Use of In Silico Physiologically Based Pharmacokinetic (PBPK) Models to Predict Food Effects on Drugs

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Purpose

To investigate the accuracy of in silico models in the prediction of in vivo drug absorption in dogs, using an evaluation of food effects as a first step in this assessment.

Background

Unlike the relative rich body of information available to support the development of in silico pharmacokinetics, there are numerous gaps confounding a correspondence of in silico population predictions for dogs. Such modeling tools can be invaluable for identifying those variables that can most strongly influence drug product performance in the targeted canine patient population and for facilitating interspecies extrapolations (dog to human and dog to dog) during the early phases of human or canine drug product development.

As a first step toward characterizing in silico models as a prognostic tool for canine in vivo drug absorption, the Simcyp software was used to predict the effect of food on two non-steroid anti-inflammatories, celecoxib (pKa = 11.1) and mavacoxib (pKa = 9.57). Both drugs are considered to be highly permeable (Cox et al., 2010; Paulson et al., 2001). Furthermore, both drugs exhibit substantial improvement in canine drug absorption when administered with food. However, while canine celecoxib elimination is rapid (t1/2 = approximately 2 – 4 hr) and was highly dependent upon protein binding (extensive binders in EM) exhibited a total systemic clearance (CL) of 0.644 L/hr/kg while poor metabolizers (PM) had a corresponding CL value of 0.216 L/hr/kg. mavacoxib is primarily eliminated as unchanged parent in the feces (approximately 60% of the drug after oral administration). Furthermore, due to its high affinity protein binding, mavacoxib is associated with a CL value of 0.0027 L/hr/kg. Lastly, to better understand in vivo differences that can impact the extrapolation of absorption information between humans and dogs, we compared the accuracy of our canine celecoxib food effect predictions to the accuracy achieved when human fed/fasted predictions were generated using the human Simcyp module.

Methods

Systemic concentration-time profiles were generated using the Simcyp Animal (V12, canine module) and Human (V12) software. Model input parameters are summarized in Table 1. Celecoxib

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<tr>
<th>Parameter</th>
<th>Value</th>
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<tbody>
<tr>
<td>Oral dose</td>
<td>100 mg/kg</td>
</tr>
<tr>
<td>Drug half-life</td>
<td>3 hr</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>0.5 L/kg</td>
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The data used for modeling canine and human celecoxib PK profiles were derived from the manuscript by Paulson et al., (2011). Canine and human PK studies were performed as previously described, following the oral administration of an identical formulation bulk drug in capsule. The human dose was 200 mg and the canine dose was 5 mg/kg. The canine datasets were subdivided into EM and PM dogs, each modeled independently.

We note that although the Paulson study provided both canine intravenous (IV) and oral data sets, these studies were conducted in different animals. It was the dogs that were administered only the oral dose that was used for our simulated comparisons. Therefore, volume and CL estimates provided in the IV dataset needed to be slightly modified to improve the accuracy of model predictions of those animals from which the fasted and fed state data were derived.

Due to the limitations in the information pertaining to the dog, a minimal PBPK model was employed. For consistency, we likewise utilized the minimal PBPK model for predicting human food effects (healthy Caucasian population module).

Segmental solubility assessments were based upon the celecoxib bileovariant fasted small intestinal fluid solubility values reported by Shono et al., (2009). These values were adjusted for dogs in an exploratory manner to facilitate our understanding of canine/canine differences. Furthermore, since we did not have in vivo solubility estimates in dogs or humans, we began our evaluation with the estimate of intrinsic solubility (IS) reported in Drugbank.ca (0.005 mg/mL). We noted that although its value worked well in describing the observed canine dataset, it failed to adequately describe the corresponding human canine differences. Therefore, the human predictions were to a considerable extent worse when compared with the predicted IS derived with the Simcyp tool. Potential reasons for the inconsistency in human-canine solubility estimates were explored.

Mavacoxib

Mavacoxib data were obtained from Cox et al., (2010). Only canine data were available for this drug, which exhibits extensive, high affinity protein binding. No phenotypic differences in drug metabolism were defined in the published dataset. Due to mavacoxib protein binding characteristics, it was necessary to estimate the intrinsic unbound hepatic clearance. This was achieved by converting the CL (from IV data) to liver microsomal intrinsic clearance based on the predicted canine phenotypic phenotype (CYP phenotype). For IS, we began our predictions using the reported value of 0.006 mg/mL. This value was modified as necessary to improve our model predictions.

Results

The absorption parameter values obtained for celecoxib and mavacoxib are provided in Table 2. Celecoxib

<table>
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Using the Drugbank estimate of IS for dogs, the canine Simcyp module provided a good approximation of peak (Cmax) and total drug exposure (AUC) for both the PM and EM dogs. For both canine populations, the model also provided an excellent qualitative estimate of the impact of food on drug absorption. The most noticeable error in the dataset was related to predictions of time to peak concentrations (Tmax). Since the relative error was similar in EM and PM dogs, this error appears to reflect absorption model mis-specification. The resulting fitted profiles (fasted and fed) are shown in Figure 1.

Discussion and Conclusions

Although in silico models have the potential to serve as important prognostic tools for predicting factors influencing canine drug absorption and inter-species extrapolation of drug absorption variables, there are several factors that have been identified as requiring additional investigation:

Discrepancies in Values Human vs. Canine for Solubility

Our first step was to show how intrinsic solubility, Cmax, from 2.11 mm/4cc/s to a value of 0.2 mm/4cc/s would not influence our prediction outcomes, therefore confirming that our examination only need focus on in vivo solubility and dissolution. To determine a potential reason for observed interspecies differences (both in terms of predictions and observed food effects), we used the human solubility estimate of 0.05 mg/mL and subsequently modified in vivo dissolution. This was accomplished by adjusting the effective diffusion layer thickness h, which is inversely correlated to dissolution rate in accordance with the Noyes Whitney equation.

Decreasing the dissolution rate (increasing h) improved our ability to estimate AUC and Cmax in the canine dataset when food was present. This was likely due to food effects that eliminated the food effect (similar to the small food effect seen in the human dataset). Thus, there appears to be an inherent difference in the human and canine GI tracts that impact the in vivo solubility (and therefore dissolution) of some molecules. Characterization of this difference requires future examination.

References


Figure 5: Regional Distribution Fraction of Dose Absorbed

We next examined the impact of prandial state and solubility estimation on the regional intestinal absorption (Figures 5 - EM dogs only). The higher solubility values resulted in a rapid and extensive drug absorption in the proximal segments of the small intestine (hence increasing Cmax) in the fasted state. Food in absorption was determined in a marked overestimation of fasted AUC thereby negating the food effects (similar to that observed and predicted in humans). This suggests that differences in food effects in dogs and humans may not only reflect interspecies differences in intestinal solubility but also differences in GI transit time.

Figure 6: Fed/Fasted Ratios

In contrast to celecoxib, mavacoxib was associated with a very long terminal depletion phase and has negligible drug metabolism. Thus, by exploring the ability to model mavacoxib in dogs, we could focus on the area under the curve (AUC) rather than in the calculation of food effects. Within the canine population, we did not have the presence of a substantial food effect, we succeeded in modeling AUC values under both fed and fasted conditions. The absolute errors in the Cmax estimates were likewise similar, although Cmax was slightly over-estimated in fasted dogs and under-estimated in fed dogs. We note that similar to that observed with celecoxib, efforts to use reported values of intrinsic solubility lead to an over inflation of the predicted concentration-time profiles. The similarity of these findings to the two drugs suggests that we are likely to introduce substantial error in our predictions when attempting to use in vitro physico-chemical drug characteristics as model parameters for generating in vivo level canine drug concentration-time profiles. Results are seen in Table 2 and Figures 3 and 4.

Figure 7: Percent Change in Cmax

In summary, our data suggests that the use of PBPK models to predict food effects in canine drug products have the potential to serve as important prognostic tools for predicting factors influencing canine drug absorption and inter-species extrapolation of drug absorption variables. There are several factors that have been identified as requiring additional investigation:

• It would appear that the error in canine Cmax estimates largely reflect the difficulty encountered with accurately defining food effects but also the precise location of drug absorption. In this regard, the dog is a more sensitive system as compared to humans.

• We need to determine why there is a 10-fold difference in between the solubility value estimates that provided the best fit for a canine versus canine dataset. In silico solubility is a function of the drug properties and not a function of the species GI tract, our results show that, predicting dissolution solely from the Cyp phenotype consider other variables associated with the GI milieu that may be as influential on drug performance as the IS itself.

• To date, we have not studied high solubility/low permeability compounds to ascertain the impact of limited information on canine GI physiology and the "what if" model scenarios that can be used to better predict drug absorption in the absence of drug specific canine absorption data. Therefore, it is impossible to determine the predict the food effects associated with drugs presenting with other physiochemical characteristics. Both the human drug classifications as defined by the BCS and the BDDS will be considered when selecting the next set of compounds for our simulation and modeling assessments.