A Performance Evaluation of Simcyp Dog - a Fully Mechanistic Physiologically-Based Pharmacokinetic Dog Model - Based upon a Variety of Celecoxib IV and Oral Formulations

D. Pade[1], D. Turner[1], M. Jamei[1], L. Antonovic[2], M. Martinez[2], A. Rostami Hodjegan[1,3]

[1]Simcyp Limited, Sheffield; [2]U.S Food and Drug Administration, Rockville, Maryland, USA; [3]University of Manchester, Manchester, UK

Introduction

Beagle dogs are widely used in preclinical studies in the assessment of oral formulation behaviour. ***Simcyp Dog v11.01*** is an *in silico* physiologically-based pharmacokinetic (PBPK) simulator. The model provides a fully mechanistic modelling and simulation (M&S) platform and incorporates *In Vitro-In Vivo* Extrapolation (IVIVE)[1] techniques to study oral drug absorption, tissue distribution, metabolism and excretion in a ***10kg 'virtual' beagle dog***. The model provides an alternative tool in the drive toward the ***refinement***, ***replacement*** and ***reduction*** of *in vivo* studies in beagles.

Purpose

To evaluate the performance of ***Simcyp Dog***, without fitting of model parameters, to predict the PK of ***Celecoxib (CXB)*** dosed ***Intravenously*** (IV), ***Oral*** (Polyethylene Glycol (PEG) solution and Immediate Release (IR)) nano-particles stabilized with sodium-l-heptane-sulfonate (SHSO)) and directly to the gastrointestinal (GI) tract: ***Intra-Gastric (IG)*** and, via ***Chronic Intestinal Access Port (CIAP),*** to the ***Duodenum***, ***Jejunum*** and ***Colon.***

Methods

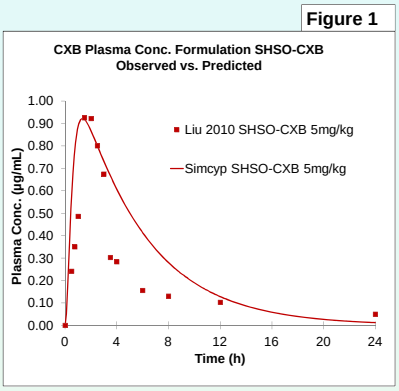
Simcyp Dog v11.01 was used to predict the plasma concentration time (Cp-t) profiles of CXB after an IV dose (5mg/kg PEG solution and IR Capsule) and 10mg/kg oral PEG solution as IG and directly into the Duodenum, Jejunum and Colon via CIAP[2]. The IR capsule was characterized by the solubility profile of CXB in Fasted State Simulated Intestinal Fluid (FaSSIF).[3]

A fully mechanistic gut wall permeability model incorporated into the Simcyp Advanced Dissolution Absorption and Metabolism-PBPK Model (ADAM) was used to predict effective regional intestinal permeability (P_{eff}). Model parameters (Gastric Emptying, P_{eff} and SI Transit time) were manipulated to permit the modelling of the direct administration of CXB to the Duodenum, Jejunum and Colon. Key simulation parameters are shown in Table 1.

Table 1

Simulation Parameter	Value
LogPo:w	3.05
fu	0.015
B/P	0.89
pKa (acid)	11.1
Predicted Dog P_{eff} ($x10^{-4}$ cm/sec)	1.44 (Jejunum I) 0.8183 (Colon)
FaSSIF solubility[3] (mg/mL)	0.0153
V_{ss} (L/kg)	2.216
CL_{IV}; PM (mL/min)	71.85
CL_{IV}; EM (mL/min)	164.6
Gastric pH	Fasted: 3.5
Gastric Emptying (h)	Fasted: 0.37
Transit Times (h)	2.39 (SI) 7.54 (Colon)

Figure 1



Results & Discussion

Table 3 * PM: Poor Metabolisers; EM: Extensive Metabolisers

Formulation (Dose mg/kg)	EM/ PM*	Tmax, h (±SD)		Cmax, µg/mL (±SD)		AUC_{0-t}, µg.hr/mL (±SD)		F (±SD)	
		Obs.	Simcyp	Obs.	Simcyp	Obs.	Simcyp	Obs.	Simcyp
Solution[2] (5)	EM	0.67 (0.17)	1.4	0.82 (0.22)	0.92	2.63 (0.59)	3.36	0.63 (0.1)	0.67
Solution[2] (5)	PM	0.5 (0)	1.67	1.32 (0.03)	1.44	10.5 (1.6)	9.86	0.88 (0.06)	0.85
IR Capsule[2] (5)	EM	1.3 (0.1)	3.1	0.28 (0.2)	0.24	0.97 (0.1)	1.27	0.24 (0.02)	0.23
IR Capsule[2] (5)	PM	1.3 (1.1)	3.6	0.32 (0.04)	0.45	3.0 (0.3)	3.76	0.27 (0.04)	0.29
SHSO-CXB[4] (5)	EM	1.5	1.31	0.924 (0.03)	0.922	4.81 (0.03)	5.94	- -	0.53
INTRA-GASTRIC[2] (10)	EM	0.69 (0.28)	0.96	1.62 (0.36)	2.05	10.3 (2)	6.9	- -	0.68
DUODENUM CIAP[2] (10)	EM	1.13 (0.63)	0.95	1.46 (0.2)	2.16	9.69 (1.57)	6.84	- -	0.68
JEJUNUM CIAP[2] (10)	EM	2.25 (1.9)	0.70	1.06 (0.21)	2.16	9.37 (0.97)	6.81	- -	0.67
COLON CIAP[2] (10)	EM	8.5 (2)	2.15	0.79 (0.12)	1.02	10 (0.9)	5.30	- -	0.52

Table 2

IV Dose (mg/kg)	EM/PM	CL (mL/min)		$t_{1/2}$ (h)		AUC_{0-t}	
		In Vivo (SD)	Simcyp	*In Vivo* (SD)	Simcyp	*In Vivo* (SD)	Simcyp
5	EM	218 (23)	165	1.3 (0.2)	1.55	4.04 (0.44)	5.07
5	PM	74 (5)	72.48	5.1 (0.5)	3.56	11.5 (0.75)	11.5

Figure 2

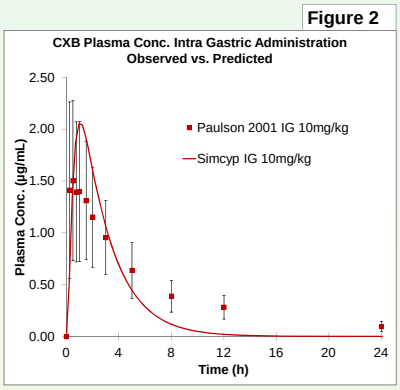


Figure 3

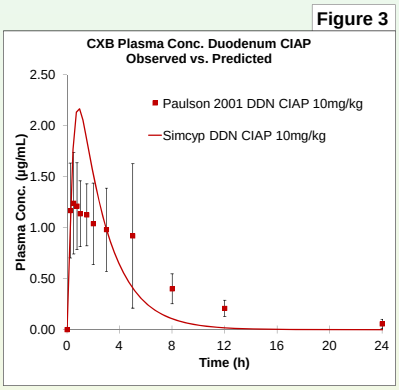
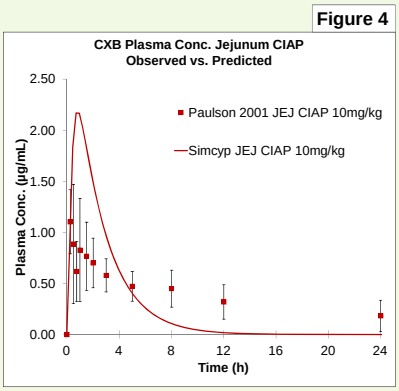


Figure 4



Tables 2 & 3: Predicted (Simcyp) vs. *in vivo* PK Parameters for IV, Oral, Intra-Gastric and CIAP administration in EM and PM beagle populations. Predicted CL (mL/min) and half-life (h) were within 2-fold of *in vivo* values (where Fold = In Vivo / Simcyp) for IV doses. All predicted C_{max} & AUC_{0-t} were within 2-fold of observed.

Figure 1: Predicted (Simcyp) vs. Observed Cp-t profile for Formulation SHSO-CXB[4] shows a good agreement between the predicted and observed T_{max}, C_{max} & AUC and (**Table 3**).

Figures 2, 3 &4: Predicted (Simcyp) vs. Observed Cp-t profiles for Intra-Gastric administration and administration to the Duodenum via CIAP: Though Cmax is over-predicted and AUC under-predicted for Intra-Gastric, CIAP Duodenum & CIAP Jejunum administration, the systemic bioavailability (F) is unchanged indicating no effect of site of absorption due to high effective permeability of CXB (**Table 3**) as explained by published data[2].

Conclusion

The Simcyp Virtual Beagle model was reasonably successful at predicting (without fitting of parameters) CXB Cp-t profiles after administration of IV and Oral formulations. Error in predicting CIAP may be related to failure to account for re-precipitation of drug after CIAP administration. This may have implications with respect to formulations of poorly soluble drugs that are intended to directly deliver drug to specific portions of the GI tract. The fully mechanistic gut wall permeability model in Simcyp Dog is sensitive to differences in site of absorption of the GI tract of the Beagle and can be used to aid study of the regional absorption of drugs from the GI tract.

References: **1.** Gibson & Rostami-Hodjegan (2007) *Xenobiotica* **37:**1013. **2.** Paulson S (2001) *JPET* **297:**638. **3.** Shono (2009) *Eur J Pharm Biopharm* **73:**107. **4.** Liu (2010) *J Pharm Pharm Sci.* **13:**589.