estimating V5 was feasible, the value was fixed to the estimated parameter value due to model instability. The estimated value was subsequently used as a fixed parameter for future model refinements. First, V5 was fixed to the value suggested by Ahn et al.[23] However, this approach was discarded due to unsatisfactory numerical and visual model fit. The IIV was estimated using an exponential error model. Residual unexplained variability (RUV) was described using an additive error model on log-transformed.

Covariates

Physiologically plausible covariate-parameter relationships were tested numerically and through visual inspections. After the univariate analysis, the influence of sex and age on irinotecan plasma clearance, GGT on SN-38 plasma clearance, and BMI, BSA, and weight on SN-38 plasma V_d were found significant. Collinearity between body measurements led to the inclusion of only weight in the model due to the largest decrease in OFV and model stability. Sex and age were excluded during the backward elimination process due to insufficient impact on the model ($p > 0.01$). Weight and GGT were included as covariates in the final model.

A median (Weight 83.4 kg) normalized power function was used to capture the covariate-parameter effect of weight on SN-38 plasma clearance (Equation 2). Adding the effect of weight improved the model fit by a dOFV of −15 ($p < 0.001$).

$$\theta_{\text{pop.cov}} = \theta_{\text{pop}} * (\text{Weigth}/83.4)^{\theta_{\text{cov}}} \quad (2)$$

A similar method to estimate the effect of GGT on SN-38 plasma clearance was utilized (Equation 3) and improved the model fit by a dOFV of −20 ($p < 0.001$).

$$\theta_{\text{pop.cov}} = \theta_{\text{pop}} * (\text{GGT}/32)^{\theta_{\text{cov}}} \quad (3)$$

Simulations for the effect of WT and GGT on SN-38 plasma V_d and clearance were performed. Predictions for a typical patient (PRED) for three WT and GGT quantiles of the study population were performed; Q1, median, and Q3. The difference in maximum concentration decreases abundantly with increasing weight due to the effect on SN-38 plasma V_d (Figure 2). Moreover, elevated GGT levels reduced SN-38 plasma clearance, leading to increased plasma concentrations (Figure 3).

Model evaluation

The VPC plots for the irinotecan and SN-38 plasma compartments show that the observations were adequately

TABLE 2 Parameter estimates of the final population PK model of IP irinotecan and SN-38.

Parameter (Unit)	Parameter estimate [Shrinkage]	RSE (%)	Bootstrap median	95% CI bootstrap
Ka (h^{-1})	1.02	9	1.002	(0.85–1.2)
MR	0.03	FIX	0.03	FIX
CL (L/h)	33.2	6	33.06	(29.4–36.99)
V2 (L)	225	11	222.65	(175.44–269.42)
Q (L/h)	13.9	17	14.143	(9.46–21.24)
V3 (L)	119	14	120.71	(87.06–159.97)
V4 (L)	15.9	26	15.74	(5.187–27.50)
CL_M (L/h)	46	12	45.57	(36.57–57.15)
CL_{PM} (h^{-1})	0.118	14	0.117	(0.09–0.156)
Ka2 (L/h)	4.68	15	4.583	(3.49–6.3)
V5 (L)	487	FIX	487	FIX
Covariates				
WT	5.31	30	5.663	(1.63–11.31)
GGT	−0.26	35	−0.257	(−0.37, −0.026)
IIV				
CL_M (CV%)	37.9 [0.1]	14	38.54	(25.8–49.53)
V4 (CV%)	84.6 [20]	34	86.88	(13.76–204.48)
Residual error				
Add ERR CMT 2	0.427 [0.1]	8	0.416	(0.34–0.49)
Add ERR CMT 4	0.247 [6]	12	0.240	(0.18–0.3)
Add ERR CMT 5	0.587 [0.1]	9	0.580	(0.46–0.66)
Conditional number	400.41			

Abbreviations: Add ERR CMT 2, additive error on irinotecan plasma compartment; Add ERR CMT 4, additive error on SN-38 plasma compartment; Add ERR CMT 5, additive error on SN-38 IP compartment; CI, confidence interval; CL, irinotecan plasma clearance; CL_M, SN-38 plasma clearance; CL_{PM}, parent to metabolite conversion rate; GGT, gamma-glutamyltransferase on SN-38 plasma clearance; IIV-CL, inter-individual variability on irinotecan plasma clearance; IIV-CL_M, inter-individual variability on SN-38 plasma clearance; IIV-V2, inter-individual variability on irinotecan central volume of distribution; IIV-V4, inter-individual variability on SN-38 central volume of distribution; Ka, irinotecan absorption rate constant; Ka2, SN-38 absorption; MR, metabolic ratio; Q, intercompartmental clearance of central and peripheral irinotecan; RSE, relative standard error; V2, irinotecan central volume of distribution; V3, irinotecan peripheral volume of distribution; V4, SN-38 plasma volume of distribution; V5, SN-38 IP volume of distribution; WT, weight on SN-38 central volume of distribution.

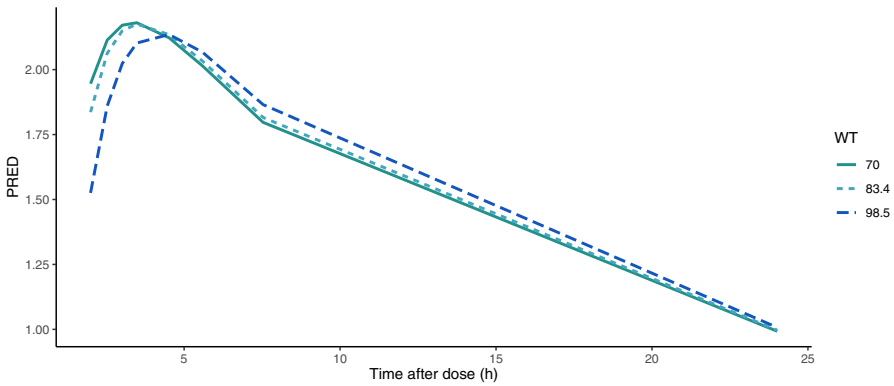

FIGURE 2 Parameter-covariate relationship of WT on SN-38 central volume of distribution. Simulations of SN-38 plasma compartment PRED for Q1, Median, and Q3 of the population WT.

described by the model (Figure 4). Overall, the percentiles (2.5th, 50th, and 97.5th) of observed concentrations were within the predicted 95% confidence interval of these percentiles, suggesting an accurate model fit. The goodness of fit (GOF) plots in Figure S4A–D confirm the good agreement between predicted and observed values for the irinotecan central compartment. The observed SN-38 plasma concentrations were also adequately described by the model except for a misspecification in the lowest concentrations at 24 h post-dose. No visible bias was detected in the CWRES vs time after dose and PRED for irinotecan and SN-38 plasma concentrations (Figures S4C,D and

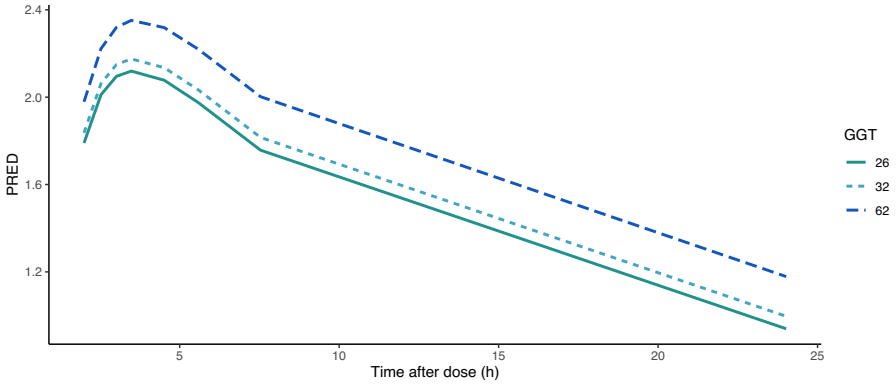

FIGURE 3 Parameter-covariate relationship of GGT on SN-38 plasma clearance. Simulations of SN-38 plasma compartment PRED for Q1, median, and Q3 of the population GGT.

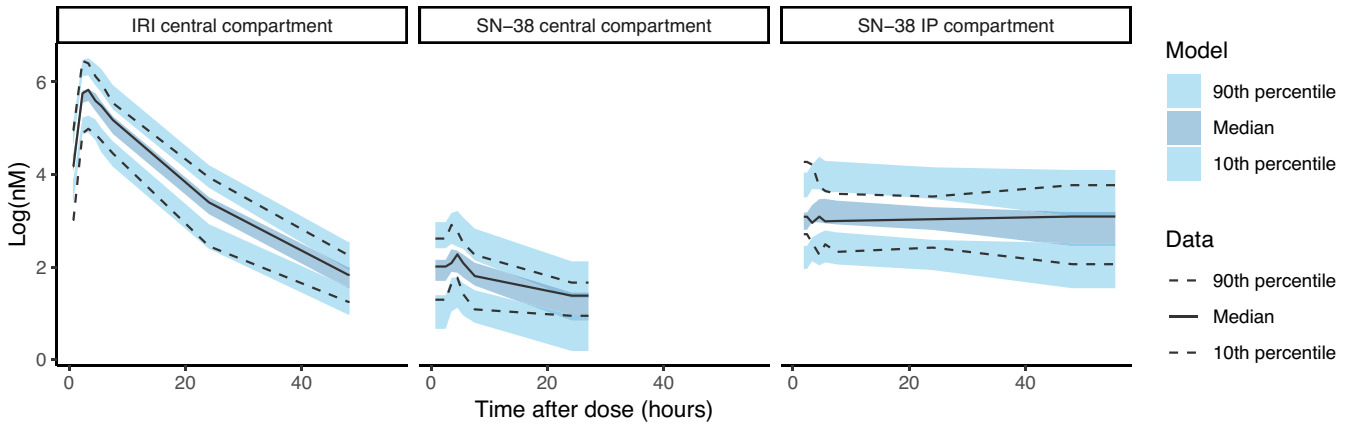

FIGURE 4 Visual Predictive Check for irinotecan in plasma (left) and SN-38 in plasma (center) and IP (right). Solid lines and dark blue areas represent the median observed values and simulated 90% CIs. Dashed lines and light blue areas represent the 10% and 90% percentiles of the observed values and 90% CIs of the simulated percentiles. Visual predictive checks consisted of 1000 simulations each. CIs, confidence intervals.

TABLE 3 Bioavailability of IP irinotecan and SN-38.

		50 mg ($n=4$)	75 mg ($n=9$)	100 mg ($n=5$)
Irinotecan	Plasma AUC_{0-24h} (ng h/mL)[a,11]	892.8	1947.1	2391.7
	F	0.479	0.696	0.641

Abbreviation: AUC, area under the curve.

[a]Data presented as geometric mean.

S5C,D). The SN-38 IP VPC plot (Figure 4) overall shows a good fit. However, there was some model misspecification at the lowest time points ($t=0$–5 h). The model does not fully capture the fast IP SN-38 formation resulting from IP irinotecan conversion, as for some patients a high initial value is observed, and for some a low value that gradually increases. This misspecification is confirmed by the GOF in Figure S3 and is probably due to high variability in IP concentrations. Mixed modeling was explored to describe the two IP conversion rate groups but a robust fit was not achieved.

The parameter precisions (RSE %) of the estimates for the compartmental population PK model were consistently considerably lower than the maximum values of 35% for fixed effect parameters and 34% for random effect parameters. A nonparametric bootstrap procedure ($n=1000$) was used for model validation.

Calculation of the bioavailability of irinotecan and SN-38

The irinotecan plasma bioavailability after IP administration was estimated to be around 63% (Table 3).

The median (min–max) SN-38 AUCs were 43 (17–85) ng h/mL and 205.4 (136–299) ng h/mL for plasma and

peritoneal fluid respectively, resulting in a median SN-38 $AUC_{IP/IV}$ ratio of 4.8.

DISCUSSION

This manuscript provides new insight into the pharmacokinetics of IP-administered irinotecan. Our results demonstrate the occurrence of the IP conversion of irinotecan to SN-38. Yet, the conversion rate is highly variable across all patients. The systemic exposure of irinotecan and SN-38 is low after IP administration and is adequately described by our developed population PK model. The final population PK model consists of 5 compartments and includes weight and GGT as covariates influencing the SN-38 plasma V_d and clearance.

Irinotecan and SN-38 pharmacokinetics are characterized by a large inter-individual variability (IIV), corresponding with our findings on IIV in Table 2.[18,24] Our model adequately described the plasma concentrations of irinotecan, and the estimated irinotecan plasma clearance and central V_d was consistent with previous findings.[18,22,25–27] The systemic metabolic ratio of irinotecan to SN-38 could not be adequately estimated and was therefore fixed at 3% based on IV irinotecan administration in literature.[22] This analysis, which combined PK data from 3 phase I studies (168 PK datasets in 107 patients), revealed a consistent metabolic ratio across various doses of irinotecan, averaging at 3%. Estimation of the SN-38 IP concentrations presented considerable challenges probably due to high inter-patient variability in initial maximum concentration and slope. The SN-38 IP V_d was carefully fixed after testing different values and did not change other parameter estimations. Yet this choice is important to consider in future studies and external validations. One critical factor in our study was the challenge of obtaining certain IP samples, which was occasionally impossible due to tip placement in the abdominal cavity or the absence of intraperitoneal fluids. Another hypothesis regarding the variability of IP SN-38 levels is a change in volume over time due to infusion fluid absorption or development of ascites over time. Furthermore, variations in tumor location, intra-abdominal adhesions, size of peritoneum, peritonectomies, intra-abdominal pressure, peritoneal permeability, and IP presence of CES among patients may also impact the IP PK of irinotecan and SN-38. Previous research has indicated that functional CES1 genes can impact the PK of irinotecan in patients undergoing irinotecan monotherapy.[28] Therefore, it may be relevant to investigate the role of peritoneal CES1 activity in the IP metabolism of irinotecan to SN-38. The abundant presence of CES in the peritoneal cavity rapidly converts IP irinotecan to SN-38, resulting in a high initial concentration of SN-38. In addition, laboratory measurement errors should be considered, yet this is unlikely since the samples were centrifuged and stored immediately after collection. Nonetheless, during an ex vivo experiment in which irinotecan was incubated in ringer lactate as the control, the measurement of SN-38 yielded unexpected results as SN-38 was formed (Figures S7 and S8).

PM and ascites may introduce physiological alterations. In addition, a large bodyweight may cause inflammation and consequently changes in PK. However, definite conclusions could not be reached regarding weight, based on previous studies with IV irinotecan.[29,30] Therefore, this will be investigated thoroughly during the external validation. Here, individuals with a large weight showed a significantly larger central V_d of SN-38. Yet, it should be emphasized that the proposed model is only applicable within the weight range of 60–100 kg and is not generalizable outside this range.

Hepatic function is known to interact with irinotecan PK.[29,31] Patients with higher GGT showed a lower reduction in SN-38 plasma clearance. A correlation between hepatic function and SN-38 plasma clearance is expected as SN-38 mainly metabolized through glucuronidation by the hepatic UGT1A1 family converting it to SN-38G.[18]

Conflicting findings regarding the impact of sex on the PK of irinotecan have been reported in previous studies.[18] Interestingly, prior to the backward elimination process, we observed a reduction in irinotecan clearance in females. Additionally, among the studies that did identify a sex-related influence on irinotecan or SN-38 PK, it was consistently observed that females displayed higher exposure or lower clearance of irinotecan or SN-38.[17,29,32] Despite differences in drug metabolism between men and women, correcting for body measurements generally eliminates most sex-dependent differences.[33]

The phase I INTERACT study findings revealed that within the peritoneal cavity, irinotecan undergoes metabolism to form SN-38. This was confirmed in the ex vivo experiment where we incubated irinotecan in ascites fluid and observed the conversion of irinotecan to SN-38 (Figures S7–S9). In our clinical study, SN-38 IP concentrations were high compared to systemic exposure, indicated by an AUC_{IPIV} ratio of 5.8, and remained present for an extended duration of up to 48 h. Additionally, the relatively low irinotecan bioavailability of 63% is favorable for IP treatment. Sugarbaker concluded in a recent narrative review about HIPEC, that based on pharmacological principles, repetitive intraperitoneal chemotherapy has advantages over traditional HIPEC in patients with PM.[34] Principally, the residence time within a tumor cell is essential and is very limited using a single cycle of perioperative IP chemotherapy.

The advantage of repetitive IP treatment is confirmed by the good response that was accomplished in the majority of patients in our phase I trial using repetitive IP irinotecan.[11] Given that PM is associated with reduced survival, achieving efficacy against tumors in the peritoneal cavity becomes crucial. Consequently, it is reasonable to anticipate that prolonged tumor exposure to chemotherapeutics by repetitive IP administration would lead to improved clinical outcomes. In this regard, IP chemotherapy also holds an advantage over standard systemic chemotherapy, as the extent to which the latter reaches PM remains uncertain. Yet, finding the appropriate dosage remains challenging, as two of our patients encountered dose-limiting toxicities (DLTs) at a relatively low dose of 100 mg, in contrast to the dose used in the previous IP irinotecan study (200 mg/m^2 monotherapy).[25] Comparatively, the systemic exposure of irinotecan and SN-38 was lower in our phase I trial compared to the registered dose of irinotecan monotherapy.[11,15] Therefore, it is important to consider the impact of the IV FOLFOX therapy regarding differences in toxicities.[11]

A previous study examined intra-tumoral concentrations in tumor nodules that were resected after irinotecan IP administration. Interestingly, the concentration was found to be higher in the tumor tissue compared to the surrounding peritoneum.[35] This finding suggests that increased direct exposure leads to a higher concentration of irinotecan within the tumor, indicating a correlation between exposure and intra-tumoral concentration and therefore providing a rationale for IP chemotherapy as to systemic chemotherapy.

Moreover, the tumor load can influence the absorption of irinotecan and SN-38 from the peritoneal cavity into the central compartment, thus affecting IP exposure. An increasing tumor load, indicated by a larger PCI score, may alternate the peritoneal barrier integrity, primarily due to the presence of inflammation.[36] Also, when the chemotherapy enters a vascularized tumor, the drug is rapidly cleared into the body compartment by the capillary blood and lymph flow.[34] However, this study did not uncover any correlation between the PCI score and SN-38 PK.

An important clinical concern revolves around the decision of whether to remove or retain ascites fluid prior to IP chemotherapy. Ascite fluid contains CES (Figure S7), which is essential for converting IP irinotecan into its active metabolite SN-38. In our study, ascites fluid was removed before IP treatment causing a higher IP irinotecan exposure due to increased concentration. Conversely, keeping the ascites fluid in place would dilute the infusion fluid but may result in a higher quantity of CES for irinotecan conversion and therefore SN-38 IP exposure. Our ex vivo study showed that larger amounts of ascites fluid led to increased irinotecan conversion to SN-38. However, due to unknown removed ascites volumes, we could not test the relationship between the volume of ascites fluid removed before treatment and the PK of irinotecan and SN-38. Additionally, it is not possible to remove all ascites prior to treatment.

Although predicting the IP PK presents a challenge, expanding our knowledge regarding the PK of chemotherapeutic agents administered via the IP route can help the development of effective IP therapies, which are promising in treating PM. The PK model we have developed serves as a valuable tool for advancing the clinical development of IP irinotecan through various approaches. Next, our model will be externally validated in the Phase I clinical trial with IP irinotecan in gastric cancer patients (NCT05379790). Additionally, the model will be used to support our Phase I clinical trial with IP irinotecan in gastric cancer and our Phase II CRC trial through simulation studies based on covariates GGT and bodyweight. Through these simulations, we can evaluate whether maintaining a uniform dosage is appropriate or if adjustments are necessary based on the model's information and limited patient sampling. Also, by analyzing the initial PK data using our model, the underlying sources of residual variability will be evaluated. Additionally, the Phase II clinical trial also aims to expand on the potential relationship between exposure and toxicity. Ultimately, our objective is to employ model-informed dose escalation strategies in this context. Additionally, this could enhance our understanding of how PK affects the efficacy and/or adverse effects of IP irinotecan.

One important drawback of this study is the lack of IP measurements for irinotecan, which was due to the access port. The IP samples were collected from the same access port used for the infusion of irinotecan, which prevented the measurement of IP irinotecan to avoid introducing bias. It would have been beneficial to have obtained IP irinotecan measurements over time as it would provide insights into the absorption of irinotecan into the bloodstream or its conversion to SN-38 within the peritoneal cavity.

In conclusion, by establishing this foundation of knowledge, we can pave the way for Model-Informed Precision Dosing in our Phase II CRC study (NCT06003998) and Phase I gastric cancer study (NCT05379790), which has the potential to optimize treatment outcomes in a more personalized manner.

AUTHOR CONTRIBUTIONS

P.C.S.R., S.D.T.S., N.A.D.G., and S.L.W.K. wrote the manuscript. P.C.S.R., S.D.T.S., R.H.J.M., B.C.P.K., and S.L.W.K. designed the research. P.C.S.R., S.D.T.S.,

N.A.D.G., R.A.G.vE., N.L.dB., T.B.M.vdH., and J.W.A.B., and S.L.W.K. performed the research. P.C.S.R. analyzed the data.

FUNDING INFORMATION

No funding was received for this work.

CONFLICT OF INTEREST STATEMENT

The authors declared no competing interests for this work.

ORCID

Pascale C. S. Rietveld https://orcid.org/0009-0001-6039-8458
Sebastiaan D. T. Sassen https://orcid.org/0000-0002-4525-638X
Niels A. D. Guchelaar https://orcid.org/0000-0001-8080-9093
Ron H. J. Mathijssen https://orcid.org/0000-0001-5667-5697

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209-249.
2. Kranenburg O, van der Speeten K, de Hingh I. Peritoneal metastases from colorectal cancer: defining and addressing the challenges. *Front Oncol*. 2021;11:650098.
3. Lurvink RJ, Bakkers C, Rijken A, et al. Increase in the incidence of synchronous and metachronous peritoneal metastases in patients with colorectal cancer: a nationwide study. *Eur J Surg Oncol*. 2021;47(5):1026-1033.
4. van Gestel YR, de Hingh IH, van Herk-Sukel MP, et al. Patterns of metachronous metastases after curative treatment of colorectal cancer. *Cancer Epidemiol*. 2014;38(4):448-454.
5. van Stein RM, Aalbers AGJ, Sonke GS, van Driel WJ. Hyperthermic intraperitoneal chemotherapy for ovarian and colorectal cancer: a review. *JAMA Oncol*. 2021;7(8):1231-1238.
6. Simkens GA, Rovers KP, Nienhuijs SW, de Hingh IH. Patient selection for cytoreductive surgery and HIPEC for the treatment of peritoneal metastases from colorectal cancer. *Cancer Manag Res*. 2017;9:259-266.
7. Guchelaar NAD, Noordman BJ, Koolen SLW, et al. Intraperitoneal chemotherapy for unresectable peritoneal surface malignancies. *Drugs*. 2023;83(2):159-180.
8. Bakkers C, Lurvink RJ, Rijken A, et al. Treatment strategies and prognosis of patients with synchronous or metachronous colorectal peritoneal metastases: a population-based study. *Ann Surg Oncol*. 2021;28(13):9073-9083.
9. Franko J, Shi Q, Goldman CD, et al. Treatment of colorectal peritoneal carcinomatosis with systemic chemotherapy: a pooled analysis of north central cancer treatment group phase III trials N9741 and N9841. *J Clin Oncol*. 2012;30(3):263-267. doi:10.1200/JCO.2011.37.1039
10. de Boer NL, Brandt-Kerkhof ARM, Madsen EVE, et al. Concomitant intraperitoneal and systemic chemotherapy for extensive peritoneal metastases of colorectal origin: protocol of the multicentre, open-label, phase I, dose-escalation INTERACT trial. *BMJ Open*. 2019;9(12):e034508.
11. van Eerden RAG, de Boer NL, van Kooten JP, et al. Phase I study of intraperitoneal irinotecan combined with palliative systemic chemotherapy in patients with colorectal peritoneal metastases. *Br J Surg*. 2023;110(11):1502-1510. doi:10.1093/bjs/znad228
12. Sugarbaker PH, Van der Speeten K, Stuart OA. Pharmacologic rationale for treatments of peritoneal surface malignancy from colorectal cancer. *World J Gastrointest Oncol*. 2010;2(1):19-30.
13. Kobayashi D, Kodera Y. Intraperitoneal chemotherapy for gastric cancer with peritoneal metastasis. *Gastric Cancer*. 2017;20(Suppl 1):111-121.
14. Lagast N, Carlier C, Ceelen WP. Pharmacokinetics and tissue transport of intraperitoneal chemotherapy. *Surg Oncol Clin N Am*. 2018;27(3):477-494.
15. de Man FM, van Eerden RAG, van Doorn GM, et al. Effects of protein and calorie restriction on the metabolism and toxicity profile of irinotecan in cancer patients. *Clin Pharmacol Ther*. 2021;109(5):1304-1313.
16. Thompson PA, Gupta M, Rosner GL, et al. Pharmacokinetics of irinotecan and its metabolites in pediatric cancer patients: a report from the Children's Oncology Group. *Cancer Chemother Pharmacol*. 2008;62(6):1027-1037.
17. Berg AK, Buckner JC, Galanis E, Jaeckle KA, Ames MM, Reid JM. Quantification of the impact of enzyme-inducing antiepileptic drugs on irinotecan pharmacokinetics and SN-38 exposure. *J Clin Pharmacol*. 2015;55(11):1303-1312.
18. de Man FM, Goey AKL, van Schaik RHN, Mathijssen RHJ, Bins S. Individualization of irinotecan treatment: a review of pharmacokinetics, pharmacodynamics, and pharmacogenetics. *Clin Pharmacokinet*. 2018;57(10):1229-1254.
19. Vanhoefer U, Harstrick A, Achterrath W, Cao S, Seeber S, Rustum YM. Irinotecan in the treatment of colorectal cancer: clinical overview. *J Clin Oncol*. 2001;19(5):1501-1518. doi:10.1200/JCO.2001.19.5.1501
20. Bergstrand M, Karlsson MO. Handling data below the limit of quantification in mixed effect models. *AAPS J*. 2009;11(2):371-380.
21. Ahn JE, Karlsson MO, Dunne A, Ludden TM. Likelihood based approaches to handling data below the quantification limit using NONMEM VI [published correction appears in *J Pharmacokinet Pharmacodyn*. 2010 Jun;37(3):305–8]. *J Pharmacokinet Pharmacodyn*. 2008;35(4):401-421. doi:10.1007/s10928-008-9094-4
22. Chabot GG, Abigerges D, Catimel G, et al. Population pharmacokinetics and pharmacodynamics of irinotecan (CPT-11) and active metabolite SN-38 during phase I trials. *Ann Oncol*. 1995;6(2):141-151. doi:10.1093/oxfordjournals.annonc.a059109
23. Ahn BJ, Choi MK, Park YS, et al. Population pharmacokinetics of CPT-11 (irinotecan) in gastric cancer patients with peritoneal seeding after its intraperitoneal administration. *Eur J Clin Pharmacol*. 2010;66(12):1235-1245.
24. Mathijssen RH, Verweij J, Loos WJ, de Bruijn P, Nooter K, Sparreboom A. Irinotecan pharmacokinetics-pharmacodynamics: the clinical relevance of prolonged exposure to SN-38. *Br J Cancer*. 2002;87(2):144-150.
25. Choi MK, Ahn BJ, Yim DS, et al. Phase I study of intraperitoneal irinotecan in patients with gastric adenocarcinoma with peritoneal seeding. *Cancer Chemother Pharmacol*. 2011;67(1):5-11.

26. Xie R, Mathijssen RH, Sparreboom A, Verweij J, Karlsson MO. Clinical pharmacokinetics of irinotecan and its metabolites in relation with diarrhea. *Clin Pharmacol Ther*. 2002;72(3):265-275. doi:10.1067/mcp.2002.126741
27. Mathijssen RH, van Alphen RJ, Verweij J, et al. Clinical pharmacokinetics and metabolism of irinotecan (CPT-11). *Clin Cancer Res*. 2001;7(8):2182-2194.
28. Sai K, Saito Y, Tatewaki N, et al. Association of carboxylesterase 1A genotypes with irinotecan pharmacokinetics in Japanese cancer patients. *Br J Clin Pharmacol*. 2010;70(2):222-233.
29. Klein CE, Gupta E, Reid JM, et al. Population pharmacokinetic model for irinotecan and two of its metabolites, SN-38 and SN-38 glucuronide. *Clin Pharmacol Ther*. 2002;72(6):638-647.
30. Sparreboom A, Wolff AC, Mathijssen RH, et al. Evaluation of alternate size descriptors for dose calculation of anticancer drugs in the obese. *J Clin Oncol*. 2007;25(30):4707-4713.
31. Chabot GG. Clinical pharmacokinetics of irinotecan. *Clin Pharmacokinet*. 1997;33(4):245-259. doi:10.2165/00003088-199733040-00001
32. Slatter JG, Schaaf LJ, Sams JP, et al. Pharmacokinetics, metabolism, and excretion of irinotecan (CPT-11) following I.V. Infusion of [(14)C]CPT-11 in cancer patients. *Drug Metab Dispos*. 2000;28(4):423-433.
33. Soldin OP, Mattison DR. Sex differences in pharmacokinetics and pharmacodynamics. *Clin Pharmacokinet*. 2009;48(3):143-157.
34. Sugarbaker PH. A narrative review of what can HIPEC do. *Eur J Surg Oncol*. 2023;49(9):106976. doi:10.1016/j.ejso.2023.07.002
35. Elias D, Matsuhisa T, Sideris L, et al. Heated intra-operative intraperitoneal oxaliplatin plus irinotecan after complete resection of peritoneal carcinomatosis: pharmacokinetics, tissue distribution and tolerance. *Ann Oncol*. 2004;15(10):1558-1565.
36. Zemel DSD, Dinkla C, Stolk LM, ten Berge IJ, Krediet RT. Effects of intraperitoneal cyclooxygenase inhibition on inflammatory mediators in dialysate and peritoneal membrane characteristics during peritonitis in continuous ambulatory peritoneal dialysis. *J Lab Clin Med*. 1995;126(2):204-215.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Rietveld PCS, Sassen SDT, Guchelaar NAD, et al. Population pharmacokinetics of intraperitoneal irinotecan and SN-38 in patients with peritoneal metastases from colorectal origin. *CPT Pharmacometrics Syst Pharmacol*. 2024;13:1006-1016. doi:10.1002/psp4.13136