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Quantification of the Impact of Enzyme-Inducing Antiepileptic Drugs on Irinotecan Pharmacokinetics and SN-38 Exposure

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Abstract

The population pharmacokinetic model reported herein was developed using data from two phase 2 trials of irinotecan for treatment of malignant glioma in order to quantify the impact of concomitant therapy with enzyme-inducing antiepileptic drugs (EIAEDs) on irinotecan pharmacokinetics. Patients received weekly irinotecan doses of 100 to 400 mg/m² and plasma samples were collected and analyzed for irinotecan and its APC, SN-38 and SN-38G metabolites. Non-linear mixed effects modeling was employed for population pharmacokinetic analysis. Concomitant therapy with phenytoin, phenobarbital or carbamazepine increased the clearances of irinotecan, SN-38 and SN-38G but not APC. SN-38 clearance was 2-fold higher with concomitant EIAED use resulting in 40% lower SN-38 exposure. Evaluation of additional covariates revealed no clinically relevant effects of sex or concomitant corticosteroid use. The population pharmacokinetic model suggests that a 1.7 fold increase in irinotecan dose may compensate for decreases in SN-38 exposure in the presence of concomitant EIAEDs. Although slightly more conservative, this dose adjustment is consistent with those recommended based on increases in maximally-tolerated dose for malignant glioma patients receiving EIAEDs, and may be an appropriate starting point for further investigation when extrapolating to other cancer types or alternative regimens.

Keywords

Irinotecan; SN-38; Enzyme-Inducing Antiepileptic Drugs; Drug-Drug Interaction

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Introduction

The camptothecin derivative, irinotecan (CPT-11), is an S-phase specific inhibitor of the enzyme, topoisomerase I [1]. Irinotecan is a pro-drug which is metabolized to the active moiety, SN-38, as well as the inactive metabolites, APC and SN-38 glucuronide (SN-38G) [2]. The efficacy and toxicity of irinotecan is dependent upon conversion to SN-38, which is > 100x more active than the parent drug [3]. SN-38 is formed through hydrolysis by human carboxylesterases (CES) 1 and 2 and is subsequently eliminated by glucuronidation to SN-38G via the activity of UDP-glucuronosyl transferases (UGT), primarily UGT1A1[1]. In contrast, inactivation of irinotecan through conversion of parent drug to APC and other minor metabolites is a cytochrome P450 (CYP)-mediated process, attributed largely to CYP3A [4].

In addition to the U.S. Food and Drug Administration approved indication for the treatment of metastatic colorectal cancer, irinotecan is used extensively off-label and has been tested in a variety of cancers, including neurological malignancies [5]. Clinical trials investigating irinotecan for activity in malignant glioma and glioblastoma demonstrate that irinotecan is more active than other topoisomerase I inhibitors [6]. Despite limited efficacy as monotherapy, promising results in the treatment of malignant glioma have been obtained for irinotecan in combination with thalidomide, temozolomide, or bevacizumab [6, 7]. Consequently, irinotecan-based combination chemotherapy regimens continue to be actively investigated for the treatment of brain malignancies.

Because irinotecan is highly dependent upon metabolism for activity and elimination, there is a high propensity for altered exposure to the key metabolites due to pharmacokinetic drug-drug interactions (DDIs). The concomitant use of drugs which induce drug metabolizing enzymes may significantly alter the pharmacokinetics of “victim” drugs such as irinotecan, resulting in therapeutic failure or increased toxicity. Drugs which are *in vivo* and/or *in vitro* inducers are frequently encountered in clinical practice, including corticosteroids [8] and the enzyme-inducing antiepileptic drugs (EIAEDs) phenytoin, phenobarbital and carbamazepine [9]. Despite their strong DDI potential, these agents are often necessary in the treatment of many conditions, including brain tumors, given the significant proportion of patients in this population with cerebral edema and/or seizures [10]. While it is now common to use non-enzyme inducing AEDs, until recent years the use of EIAEDs was standard practice to treat seizures secondary to neurological malignancies. Currently, EIAEDs are used for refractory cases and are still widely prescribed to treat epilepsy.

Previous studies evaluating the use of irinotecan in malignant glioma have demonstrated that the efficacy and toxicity of irinotecan is altered by EIAEDs [7, 11-19]. Concomitant administration of EIAEDs resulted in increases in the irinotecan maximally-tolerated dose (MTD), due at least in part to changes in the pharmacokinetics of irinotecan and its metabolites. Consequently, when the concomitant use of these agents cannot be avoided, increased irinotecan dosages are required to ensure that patients receive adequate treatment. Although a range of dose adjustments may be made based on the increased MTDs seen in the earlier studies, this approach is confounded by inter-study differences in treatment

schedule, range of doses, combination regimen and criteria for determination of dose-limiting toxicity (DLT). Moreover, MTD-based dose adjustments may not be sufficient for extrapolation to alternative regimens or different cancer types and thus adjustments based on changes in irinotecan pharmacokinetics may be more appropriate. Hence, a population pharmacokinetic model was developed for irinotecan and its metabolites which builds on earlier models [20-26] and is the first to quantify the drug-drug interaction between EIAEDs and this agent. Using the derived model, dose adjustments required to maintain adequate exposure to SN-38 were determined and compared to previous recommendations in the literature.

Methods

Study population

Data for pharmacokinetic modeling were obtained from two phase 2 studies of irinotecan (Camptosar®; CPT-11) in patients with either newly diagnosed glioblastoma or recurrent glioma (NCCTG trials N997D and 96-72-51, respectively). Both studies received institutional review board (IRB) approval and are described in detail elsewhere [11, 27].

Drug administration and analytical procedure

The irinotecan treatment schedule varied between the two trials used in this analysis. In the first study, patients receiving therapy with or without concomitant EIAEDs were administered weekly doses of irinotecan at 400 mg/m² or 125 mg/m², respectively [11]. Irinotecan dosing in the second study was modified depending upon history of prior chemotherapy with nitrosoureas, with patients who had not previously received nitrosoureas dosed at 125 mg/m² (weekly) or 300 mg/m² (every three weeks) compared to 100 mg/m² (weekly) or 250 mg/m² (every three weeks) for those who had received prior nitrosoureas [27]. Irinotecan was administered as a continuous intravenous infusion over 90 min and blood samples were collected prior to infusion, immediately following infusion, as well as 1, 2, 4 and 24 hours following the end of the infusion on Day 1 of Cycle 1 in both studies. Plasma concentrations of irinotecan, APC, SN-38 and SN-38G were quantified by a validated HPLC method as described previously [11]. A total of 1,723 plasma concentrations were available for analysis, of which 21 SN-38 concentrations reported as below the lower limit of quantitation (LLOQ) of 1 ng/mL were imputed as LLOQ/2.

Population pharmacokinetic analysis

The plasma concentration – time data for irinotecan, APC, SN-38 and SN-38G were analyzed using NONMEM®, Version 7 (ICON Development Solutions, Ellicott City, MD, USA) as implemented through PsN-Toolkit, Version 3.4.2 [28]. Results from NONMEM runs were assessed in R (Version 2.12.2 [29]), using the package, Xpose (Version 4.3.2 [30]). All model evaluations utilized the Monte Carlo Importance Sampling Expectation Maximization method assisted by mode *a posteriori* estimation (IMPMAP) [31]. Default settings were maintained for IMPMAP estimation except for NITER = 5,000 to allow for convergence testing ($\alpha = 0.05$) with CTYPE=3, CINTERVAL=10. Since the slope of the objective function value (OFV) at convergence is not statistically different from zero [31],

the median OFV of the final 10 iterations from the IMPMAP output was used for hypothesis testing.

Appropriate model structures for irinotecan and its metabolites were guided by prior information from previous studies [20-26], as well as the likelihood ratio test, shrinkage estimates, reasonableness of parameter estimates and goodness-of-fit plots [32]. Stepwise structural modeling was conducted by adding data from irinotecan, APC, SN-38 and SN-38G sequentially once a sufficient compartmental model was delineated for the preceding species. All models were first-order, with 1, 2 or 3-compartment models assessed for all drug moieties. Between subject variability (BSV) terms were included for model parameters where supported and were modeled as log-normal with mean 0 and covariance matrix Ω . For diagonal Ω elements, inclusion was based on the likelihood ratio test with significant OFV based on a modified χ^2 distribution for 1 degree of freedom [32]. Off-diagonal Ω elements with correlations having an absolute value ≥ 0.5 were included in the model where possible. Residual unexplained variability (RUV) was modeled using an additive plus proportional error model [32], with separate models for each study.

Covariates available for assessment from both studies included: sex, age, body surface area (BSA), grade of disease, ECOG performance status, dose level as well as corticosteroid (prednisone or dexamethasone) and EIAED use. Patient-specific UGT1A1 genotypes and individual dose levels of corticosteroids and EIAEDs were not available for all patients and thus were not investigated. The effects of corticosteroids and EIAEDs were tested by directly incorporating these effects on all model parameters. Other covariates were included in the model based on generalized additive modeling (GAM) of individual post-hoc BSV parameter estimates and stepwise addition-deletion using the likelihood ratio test, with respective significance levels of 0.05 and 0.01. Continuous covariates were modeled as linear additive effects, whereas categorical covariates were modeled using a fractional change model [32]. Differences in distributions of categorical covariates between subgroups were investigated using either the Pearson χ^2 test or Fisher's exact test.

Throughout model development, jackknife analysis was employed to detect potential outliers [32]. The reliability of final model estimates was assessed by non-parametric bootstrap ($n = 1,000$) with only those runs that terminated successfully used for calculation of relative standard errors and 95% confidence intervals. Model performance was assessed by visual predictive check using 500 replicates of the original dataset and mean parameter estimates. Simulation results were compared graphically by overlaying the 5th, 50th and 95th percentiles from the simulations with observed plasma concentrations. Additionally, the area under the plasma concentration-time curve from time 0 to last measured time point (AUC_{0-t}) was calculated from simulations based on the final population pharmacokinetic model and compared between population subgroups via t-test on log-transformed values.

Results

The combined datasets from the two North Central Cancer Treatment Group (NCCTG) trials provided data from 86 patients for a total of 425 observations each for irinotecan and APC and 426 observations each for SN-38 and SN-38G. Table 1 lists relevant demographic

information for all patients included in the analysis. During model development, several data points were identified as outliers, resulting in the complete removal of one subject from the dataset and single observations from three separate subjects. In the former case, all sample collection times appear to have been incorrectly specified on study source documents whereas for the latter three subjects, the post-infusion blood draw was excluded due to implausibly high irinotecan concentrations (attributed to improper sample collection).

The final compartmental model describing the pharmacokinetics of irinotecan and its metabolites is presented in Figure 1 and is consistent with those previously reported [20-26]. Due to the small number of plasma samples collected per subject in both studies, more complex models featuring enterohepatic recirculation were not evaluated. Corresponding goodness-of-fit plots for the final model are shown in Figure 2 and demonstrate that our model sufficiently describes the pharmacokinetics of irinotecan and its metabolites. Table 2 lists the point estimates as well as the bootstrap means, relative standard errors and 95% confidence intervals for all final model parameters.

A full statistical model including BSV terms on all structural model parameters was initially utilized, but was reduced in the final model as three BSV terms were not statistically significant with stepwise deletion. Data were insufficient to characterize BSV in APC intercompartmental clearance and central volumes of distribution for SN-38 and SN-38G (Q_{APC}/F_{APC} , V_c/F_{SN-38} , V_c/F_{SN-38G} , respectively). Table 2 demonstrates that BSV was moderate with coefficient of variation (% CV) values ranging from 32 – 79%. Individual post-hoc BSV estimates were sufficiently informative for use in covariate assessment as all shrinkage estimates were < 15% [33]. Correlations with an absolute value greater than 0.5 were included where supported. The final model featured a banded Ω matrix, with three separate \$OMEGA blocks specifying correlations between all irinotecan parameters, between all APC parameters and correlations across all SN-38 and SN-38G parameters.

An additive plus proportional error structure was used to model RUV and included separate models for each trial. Notably, jackknife analysis revealed that the removal of one influential patient lead to an 80% decrease in one of the additive RUV parameters. Since inspection of the patient's plasma concentration-time data did not reveal any obvious reason for this influence, this individual was maintained in the dataset but their RUV was modeled as proportional only. The final model estimates listed in Table 2 for the additive and proportional components demonstrate that RUV is low.

The primary objective of this investigation was the quantification of the effect of concomitant use of EIAEDs on the metabolism and disposition of irinotecan. As expected, patients who received concomitant therapy with EIAEDs exhibited higher clearances of irinotecan, SN-38 and SN-38G ($CL_{irinotecan}$, CL_{SN-38} and CL_{SN-38G}) as compared to those who did not (increases of 19.3, 106 and 26.9%, respectively; Table 3). Given the correlation between EIAED status and clearance parameters, attempts were made to differentiate the effects of individual EIAEDs. However, due to the large number of patients on phenytoin relative to carbamazepine and phenobarbital, the data was insufficient to assess differences between the agents. Thus, the effect of EIAEDs was modeled under the assumption that all

EIAEDs would induce irinotecan metabolism to a similar extent at the doses utilized for seizure control.

In order to account for other sources of variability in irinotecan pharmacokinetics, correlations between additional covariates and the pharmacokinetics of the various irinotecan species were evaluated. Previous studies have found that age, sex, BSA and ECOG performance status are correlated with variability in irinotecan pharmacokinetic parameters [20, 24]. These covariates were included among those assessed in the present analysis, as was an additional covariate describing concomitant corticosteroid use. As this latter covariate was of exploratory interest due to the theoretical ability for this drug class to induce irinotecan metabolism, corticosteroid status was tested for significance on all model parameters. The data of Table 3 shows that in contrast to the significant impact of EIAEDs across the irinotecan metabolic pathway, corticosteroid use only affected APC metabolism, increasing APC clearance (CL_{APC}) by 26.7% compared to patients who did not receive corticosteroids.

Of the remaining covariates included in this analysis, only sex and grade 2 disease status were included in the final model along with concomitant EIAED and corticosteroid use. Compared to male patients, females exhibited a 37.7 and 24.3% decrease in CL_{SN-38} and CL_{SN-38G} , respectively. Patients with grade 2 disease were found to have a 17.1% higher clearance than patients with other grades of disease. Overall, inclusion of covariates in the model decreased the respective BSV in $CL_{irinotecan}$, CL_{APC} , CL_{SN-38} and CL_{SN-38G} by 4.0, 2.4, 18.1 and 7.5% and resulted in a OFV of -134.19. Table 3 lists the statistically significant covariates, their effects on the correlated model parameters and the associated p -value from stepwise deletion.

Reliability of the final population pharmacokinetic model parameter estimates was assessed via non-parametric bootstrap, with only small differences noted between bootstrap means and model-derived estimates (Tables 2 and 3). The performance of the final model is illustrated in Figure 3, demonstrating close agreement between observed and simulated plasma concentrations for all irinotecan species. Additional numerical checks comparing geometric means of simulated dose-normalized SN-38 AUC_{0-t} values to those from the original dataset revealed that the latter values were ~17% higher ($p = 0.024$). Upon close inspection, this was attributed to three patients in the non-EIAED group which exhibited abnormally high SN-38 exposures. Although this is reminiscent of the hypothesis that SN-38 population pharmacokinetics may best be modeled as two distinct subgroups [20], a mixture model was not employed as comparison of AUC values after removal of these subjects revealed no statistically significant differences ($p > 0.1$). Hence, it was concluded that the model described herein adequately characterizes the SN-38 disposition in the majority of the patient population.

Discussion

Through the use of population pharmacokinetic modeling, we have quantified the impact of EIAEDs on the pharmacokinetics of irinotecan and its metabolites. Our model is viewed as an extension of earlier population pharmacokinetic models of irinotecan in that it is the first

such model to identify specific portions of the irinotecan metabolic pathway influenced by concomitant EIAED therapy and to quantify the magnitude of the EIAED effects. Moreover, the model described herein also explored the theoretical effect of corticosteroid use on irinotecan pharmacokinetics and supported an earlier observation that sex may play a role in the metabolism and disposition of SN-38 [20]. Based on the favorable results of the bootstrap analysis as well as visual and numerical predictive checks, our model is suitable for clinical use.

The pharmacokinetic model (Figure 1) is in accord with previous reports in the literature for irinotecan and its metabolites [20-26]. In earlier studies, 1, 2 and 3-compartment models have been used to describe the metabolism and disposition of irinotecan, APC and SN-38. SN-38G was best fit by a one-compartment model, a finding consistent with the polar molecular characteristics of this metabolite. It should be noted that while the parameter estimates and bootstrap confidence intervals are in good agreement with those published previously for irinotecan and its metabolites [20-26], earlier estimates for the various pharmacokinetic parameters vary depending upon model structure, parameterization and inclusion of covariates. In our model, parameters describing metabolite disposition are normalized to the fraction of parent drug converted to each metabolite species (*viz.* CL / F_{met}). Consequently, the influence of covariates on the apparent metabolite clearances may be attributed to either changes in metabolite clearance (numerator), or a decrease in the fractional conversion to that metabolite (denominator). In consideration of our results, it was reasoned that changes in the fractional conversion of irinotecan to each metabolite should affect all of the pharmacokinetic parameters for the metabolite in question. This was not observed, as the significant covariates only altered the central clearance for each metabolite. Therefore, associations between covariates and apparent metabolite clearances are attributed to changes in the “true” metabolite clearance.

The primary focus of this investigation was to quantify the effect of concomitant EIAED therapy on the metabolism and disposition of irinotecan. Our results indicate that the net effect of concomitant EIAED use is increased clearances of irinotecan, SN-38 and SN-38G. The increase in the clearance of parent drug was expected, as it is well established that multiple metabolic pathways are induced by phenytoin, phenobarbital and carbamazepine [9]. However, it was surprising that the overall effect of EIAEDs on irinotecan clearance was low, with an increase in clearance by only 19.3%. Given that a complete subject-level listing of concomitant medications was not available for analysis, it is possible that the modest effect on parent drug clearance reflects lower than normal EIAED exposure and/or possible contributions of other drugs that may inhibit irinotecan metabolism. This is a limitation of the model, and as such the magnitude of the covariate effect of concomitant EIAED use should be interpreted with this caveat in mind. Irrespectively, the observed changes in $CL_{irinotecan}$ with concomitant EIAED use affect the entire metabolic pathway, as the plasma metabolite concentrations are dependent upon this parameter. For example, simulations based on our model show that patients on concomitant EIAED therapy have increased APC plasma levels compared to patients not receiving EIAEDs (median C_{max} values of 345 and 309 ng/mL, respectively). The EIAED-mediated increase in $CL_{irinotecan}$ is likely a consequence of enzyme induction via activation of the pregnane X receptor (PXR)

and constitutive androgen receptor (CAR). EIAEDs are known to activate both induction pathways, which in turn up-regulate expression of CYP3A [34] and carboxylesterases [35]. As CYP3A and CES are responsible for conversion of irinotecan to APC and SN-38, respectively, the observed EIAED-mediated increases in $CL_{\text{irinotecan}}$ are attributed to induction of these enzymes.

The most striking effect of concomitant EIAED use on irinotecan pharmacokinetics was the >100% increase in the clearance of SN-38 for patients on EIAEDs. This is largely due to increased clearance to SN-38G, as evidenced by simulation results showing an increase in the SN-38G / SN-38 AUC_{0-t} ratio from 3.5 to 5.6 with concomitant EIAED use. The increased glucuronidation of SN-38 with EIAED use is attributed to elevated UGT activity, as phenytoin, phenobarbital and carbamazepine all induce expression of UGT isoforms via CAR [36]. In consideration of effects on UGT activity, the model is limited in that insufficient UGT1A1 genotype information was available for analysis which precluded inclusion of this covariate in the model. Thus the model assumes that EIAEDs will alter SN-38 clearance by a similar magnitude irrespective of UGT1A1 genotype, which may not be appropriate if an interaction exists between genotype and EIAED-mediated changes in UGT1A1 activity.

The effect on the formation and elimination of SN-38 is in accord with previous studies demonstrating an impact of concomitant EIAEDs on irinotecan-containing regimens [7, 11-19]. The net effect of concomitant therapy with EIAEDs predicted by the current model is a mean decrease in SN-38 exposure by 41% compared to patients not receiving EIAEDs. This effect is of similar magnitude to those noted in earlier studies which compared SN-38 non-compartmental pharmacokinetic parameters in the absence and presence of EIAEDs [14-16]. The decreased exposure to SN-38 is also consistent with the increased MTDs of irinotecan-containing regimens in malignant glioma patients on concomitant EIAEDs. Reported MTDs for weekly administration of irinotecan in the presence of concomitant EIAED therapy are in the range of 225 – 411 mg/m², 1.8 to 3.3 fold higher than the established MTD of 125 mg/m² without concomitant EIAED use [12, 13, 17-19]. Interestingly, the range of fold increases in MTD are slightly higher than the results of the present analysis which indicate an equivalent AUC_{0-t} will be obtained with a dose increase of 1.7 fold in patients using EIAEDs compared to patients not on EIAEDs.

It should be emphasized that this putative dose adjustment is based solely on changes in SN-38 exposure and suggests a weaker effect of EIAEDs on irinotecan therapy versus that indicated by the relative MTDs with and without EIAEDs. This may reflect disparities between the studies with regard to specific EIAEDs used and their doses, factors which could not be evaluated in the present study. Alternatively, it is probable that EIAEDs affect other pharmacokinetic or pharmacodynamic pathways important in determining the efficacy and tolerability of irinotecan in patients with neurological malignancies. This premise is supported by the analysis of Jaeckle *et al.* which demonstrated an improved overall survival in patients with newly diagnosed glioblastoma multiforme treated with EIAEDs as compared to those who did not receive these agents [27]. Thus, the irinotecan dosage increase of 1.7 fold suggested by the model is likely a conservative estimate for patients with malignant gliomas. In contrast, for use in other malignancies, it is notable that while the

FDA-approved prescribing information for irinotecan indicates that EIAEDs alter SN-38 exposure, the magnitude of this effect is not described and discontinuation in favor of non-inducing AEDs is recommended [37]. As substitution of non-inducing AEDs is not always appropriate and no dose adjustment is recommended in the labeling, the 1.7 fold increase suggested by the model may be suitable for further investigation in patients with other malignancies who require concomitant EIAED therapy.

In contrast to the significant impact of EIAEDs, exploration of the impact of concomitant corticosteroid on irinotecan pharmacokinetics appears to be limited to a small increase in APC clearance. The absence of effects on irinotecan or SN-38 clearance suggests that corticosteroids do not induce CYP, CES or UGT-mediated metabolism at the doses used to treat cerebral edema. This is consistent with the premise that corticosteroids induce metabolic pathways to only a minor extent at clinically relevant doses [38]. Consequently, given that APC is an inactive metabolite and there is no effect on irinotecan or SN-38 pharmacokinetics, we conclude that there is no clinically relevant DDI between irinotecan and corticosteroids, consistent with the FDA-approved prescribing information for irinotecan [37].

Of the remaining covariates, only sex was correlated with SN-38 clearance, as was reported in an earlier population pharmacokinetic study [20]. Compared to males, in the present analysis females exhibited 38% and 24% decreases in SN-38 and SN-38G clearance, respectively. Despite the lower SN-38 and SN-38G clearances for female patients, simulations show that this increases mean SN-38 AUC_{0-t} by only 8%. Although previous studies have postulated that women exhibit higher SN-38 levels compared to men [39], the minor increase in SN-38 exposure demonstrated herein suggests that this difference is not clinically significant. Similarly, the observed correlation between grade 2 disease at baseline with increased irinotecan clearance is also not considered to be clinically relevant as it reflects the greater seizure frequency in patients with lower grade disease [40]. This is supported by our data which demonstrates that 15 of the 16 patients with grade 2 disease were on an EIAED. Thus, the minor increase in irinotecan clearance exhibited by lower grade patients is not a specific characteristic of this sub-group, but rather reflects more frequent EIAED use.

In conclusion, we have developed a population pharmacokinetic model which quantifies the impact of concomitant EIAED use on the metabolism and disposition of irinotecan. Our model suggests that a 1.7 fold increase in dose may compensate for decreases in SN-38 exposure in the presence of concomitant EIAEDs. Although this dose adjustment may be overly conservative for use with established regimens for malignant glioma, it may be appropriate for further investigation when evaluating alternative irinotecan regimens or in the treatment of other malignancies in patients on concomitant EIAED therapy.

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References

1. Mathijssen RH, et al. Pharmacology of topoisomerase I inhibitors irinotecan (CPT-11) and topotecan. *Current cancer drug targets*. 2002; 2(2):103–23. [PubMed: 12188913]
2. Rivory LP, et al. Pharmacokinetic interrelationships of irinotecan (CPT-11) and its three major plasma metabolites in patients enrolled in phase I/II trials. *Clinical Cancer Research*. 1997; 3(8):1261–6. [PubMed: 9815808]
3. Kawato Y, et al. Intracellular roles of SN-38, a metabolite of the camptothecin derivative CPT-11, in the antitumor effect of CPT-11. *Cancer Research*. 1991; 51(16):4187–91. [PubMed: 1651156]
4. Santos A, et al. Metabolism of irinotecan (CPT-11) by CYP3A4 and CYP3A5 in humans. *Clinical Cancer Research*. 2000; 6(5):2012–20. [PubMed: 10815927]
5. DRUGDEX® System [internet database]. Thomson Reuters (Healthcare) Inc.; Greenwood Village, CO: Irinotecan.
6. Sasine JP, Savaraj N, Feun LG. Topoisomerase I inhibitors in the treatment of primary CNS malignancies: an update on recent trends. *Anti-cancer agents in medicinal chemistry*. 2010; 10(9):683–96. [PubMed: 21235438]
7. Vredenburgh JJ, et al. Experience with irinotecan for the treatment of malignant glioma. *Neuro-oncology*. 2009; 11(1):80–91. [PubMed: 18784279]
8. Shou M, et al. Modeling, prediction, and in vitro in vivo correlation of CYP3A4 induction. *Drug metabolism and disposition: the biological fate of chemicals*. 2008; 36(11):2355–70. [PubMed: 18669588]
9. McNamara, JO. Drugs Effective in the Therapy of the Epilepsies. In: Hardman, JG.; Limbird, LE., editors. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. McGraw-Hill; New York: 2001. p. 521-547.
10. Wen PY, et al. Medical management of patients with brain tumors. *Journal of neurooncology*. 2006; 80(3):313–32.
11. Santisteban M, et al. Phase II trial of two different irinotecan schedules with pharmacokinetic analysis in patients with recurrent glioma: North Central Cancer Treatment Group results. *Journal of neuro-oncology*. 2009; 92(2):165–75. [PubMed: 19066728]
12. Jaeckle KA, et al. Phase II NCCTG trial of RT + irinotecan and adjuvant BCNU plus irinotecan for newly diagnosed GBM. *Journal of neuro-oncology*. 2010; 99(1):73–80. [PubMed: 20063115]
13. Gilbert MR, et al. Phase I clinical and pharmacokinetic study of irinotecan in adults with recurrent malignant glioma. *Clinical Cancer Research*. 2003; 9(8):2940–9. [PubMed: 12912940]
14. Friedman HS, et al. Irinotecan therapy in adults with recurrent or progressive malignant glioma. *Journal of Clinical Oncology*. 1999; 17(5):1516–25. [PubMed: 10334539]
15. Lohin ME, et al. Phase I study of temozolomide and irinotecan for recurrent malignant gliomas in patients receiving enzyme-inducing antiepileptic drugs: a north american brain tumor consortium study. *Clinical Cancer Research*. 2007; 13(23):7133–8. [PubMed: 18056194]
16. Prados MD, et al. Phase 1 trial of irinotecan (CPT-11) in patients with recurrent malignant glioma: a North American Brain Tumor Consortium study. *Neuro-oncology*. 2004; 6(1):44–54. [PubMed: 14769140]
17. Quinn JA, et al. Phase 1 trial of irinotecan plus BCNU in patients with progressive or recurrent malignant glioma. *Neuro-oncology*. 2004; 6(2):145–53. [PubMed: 15134629]
18. Reardon DA, et al. Phase I trial of irinotecan plus temozolomide in adults with recurrent malignant glioma. *Cancer*. 2005; 104(7):1478–86. [PubMed: 16088964]
19. Vredenburgh JJ, et al. Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2007; 25(30):4722–9. [PubMed: 17947719]
20. Klein CE, et al. Population pharmacokinetic model for irinotecan and two of its metabolites, SN-38 and SN-38 glucuronide. *Clinical Pharmacology and Therapeutics*. 2002; 72(6):638–47. [PubMed: 12496745]

21. Poujol S, et al. A limited sampling strategy to estimate the pharmacokinetic parameters of irinotecan and its active metabolite, SN-38, in patients with metastatic digestive cancer receiving the FOLFIRI regimen. *Oncology reports*. 2007; 18(6):1613–321. [PubMed: 17982652]
22. Rosner GL, et al. Pharmacogenetic pathway analysis of irinotecan. *Clinical Pharmacology and Therapeutics*. 2008; 84(3):393–402. [PubMed: 18418374]
23. Thompson PA, et al. Pharmacokinetics of irinotecan and its metabolites in pediatric cancer patients: a report from the children's oncology group. *Cancer Chemotherapy and Pharmacology*. 2008; 62(6):1027–37. [PubMed: 18278496]
24. Xie R, et al. Clinical pharmacokinetics of irinotecan and its metabolites: a population analysis. *Journal of Clinical Oncology*. 2002; 20(15):3293–301. [PubMed: 12149304]
25. Younis IR, et al. Enterohepatic recirculation model of irinotecan (CPT-11) and metabolite pharmacokinetics in patients with glioma. *Cancer Chemotherapy and Pharmacology*. 2009; 63(3): 517–24. [PubMed: 18496691]
26. Chabot GG, et al. Population pharmacokinetics and pharmacodynamics of irinotecan (CPT-11) and active metabolite SN-38 during phase I trials. *Annals of oncology*. 1995; 6(2):141–51. [PubMed: 7786822]
27. Jaeckle KA, et al. Correlation of enzyme-inducing anticonvulsant use with outcome of patients with glioblastoma. *Neurology*. 2009; 73(15):1207–13. [PubMed: 19822870]
28. Lindbom L, Pihlgren P, Jonsson EN. PsN-Toolkit--a collection of computer intensive statistical methods for non-linear mixed effect modeling using NONMEM. *Computer methods and programs in biomedicine*. 2005; 79(3):241–57. [PubMed: 16023764]
29. Ihaka R, Gentleman R. R: A Language for Data Analysis and Graphics. *Journal of Computational and Graphical Statistics*. 1996; 5(3):299–314.
30. Jonsson EN, Karlsson MO. Xpose—an S-PLUS based population pharmacokinetic/ pharmacodynamic model building aid for NONMEM. *Computer methods and programs in biomedicine*. 1998; 58(1):51–64. [PubMed: 10195646]
31. Bauer, RJ. NONMEN Users Guide. ICON Development Solutions; Ellicott City, MD.: 2009. Introduction to NONMEN 7.
32. Bonate, PL. Pharmacokinetics, Modeling and Simulation. Springer; 2011.
33. Savic RM, Karlsson MO. Importance of shrinkage in empirical bayes estimates for diagnostics: problems and solutions. *The AAPS journal*. 2009; 11(3):558–69. [PubMed: 19649712]
34. Luo G, et al. CYP3A4 induction by xenobiotics: biochemistry, experimental methods and impact on drug discovery and development. *Current drug metabolism*. 2004; 5(6):483–505. [PubMed: 15578943]
35. Xu C, Wang X, Staudinger JL. Regulation of tissue-specific carboxylesterase expression by pregnane x receptor and constitutive androstane receptor. *Drug metabolism and disposition: the biological fate of chemicals*. 2009; 37(7):1539–47. [PubMed: 19359405]
36. Bock KW. Functions and transcriptional regulation of adult human hepatic UDP-glucuronosyl-transferases (UGTs): mechanisms responsible for interindividual variation of UGT levels. *Biochemical Pharmacology*. 2010; 80(6):771–7. [PubMed: 20457141]
37. CAMPTOSAR® Irinotecan hydrochloride injection, solution [package insert]. Pfizer, Inc.; New York, NY.: 2014.
38. McCune JS, et al. In vivo and in vitro induction of human cytochrome P4503A4 by dexamethasone. *Clinical Pharmacology and Therapeutics*. 2000; 68(4):356–66. [PubMed: 11061575]
39. Han JY, et al. Integrated pharmacogenetic prediction of irinotecan pharmacokinetics and toxicity in patients with advanced non-small cell lung cancer. *Lung cancer*. 2009; 63(1):115–20. [PubMed: 18221820]
40. van Breemen MS, Wilms EB, Vecht CJ. Epilepsy in patients with brain tumours: epidemiology, mechanisms, and management. *Lancet neurology*. 2007; 6(5):421–30. [PubMed: 17434097]

Figure 1.

Compartmental model for irinotecan and its metabolites. R_0 indicates the infusion of irinotecan, CL and Q refer to the central and inter-compartmental clearances, respectively, and F describes the fraction of irinotecan converted to each metabolite. The central (V_c) and peripheral (V_p) volumes of distribution are indicated within the corresponding compartments for each metabolite.

Figure 2.

Goodness of fit plots for irinotecan (CPT-11), APC, SN-38 and SN-38G from the final model (top to bottom panels, respectively). For each drug moiety, the left panel shows the logarithmic plots of the observed and population expected concentrations, whereas the right panel depicts the expected conditional weighted residuals (ECWRES) as a function of time post start of infusion. EPRED and ECWRES are exact, Monte Carlo generated PRED and CWRES values, calculated directly by NONMEM (ESAMPLE=1,000) [31]. The solid line indicates the line of unity (left panels) or zero for ECWRES (right panels) and the dashed lines illustrate a LOESS fit.

Figure 3.

Visual predictive checks for irinotecan (CPT-11), APC, SN-38 and SN-38G. Data are depicted as semi-logarithmic plots, with the corresponding drug moiety indicated within the y-axis label. Observed concentrations are given by the open circles, whereas lines depict the median (dashed) as well as 5th and 95th percentiles (solid) from 500 simulations based on the original dataset.

Table 1Demographic covariates for the study patients ($n = 86$)

Baseline covariate	
Sex, n (%)	
• Male	54 (62.8%)
• Female	32 (37.2%)
Age (years)	
• Mean $\pm$ SD	53.1 $\pm$ 13.8
Body surface area (m^2)	
• Mean $\pm$ SD	1.97 $\pm$ 0.26
NCCTG study, n (%)	
• 96-72-51	56 (65.1%)
• N997D	30 (34.9%)
ECOG performance status, n (%)	
• 0	28 (32.6%)
• 1	42 (48.8%)
• 2	16 (18.6%)
Grade of disease, n (%)	
• 1	1 (1.1%)
• 2	16 (18.6%)
• 3	8 (9.3%)
• 4	58 (67.4%)
• Unknown	3 (3.4%)
Concomitant corticosteroid, n (%)	
• Yes	67 (77.9%)
• No	19 (22.1%)
Concomitant EIAED, n (%)	
• Yes	56 (65.1%)
• No	30 (34.9%)
EIAED type, n (%)	
• None/non-inducing AED	30 (34.9%)
• Phenytoin	36 (41.9%)
• Carbamazepine	9 (10.5%)
• Phenobarbital	3 (3.5%)
• 2 or more EIAEDs	8 (9.3%)
Dose level, n (%)	
• 100 mg/m^2	19 (22.1%)
• 125 mg/m^2	26 (30.2%)
• 250 mg/m^2	23 (26.7%)
• 300 mg/m^2	6 (7.0%)
• 400 mg/m^2	12 (14.0%)

Table 2Parameter estimates and bootstrap results from the final model^a

Parameter	θ estimate	Bootstrap		
		Mean	% RSE	95% CI
Structural model parameters				
CL _{irinotecan} (L/hr)	43.8	43.8	5.19	(39.4, 48.5)
irinotecan V _C (L)	153	152	6.49	(132, 172)
Q _{irinotecan} (L/hr)	27.6	27.6	10.1	(22.3, 33.1)
irinotecan V _P (L)	147	146	5.62	(132, 163)
CL _{APC} / F _{APC} (L/hr)	137	137	8.59	(116, 163)
APC V _C / F _{APC} (L)	232	235	10.2	(190, 285)
Q _{APC} / F _{APC} (L/hr)	125	127	18.8	(90.1, 183)
APC V _P / F _{APC} (L)	234	234	9.84	(192, 282)
CL _{SN-38} / F _{SN-38} (L/hr)	1,760	1,749	8.95	(1,454, 2,050)
SN-38 V _C / F _{SN-38} (L)	270	311	51.8	(34.7, 666)
Q _{SN38} / F _{SN-38} (L/hr)	2,650	2,670	7.64	(2,276, 3,085)
SN-38 V _P / F _{SN-38} (L)	26,300	26,700	13.6	(20,500, 34,900)
CL _{SN38G} / F _{SN-38G} (L/hr)	535	534	12.54	(406, 670)
SN-38G V _C / F _{SN-38G} (L)	82.6	80.0	16.88	(53.9, 106)
Between subject variability (as % CV)				
CL _{irinotecan}	32.1	32.2	13.5	(27.8, 36.3)
Irinotecan V _C	43.7	44.4	31	(31.6, 58.2)
Q _{irinotecan}	67.2	65.4	25	(45.4, 79.3)
Irinotecan V _P	39.4	39.1	20.1	(31.0, 46.4)
CL _{APC} / F _{APC}	53.1	56.2	15.8	(45.7, 60.4)
APC V _C / F _{APC}	72.7	73.4	21.6	(56.8, 87.7)
APC V _P / F _{APC}	47.1	48.7	40.7	(28.2, 68.3)
CL _{SN-38} / F _{SN-38}	46.6	45.7	20.6	(35.9, 54.6)
Q _{SN-38} / F _{SN-38}	67.5	66.5	19.6	(52.9, 78.7)
SN-38 V _P / F _{SN-38}	79.2	79.7	20.4	(63.7, 95.9)
CL _{SN-38G} / F _{SN-38G}	46.7	45.7	19.2	(36.8, 53.9)
Residual unexplained variability				
N997D Additive (ng/mL)	0.26	0.27	23.9	(0.15, 0.40)
N997D Proportional (% CV)	10.5	10.5	18.6	(8.50, 12.4)
96-72-51 Additive (ng/mL)	0.013	0.018	164	(0.001, 0.048)
96-72-51 Proportional (% CV)	14.3	14.7	15.8	(12.4, 16.9)

CV = coefficient of variation

^a959 successful bootstrap replicates

Table 3

Parameter estimates, bootstrap results and p-values for covariates included in the final model

Parameter	θ estimate ^a	Bootstrap Mean (95% CI)	p-value ^b
EIAED (+) status			
CL _{irinotecan}	0.194	0.193 (0.088, 0.293)	< 0.0001
CL _{SN-38} / F _{SN-38}	1.03	1.06 (0.678, 1.51)	< 0.0001
CL _{SN-38G} / F _{SN-38G}	0.248	0.270 (-0.027, 0.641)	0.001
Steroid (+) status			
CL _{APC} / F _{APC}	0.262	0.267 (0.051, 0.504)	0.006
Female sex			
CL _{SN-38} / F _{SN-38}	-0.247	-0.243 (-0.394, -0.092)	0.001
CL _{SN-38G} / F _{SN-38G}	-0.381	-0.377 (-0.493, -0.242)	< 0.0001
Grade 2 disease (at initial diagnosis)			
CL _{irinotecan}	0.169	0.171 (0.072, 0.273)	0.001

^a θ indicates fractional change compared to male, EIAED(-), steroid(-), non-grade 2 patients^bp-value calculated from stepwise deletion phase using the likelihood ratio test