TPII-79

Simultaneous Population Pharmacokinetic (PPK) Modeling of Irinotecan (CPT-11) and Its Major Metabolites, SN-38 and SN-38G

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ABSTRACT

Purpose. To develop a PPK model in NONMEM® that simultaneously predicts the plasma concentration (Cp) profiles of CPT-11 (C) and its metabolites, SN-38 (S) and SN-38G (G).

Methods. Data were available from 5 phase II multicenter trials for 375 patients (pts) (2505, 2499 and 715 samples for C, S, and G, respectively) with colorectal or lung cancer who were started on doses (IV over 90 mins) of 100 (235 pts), 125 (130 pts), or 150 mg·m^{-2} (10 pts) wkly for 4 wks, followed by a 2-wk rest period. Sampling was performed immediately before infusion, at 0, 1, 2, 4, and 24 h post infusion during Week 1 and/or Week 3 of Course 1. Data were randomly selected (80%-20%) for development and validation of the model.

Results. A 5-compartment model (2 for C, 1 for S, and 2 for G) with the S+G pathway pre-specified to represent 12% of the dose was developed, with clearances of C, S, and G estimated as means±SE (interindividual variability, %CV): 23.4±1.9 (52.7), 7.62±0.66, and 9.15±1.24 (53.1) L/hr; central volumes of distribution estimated as 108±4.7, 39.3±13.4, and 5.23±1.57 L; and conversion clearance from C to S, S to G, and G to S estimated as 3.18±0.14 (29.1), 215±34 (48.7), and 27.7 (35.5), respectively. The residual variability for C, S, and G were 27.6, 36.9, and 19.4%CV, respectively.

Conclusions. Using prior information on metabolic pathways and elimination characteristics, this model provided good simultaneous fits to the Cp profiles of C, S, and G for development and validation data.

INTRODUCTION

- Irinotecan (CPT-11), a camptothecin-derived inhibitor of topoisomerase I, is a prodrug that undergoes metabolism to an active metabolite, SN-38. This metabolite is further conjugated to form the secondary metabolite, SN-38G.
- Plasma concentrations of SN-38 are lower than concentrations of CPT-11 and SN-38G, but SN-38 is approximately 1000 times more potent than CPT-11 in inhibiting topoisomerase I.
- The pharmacokinetics (PK) of CPT-11 have been previously described using non-compartmental analysis or multi-compartment models but these did not consider the three species, CPT-11, SN-38, and SN-38G, simultaneously.
- Since diarrhea and myelosuppression associated with irinotecan therapy may relate to prodrug/metabolite exposure, a better understanding of the PK of CPT-11 and its metabolites would contribute to more precise evaluation of these relationships.
- This analysis describes the development and validation of a 5-compartment PPK model that simultaneously fits the plasma concentration profiles for CPT-11, SN-38, and SN-38G.

METHODS

Study Design and Data

- Five Phase II clinical trials of CPT-11 in patients with colorectal (three trials) or non-small-cell lung (NSCLC) cancer (two trials)
- Dose: 100-150 mg·m^{-2} infused over 90 minutes weekly for 4 weeks, followed by 2-week rest (6-week cycle). Dose adjustments were based on predefined criteria.

- PK sampling: weeks 1 and 3 at pre-dose, end of infusion, 1, 2, 4, and 24 hours post-infusion in four studies and only during week 1 (without 1 and 4 hour post-infusion in one colorectal cancer study)
- Species measured: CPT-11/SN-38 – all studies; also SN-38G in one NSCLC and one colorectal study (Table 3)

Bioanalytical Assay Method

- Total (sum of lactone-hydroxyacid formed) CPT-11/SN-38 concentrations determined by HPLC
- SN-38G concentrations were estimated as the increase in SN-38 concentrations after incubation of plasma with beta-glucuronidase
- Mean interassay precision: ≤ 6% for all species
- Mean interassay QC sample recovery range: 92-112% for all species

Pharmacostatistical Model

- NONMEM® V using first-order estimation

  Model Development: Uses 80% of the available patients
  - 2011 samples for CPT-11
  - 2006 samples for SN-38
  - 580 samples for SN-38G
- Model Validation: Uses the remaining 20% of the available patients
  - 494 samples of CPT-11
  - 493 samples for SN-38
  - 135 samples for SN-38G
- Exponential error model evaluated for interindividual error
- Constant coefficient of variation and combined additive plus constant coefficient of variation error models evaluated for residual error
- Model selection based on:
  - goodness-of-fit plots (each species and overall)
  - precision (%SEM) of the parameter estimates
  - changes in the interindividual and residual variability
  - physiologic relevance
  - numerical stability
  - model validation: using dataset of remaining 20% of patients
    - goodness-of-prediction plots for the validation dataset (each species and overall)
    - model predictions versus measurements plots
    - deviation distribution plots

RESULTS

Table 1: Patient Demographics

Age [Mean, Range] (yrs)	**60 (25-84)**
Weight [Mean, Range] (Kg)	**76 (43-139)**
Body Surface Area [Mean, Range] (m^2)	**1.9 (1.4-2.5)**
Gender	
Male	**169 (55.8%)**
Female	**134 (44.2%)**
ECOG Performance Status:	
0	**156 (51.5%)**
1	**126 (41.6%)**
2	**21 (6.9%)**
Ethnic Origin:	
Caucasian	**255 (84.2%)**
Non-Caucasian	**48 (15.8%)**

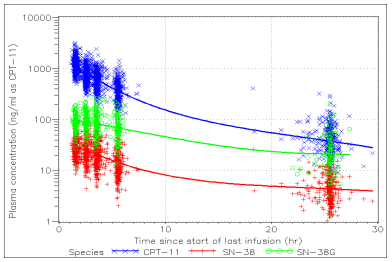
Table 2: Patient Baseline Laboratory Values

	Mean (sd)	Range
Creatinine Clearance (mL/min)	**85.5 (31.6)**	**34.2 - 206.3**
Aspartate Aminotransferase (U/L)	**36.3 (25.1)**	**8 - 201**
Total Bilirubin (mg/dL)	**0.6 (0.3)**	**0.1 - 1.2**
Hemoglobin (g/dL)	**12.7 (1.7)**	**8.3 - 17.9**

Table 3: Distribution of PK Samples by Study and Week

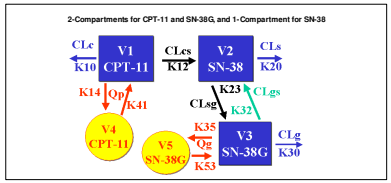
			Number of PK samples collected					
			Week 1			Week 3		
Study	No. of pts enrolled	No. of pts sampled	CPT-11	SN-38	SN-38G	CPT-11	SN-38	SN-38G
1	48	35	105	104	0	79	78	0
2	167	162	791	789	0	601	601	0
3	48	31	142	141	0	72	72	0
4	45	24	102	102	102	44	44	44
5	183	123	569	568	569	0	0	0
Total	491	375	1709	1705	671	796	795	44

Figure 1: Observed Concentration-Time Profiles



Solid lines represent trend in concentration-time profile using cubic functions

Figure 2: 5-Compartment Model



Model Assumptions

- The back-conversion of SN-38G to SN-38 was included to represent the hydrolysis of SN-38G to SN-38 and subsequent reabsorption in the intestine.
- Elimination ratio: fixed as CPT-11:SN-38:SN-38G = 88%:1.5%:10.5% (% of total dose) based on a previous mass balance study[1] where:
  - CLcs/CLc = 0.136 was used to express the ratio of (SN-38 + SN-38G) to CPT-11 (12%:88%) where CLcs and CLc represent the clearance of CPT-11 by transformation to SN-38 and elimination, by other pathways, respectively; and
  - CLs/CLsg*(CLgs/CLg+1) = 1/7 was used to assign the ratio of SN-38 to SN-38G elimination (1.5%:10.5%), where CLs and CLsg represent clearance of SN-38 by intact elimination and by conversion to SN-38G, respectively, and CLg and CLgs represent clearance of SN-38G through intact elimination and conversion to SN-38 (Fig 2).

Table 4: Final Parameter Estimates and Standard Errors for the Pharmacokinetic Model

	Population Mean		Interindividual Variability (%CV)	
Parameter	Estimate	%SEM	Estimate	%SEM
CLc (L/hr)	23.4	4.3	52.7	17.1
Ratio of CL:CLcs/CLc	0.136 Fixed	NA	NA	NA
CLcs (L/hr)	NA	NA	29.1	16.4
CLs (L/hr)	7.62	8.7	NE*	NE*
Ratio of CL:CLsg/CLs	28.2	15.9	48.7	18.3
CLg (L/hr)	9.15	13.6	53.1	29.8
Excretion Ratio: SN-38 to SN-38G	0.143 Fixed	NA	NA	NA
CLgs (L/hr)	NA	NA	35.5	87.3
V1, V2, V3, V4, V5 (L)	108, 39.3, 5.23, 128, 140	4.4, 13.4, 30.0, 23.2, 11.1	NE	NE
Qp (L/hr)	14.2	14.0#	NE	NE
Qg (L/hr)	24.0	7.8	NE	NE
Residual Variability, CPT-11 (%CV)	27.6	9.7	NA	NA
Residual Variability, SN-38 (%CV)	36.9	9.7	NA	NA
Residual Variability, SN-38G (%CV)	19.4	31.7	NA	NA

NA = Not Applicable; NE = Not Estimated; NE* = Not Estimable; and # = Calculated mean of the %SEM for V4 (128 ± 23.2%SEM) and the %SEM for $\theta_{42} = Qp*V4^{0.5}$ (161 ± 4.8%SEM).

Figure 3: Goodness-of-Fit for CPT-11 Concentrations

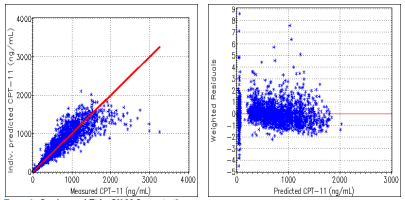


Figure 4: Goodness-of-Fit for SN-38 Concentrations

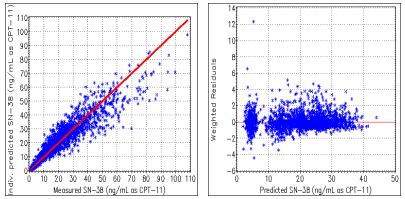
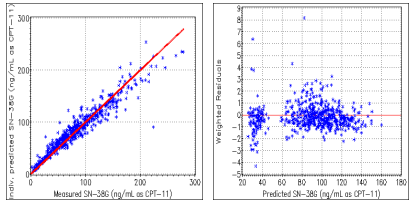


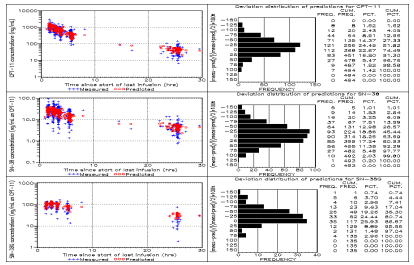
Figure 5: Goodness-of-Fit for SN-38G Concentrations



Model Validation

- The PK model was found to reasonably predict the concentration-time profiles for the validation dataset.
- The deviations were approximately normally distributed around zero for both SN-38 and CPT-11.
- The model slightly overestimated SN-38G at low concentrations:
  - Biased sampling for the validation dataset
  - Influence of outliers
  - Potential covariate effects
  - Limited data on SN-38G

Figure 6: Model Predictions and Deviation Distribution for Validation Data (by Species)



CONCLUSIONS

- A 5-compartment pharmacokinetic model provides a reasonable simultaneous fit to the concentration-time profiles for CPT-11, SN-38, and SN-38G.
- Pharmacokinetic parameter estimates from this model are physiologically reasonable and consistent with previous reports.
- This model provides the basis for evaluation of the influence of patient covariates on the pharmacokinetics of CPT-11 and its metabolites.
- The methodology developed in this analysis has potential for further application in the clinical development of other agents with complex metabolism.

REFERENCES

1. Slatter et al, Drug Metabolism and Disposition 2000;28(4):423-433