T2348

A Physiologically-Based Pharmacokinetic Model to Predict the Disposition of Topotecan in Transporter Wild Type and Knock-Out Mice

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Introduction: Active efflux transporters in the intestinal epithelium such as, P-glycoprotein (P-gp) and breast cancer resistance protein (Bcrp) can be very efficient in limiting the oral absorption of drugs[1]. Bcrp, a multidrug resistance protein, can render tumour cells resistant to anticancer agents such as Topotecan **(TPT)**[2]. Surfactants such as Pluronic P85 and Tween 20, which are used to improve the dissolution of poorly soluble drugs, are known to inhibit the intestinal efflux action of P-gp and Bcrp[1]. Simcyp Mouse is a physiologically based pharmacokinetic **(PBPK)** mouse model and can be used to virtually knock-in or knock-out **(KO)** liver and gut transporters in a virtually generated mouse to study the effect on the PK of a particular drug, in this case TPT.

Purpose:

- To build a PBPK model for TPT in Simcyp Mouse.
- To verify the performance of the model by comparing results to observed data.
- To predict the effect of hepatic (bile canaliculi) efflux and intestinal luminal efflux via Bcrp on the PK of TPT in an ***in silico* wild type (WT) and KO mouse**.

Methods: The **full PBPK model (Figure 1A)**, the permeability-limited liver model **(PerL, Figure 1B)** and the Advanced Dissolution, Absorption and Metabolism model **(ADAM, Figure 1C)** readily available within Simcyp Mouse Version 13 Release 2 (Sheffield, UK) were used to predict the PK of TPT in virtual WT and Bcrp KO mouse. Simulations were performed for a representative, 'generic' 28 g mouse strain.

Various *in vitro* and *in vivo* parameters for TPT were either obtained from an exhaustive literature search followed by meta-analysis or predicted using built-in models and fed into the simulator (**Table 1)**. Mouse specific parameters that were not available in literature, were substituted by parameters available for rat.

Predicted plasma concentration-time profiles and PK parameters t_{max}, C_{max} and $AUC_{0\text{-}4h}$ were compared with observed mean data obtained for WT and Bcrp KO Friend Virus B/NIH Jackson (FVB) strain mice as published by Yamagata *et al.* and Jonker *et al.*[1,2]. TPT was dosed as a 1 mg/kg oral solution. The full PBPK model based on the Rodgers and Rowland method of predicting tissue-to-plasma partition coefficients was used to predict the volume of distribution at steady state **(V_{ss})**.

The simulator also includes the **'MechPeff' model** which allows the user to predict regional intestinal effective passive permeability with minimal drug parameter inputs such as $logP_{O:W}$ or intrinsic transcellular permeability[3]. Briefly, **'MechPeff'** takes into consideration the explicit gastro-intestinal morphology and the regional differences in the species specific intestine.

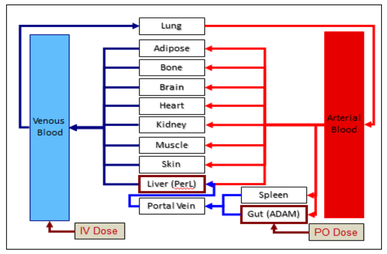

Figure 1A. Simcyp Mouse Full PBPK Model

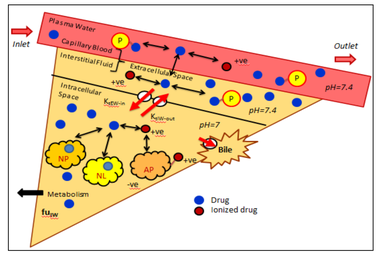

Figure 1B. PerL Model

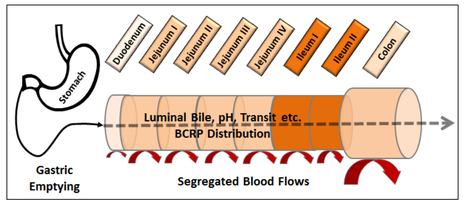

Figure 1C. ADAM Model

Table 1. Topotecan PBPK Model Input Parameters

PARAMETER	VALUE
Mol. Wt. (g/mol)	421
log $P_{O/W}$	1.88
pKa (type)	10.5; 7 (Diprotic Acid)
Blood-to-plasma ratio	1.15
Plasma fu	0.78
Regional gut wall permeability ($P_{eff,man}$) (10^{-4} cm/s)	Predicted using the 'MechPeff' model included in the simulator.
V_{SS}, predicted (L/kg)	1.50 (Predicted using Full PBPK)
Renal clearance, CL_R (mL/min)$	WT: 1.22; KO: 0.56
Hepatic transporter $Cl_{int,T}$ – Sinusoidal Uptake (µL/min/10^6 cells)	3.18 (Oatp2b1) [via SCHH]*
Hepatic transporter $Cl_{int,T}$ – Canalicular Efflux (µL/min/10^6 cells)	3.94 (Bcrp1) [via SCRH]#
Intestinal transporter $Cl_{int,T}$ – P-gp Apical Efflux (µL/min)	0.157 [via Caco-2 permeability experiments]
Intestinal transporter $Cl_{int,T}$ – Bcrp Apical Efflux (µL/min)	0.215 [via Caco-2 permeability experiments]
Sinusoidal uptake transporter	Oatp2b1
Canalicular efflux transporter	Bcrp
Dose and route of administration	1 mg /kg oral solution
Fasted / fed status	Fasted gut physiology (pH, bile salts, gastric emptying, basal fluid volumes) [4]
Trial duration	24 hours

$ WT CL_R obtained via multiple species allometry; KO CL_R calculated from studies [1,2]
* SCHH: Sandwich Cultured Human Hepatocytes; # SCRH: Sandwich Cultured Rat Hepatocytes (both scaled to mouse hepatocytes)

Results:

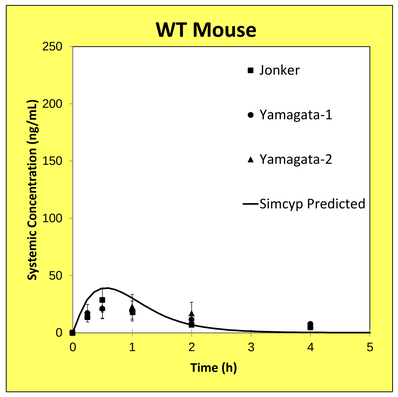

Figure 4A.

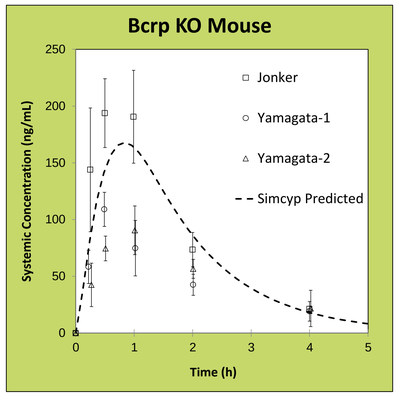

Figure 4B.

Figure 4A & 4B: Predicted and Observed plasma concentration-time profiles for WT and Bcrp1 KO mouse. 'Yamagata-1' KO is genetic Bcrp KO mice; 'Jonker' & 'Yamagata-2' KO are mice pre-treated with Bcrp inhibitors (GF120918, Pluronic P85, Tween 20).

Table 2. Mean Predicted and Observed PK Parameters

Study	t_{max} (h)	C_{max} (ng/mL)	$AUC_{(0\text{-}4h)}$ (ng.hr/mL)	C_{max} Ratio	AUC Ratio
Jonker WT	0.50	28.6	41	1.37	1.26
Yamagata-1 WT	0.50	20.9	50	1.87	1.03
Yamagata-2 WT	1.00	22.6	59	1.73	0.87
Simcyp Predicted WT	**0.56**	**39.1**	**52**		
Jonker Bcrp KO	0.50	193.8	362	0.87	0.92
Yamagata-1 Bcrp KO	0.50	109.0	192	1.85	1.61
Yamagata-2 Bcrp KO	1.01	90.57	207	1.68	1.67
Simcyp Predicted Bcrp KO	**0.84**	**167.9**	**333**		

Predicted-to-observed t_{max}, C_{max} and $AUC_{0\text{-}4h}$ ratios for TPT in WT and Bcrp KO mice were within 2-fold using a full-PBPK model (**Table 2**). The C_{max} and $AUC_{0\text{-}4h}$ for the KO mice were slightly under-predicted (1.1-fold) when compared to observed data from Jonker *et al.* and were over-predicted (1.7-fold) compared to observed data from Yamagata *et al*.[1,2]

Conclusion: Considering that a *generic strain* mouse model was used, and the significant variability observed between the reported PK parameters for the *same strain* of WT and Bcrp KO mice, Simcyp Mouse successfully predicted the PK of oral TPT. TPT being a substrate for sinusoidal uptake and canalicular efflux transporters in the liver, the predicted PK profiles in WT mouse were in good agreement with the observed data. The significant variability in observed data for KO mice can be attributed to differences in the extent of Bcrp KO by different inhibitors or activation of other transporters, since this variability is not reflected in the WT mice PK profiles.

References: **[1]**. Yamagata T. *et al.*, (2007) Drug Metab Dispos. 35(7):1142-8. **[2].** Jonker JW. *et al.*, (2000) J Natl Cancer Inst. 92(20):1651-6. **[3].** Pade D. *et al*. (2013) Poster at AAPS Annual Meet, San Antonio, USA. **[4].** Jamei M. *et al.*, (2009) *AAPS Journal* 11:225-237.