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) 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 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)⁴, 3 IR tablets (formulations A 100mg, B 125mg, C 170mg, n=6)⁵ and 3 SR 200mg formulations (TheoDur, TGM, Theo 24 Capsules (food effects), n=25)⁶. IR formulations were characterized by the pH-solubility profile of THP and SR formulations were characterized by their respective in vitro dissolution profiles⁶,⁷,⁸. A fully mechanistic gut wall permeability model incorporated in the Simcyp Advanced Dissolution 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.

Table 1.

Parameter | Description/Value
---|---
Log P⁹ | 0.22
lip | 0.58
B/P | 0.815
pKa 1: pKa 2 | 8.8: 0.99
Predicted Dog Pk | 0.49 (Jenuman I)
PH (Solubility- mg/mL) | 1.2 (12); 4.0 (16); 6.0 (12.5); 6.8 (13.9); 8.0 (17.9)
Vss (L/kg) | 0.05
CL (ml/min) | 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

In order to validate the model results against the observed data, Table 2 contains the comparison of Observed and Predicted THP Plasma Concentration for both Formulation A 100mg and Formulation C 170mg.

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 Cmax, AUC and F (Table 3). Over prediction of Tmax 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 Cmax, AUC and F values (Table 3). Figure 5: Predicted (Simcyp) vs. Observed Cp-t profiles for Theo24 capsules in Fasted and Fed state. Tmax for the Fed state is slightly under predicted. There seems to be a good agreement between the predicted and Observed Cmax, AUC and F values.

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 Tmax 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: