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

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Introduction

Beagle dogs are widely used as a surrogate absorption model for human assessment of oral drug absorption. ***Simcyp Dog V3.0*** is an *in silico* physiologically-based pharmacokinetic (PBPK) Simulator. The model provides a fully mechanistic modelling and simulation (M&S) platform coupled with *In Vitro-In Vivo* Extrapolation (IVIVE)[1] techniques to study oral drug absorption, tissue distribution, metabolism and excretion of drugs in a ***10kg 'virtual' beagle dog***. The concept of M&S in a ***'virtual' beagle dog*** provides an alternative tool towards the ***refinement***, ***replacement*** and eventual ***reduction*** of drug absorption studies in beagles.

Purpose

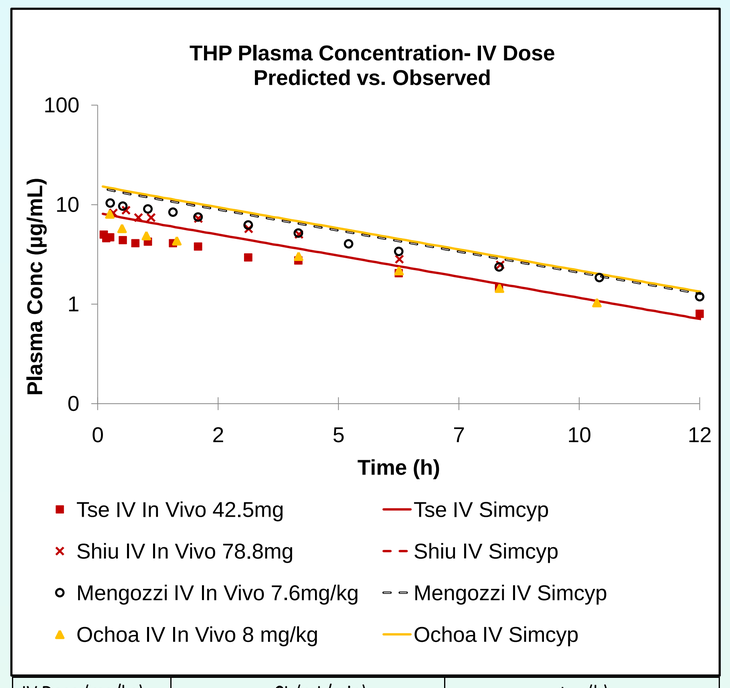
To evaluate the performance of ***Simcyp Dog*** – a PBPK dog model – to predict the pharmacokinetics of ***Theophylline*** (THP) following ***Intravenous*** (IV) and ***Oral*** (immediate release (IR) and sustained release (SR) formulations) dosing.

Methods

Simcyp Dog V3.0 was used to predict the plasma concentration time (Cp-t) profiles of THP after 4 IV doses (42.5 mg, 78.8 mg, 7.6 mg/kg, 8 mg/kg, *n*=1)[2-5], 3 IR tablets (formulations A 100mg, B 125mg, C 170mg, *n*=6)[2] and 3 SR 200mg formulations (TheoDur, TGM, Theo 24 Capsules (food effects[3]), *n*=25)[4-5]. IR formulations were characterized by the pH-solubility profile of THP[6] and SR formulations were characterized by their respective *in vitro* dissolution profiles[5,7,8]. A fully mechanistic gut wall permeability model incorporated in the Simcyp Advanced Dissolution Absorption and Metabolism-PBPK Model (ADAM) was used to predict the effective intestinal permeability and Cp-t profiles in beagle populations; some key simulation parameters are shown in Table 1.

Parameter	Description/Value
Log P	-0.02
fup	0.58
B/P	0.815
pKa 1; pKa 2	8.8; 0.99
Predicted Dog P_{eff} x10^{-4} cm/sec	0.49 (Jejunum I)
pH (Solubility-mg/mL) [7]	1.2 (12); 4.0 (16); 6.0 (12.5); 6.8 (13.9); 8.0 (17.9)
Vss (L/kg) [2-5]	0.65
CL (mL/min) [2-5]	17.59
Gastric pH	Fasted: 3.5; Fed: 2.1
Gastric Emptying (h)	Fasted: 0.37; Fed: 0.59
Formulation Gastric Emptying (h)	Fasted: 1.48 ; Fed 4.18
SI Transit (h)	2.39

Table 1.



IV Dose (mg/kg)	CL (mL/min)			$t_{1/2}$ (h)		
	In Vivo (SD)	Simcyp	Fold	In Vivo (SD)	Simcyp	Fold
4.25 (Tse et al.)	18 (4.24)	16	1.12	5.1 (1.8)	3.37	1.51
7.88 (Shiu et al.)	21.33 (1.4)	14.56	1.46	4.54 (0.21)	3.37	1.34
8.0 (Ochoa et al.)	38.33 (0.5)	16	2.39	4.08 (0.74)	3.37	1.21

Figure 1 & Table 2.

Results

Formulation/ (Dose mg)	Fig.	Tmax, h (±SD)		Cmax, µg/mL (±SD)		AUC, µg.hr/mL (±SD)		F (±SD)	
		Obs.	Simcyp	Obs.	Simcyp	Obs.	Simcyp	Obs.	Simcyp
IR-A [2] (100)	2	1.45 (0.35)	2.66	10.65 (0.49)	8.26	43.05* (14.21)	30.91*	1.05 (0.07)	0.9
IR-B [2] (125)		3 (0.70)	2.66	12.45 (1.34)	11.78	43.65* (8.41)	29.37*	1.3 (0.14)	0.87
IR-C [2] (170)		1.05 (0.77)	2.16	16.15 (0.21)	13.74	34.8* (0.42)	27.25*	0.93 (0.007)	0.83
SR-TheoDur [4] (200)	3	4.5 (0.27)	3.85	12.67 (0.9)	12.02	159.18 (17.85)	111.37	0.99 (0.18)	0.8
SR-TGM [5] (200)	4	3.17 (0.98)	4.95	2.55 (0.82)	3.08	33 (9)	32.49	0.46 (0.15)	0.40
SR-Theo 24 [5] (200)(FASTED)	5	5.5 (4.36)	5.55	3 (0.4)	2.52	47 (24.1)	25.43	0.31 (0.17)	0.49
SR-Theo 24 [3] (200)(FED)		9 (4.76)	7.95	4.67 (3.16)	5.18	65.4 (20.9)	57.04	0.42 (0.14)	0.59

Table 3. *AUC normalised to a dose of 42.5mg of THP as described in Tse 1982[2]

Figure 1 & Table 2: Predicted (Simcyp) vs. *in vivo* Cp-t profiles for 4 different IV doses. Predicted CL (mL/min) and half life (h) were within 2-fold of *in vivo* values (Fold=In Vivo/Simcyp) for all doses except clearance for 8mg/kg (2.4-fold under prediction).

Figure 2: Predicted (Simcyp) vs. Observed Cp-t profiles for IR formulations A, B & C shows a good agreement between the predicted and observed C_{max}, AUC and F (**Table 3**). Over prediction of T_{max} is observed for Formulation A and C and slight under prediction for Formulation B.

Figure 3 & 4: Predicted (Simcyp) vs. Observed Cp-t profiles for SR TheoDur & TGM formulations show a very good match of the C_{max}, AUC and F values **(Table 3**).

Figure 5: Predicted (Simcyp) vs. Observed Cp-t profiles for Theo24 Capsules in Fasted and Fed state. T_{max} for the Fed state is slightly under predicted. There seems to be a good agreement between the predicted and Observed C_{max}, AUC and F values.

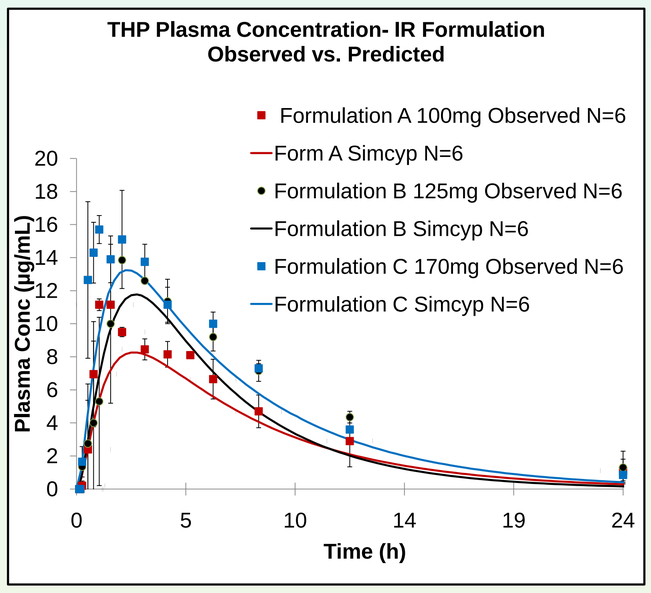


Figure 2.

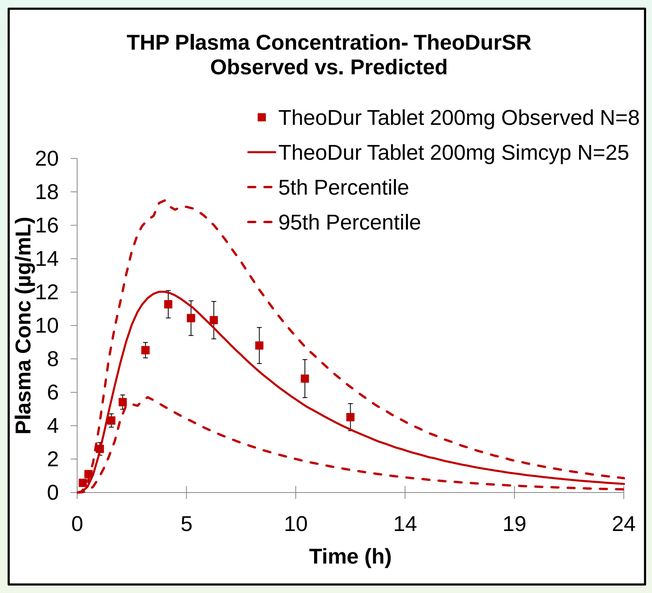


Figure 3.

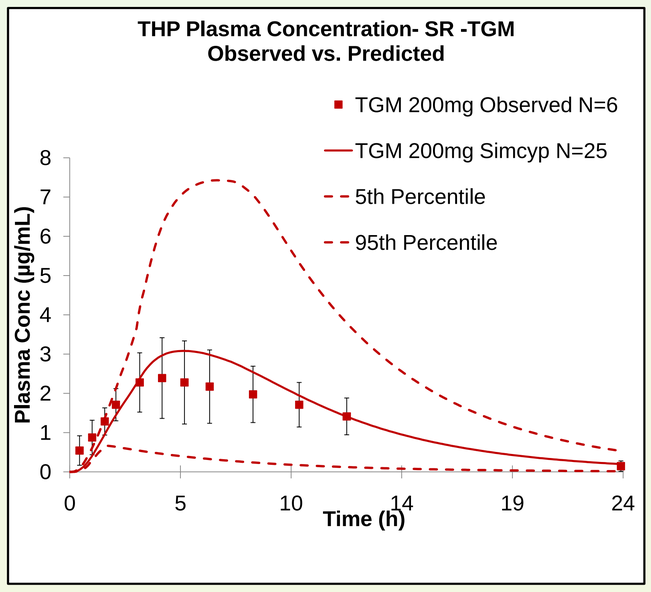


Figure 4.

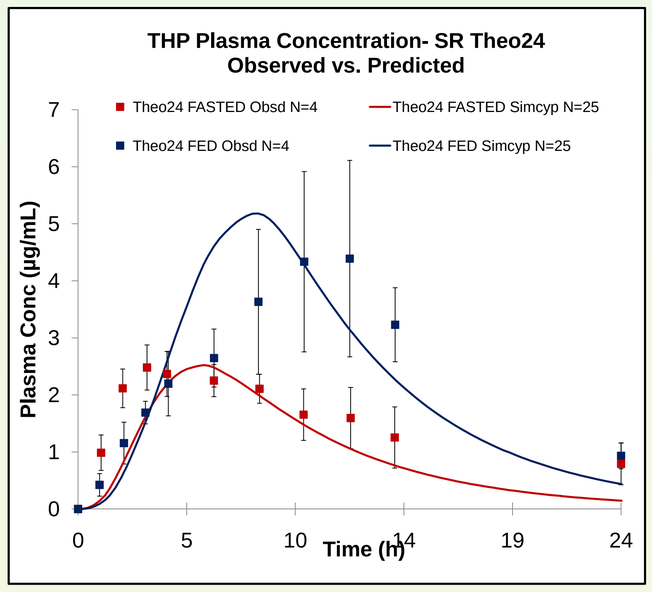


Figure 5.

Conclusion

The Simcyp Virtual Beagle model was reasonably successful in predicting THP Cp-t profiles after administration of IV, IR and SR formulations (with food effects). Most of the predicted PK parameters were within 2-fold of observed values. There is a slight trend of under prediction of T_{max} which can be attributed to various factors including gastric emptying and *in vitro* and *in vivo* dissolution rate differences. This study successfully demonstrates that the Simcyp Virtual Beagle model can be used as a potential reduction, refinement and replacement tool in the veterinary drug development process to reduce the use of live beagles.

References: **1.** Gibson G. G. & Rostami-Hodjegan 2007, *Xenobiotica*, Oct-Nov; 37 (10-11): 1013-1014. **2.** Tse *et al* 1982, *J Pharm Sci. 71(11):1301-3.* **3.** Shiu *et al* 1989, *Pharm Res.6(12):1039-42.* **4.** Mengozzi *et al* 1998, *Pharmacol Res. 38(6):481-5.* **5.** Ochoa *et al 2010*, *Eur J Pharm Biopharm. 75(2):232-7. Epub.* **6.** Lentz *et al 2002*, http://www.dow.com/PublishedLiterature/dh_0035/0901b803800355ea.pdf?filepath=methocel/pdfs/noreg/198-02069.pdf&fromPage=GetDoc **7.** El-Arini *et al 1990*, *Pharm Res. 1990 Nov;7(11):1134-40.* **8.** Maturu *et al 1986*, *J Pharm Sci. 1986 Dec;75(12):1205-6.*