Propofol: A Tail of Drug Disposition and Dynamics in Different Dog Breeds

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Abstract

It has been reported that greyhounds exhibit different disposition to certain anaesthetics compared to other dog breeds.[1] Key reasons may include differences in body composition and haematocrit. Greyhounds also exhibit slower Cyp2b11-mediated metabolism, which is the major route of propofol elimination in dogs.[2]
Physiologically Based Pharmacokinetic (PBPK) modelling allows for the bottom up prediction of differences in drug disposition between populations due to differences in tissue composition, blood flow, and metabolism. The bottom up nature also enables prediction of concentration at the tissue effect site, potentially explaining observed differences in pharmacodynamics (PD) responses between breeds.
A canine PBPK-PD model for Propofol was developed, and applied to predict the difference in disposition and effect of propofol in greyhound and beagle. A bottom-up prediction of concentration at the effect site (cranial cerebrospinal fluid) is made, and used as input to a PD model for Electroencephalographic Approximate Entropy (ApEn).

Methods

The default dog parameters in Simcyp (Dog V18R1) represent a 10kg beagle. The greyhound model (developed as part an FDA CRADA) differs from the beagle in having a different weight, cardiac output, tissue composition, and proportional blood flow. Anatomy and physiology parameter values were determined by thorough meta-analysis. Both the greyhound and beagle models were adjusted to reflect the mean weight of each trial simulated.

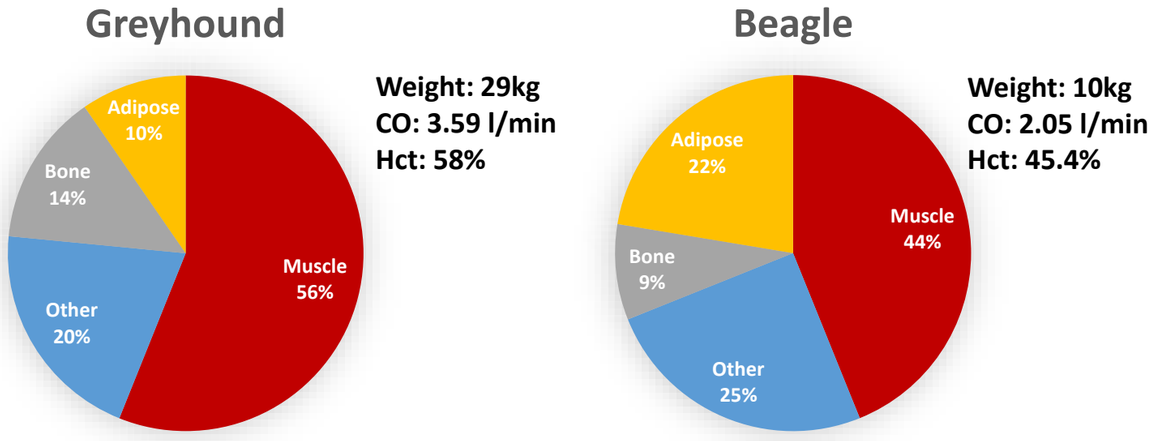

Figure 1. Major physiological differences between greyhound and beagle

A canine full PBPK model for propofol was developed in the Simcyp Dog simulator (V18R1). Propofol input parameters are given in Table 1. Volume of distribution and Tissue:Plasma partition coefficients were calculated using the method described by Rodgers and Rowland[3]. All tissues were assumed to be perfusion limited, with the exception of the brain, for which a five compartment permeability limited model was used (Spinal CSF, Cranial CSF, ICF, ISF and Brain Blood).

Table 1. Compound parameters for Propofol

Parameter	Value	Comment
Molecular Weight (g/mol)	178.28[4]	
Log Po:w	3.79[4]	
Compound Type	Monoprotic Acid	
pKa	11.1[4]	
Blood:Plasma ratio	1	Assumption for acid
Fraction unbound in plasma	0.014[5]	

The intravenous clearance of propofol in beagles was determined by non-compartmental analysis of published data[6]. The retrograde model within Simcyp Dog Simulator was used to back-calculate the hepatic intrinsic clearance of propofol via Cyp2b11. The greyhound was differentiated from the beagle by reducing the liver abundance of Cyp2b11 by 3-fold from 57 to 19 pmol/mg microsomal protein, based on liver microsome activity[2].

The blood brain barrier (BBB) passive permeability surface area product was calculated based on allometric scaling from the human value (510 ml/min) [7]. The permeability surface area product of the blood-CSF barrier (BCSFB) was calculated as half that of the BBB. The permeability surface product of the brain-CSF barrier was set to 300 mL/min to make it non-permeability-limited. The model incorporates population variability in hepatic Cyp2b11 abundance and CSF flow rates. The mean of 10 simulated dogs was used for prediction.

Results

The model was compared against experimental data not used for development.[8,9] Parameters were matched to the average weight of dogs in each trial. A reasonable prediction of beagle pharmacokinetics was achieved, and the model captured the lower volume of distribution and slower clearance in greyhounds compared to other dogs (Fig 2). Blood concentration 24h post-dose was underpredicted (Fig 2a). This may be due to concentration dependent fraction unbound in plasma.[10] The late terminal phase could be recovered with an fuP of 0.04. Prediction errors of AUC and CMax were within 2.5 fold (Table 2).

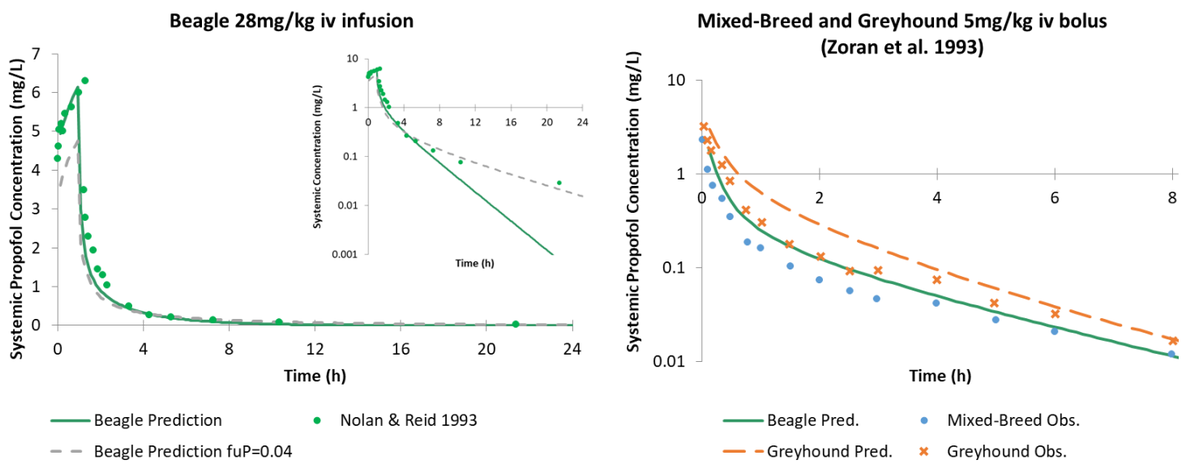

Figure 2. Left: Simulation of 28mg/kg infusion in Beagle (21.25kg)[8] Right: Prediction of 5mg/kg iv bolus in Mixed-Breed (13.3kg) and Greyhound (32.7kg)[9]

Table 2. Observed and predicted PK parameters

					AUC mg.h/L			CMax (mg/L)*		
Study	**Breed**	**Mean Weight (kg)**	**Dose (mg/kg)**	**Infusion Time**	**Obs**	**Pred**	**Fold**	**Obs**	**Pred**	**Fold**
Nolan & Reid 1993	Beagle	21.25	28	1 h	7.00	10.89	1.56	6.30	6.15	0.98
Zoran et al. 1993	Mixed Breed~	13.3	5.44	1 min	0.84	1.85	2.20	2.30	3.87	1.68
Zoran et al. 1993	Greyhound	32.7	5.29	1 min	3.39	3.57	1.05	3.29	8.06	2.45

*Time matched
~Beagle parameters

Greyhounds have been observed to recover from propofol anaesthesia at a later time, and at a higher plasma concentration than mixed breed dogs.[9] The addition of a PD model with cranial CSF as the effect compartment captured this phenomenon (Fig. 3). The impact of Cyp2b11 metabolism was assessed by running simulations for a “high Cyp2b11 greyhound” and “low Cyp2b11 beagle”, by swapping the breed liver Cyp2b11 abundances.

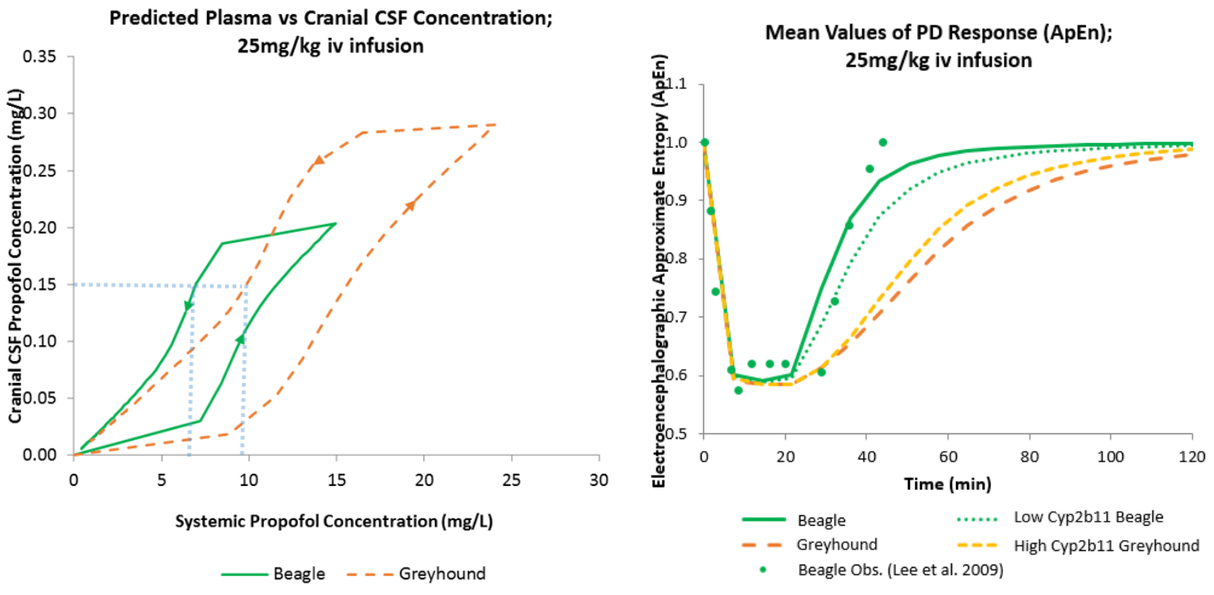

Figure 3. Left: Predicted plasma vs. cranial CSF concentration Right: Simulation of ApEn[6] with cranial CSF as the effect compartment

Conclusions

The PBPK model was able to predict the effect of difference in body composition and Cyp2b11 metabolism between dog breeds on the pharmacokinetics of propofol. The difference between greyhounds and other breeds in terms of recovering from propofol more slowly, but at a higher plasma concentration was also captured. While differences in Cyp2b11 metabolism contributed to the speed of recovery, the main differences between simulated dog breeds were due to body composition. This is in contrast to the hypothesis that the main difference in propofol disposition between the dog breeds is due to Cyp2b11.[2]

References

1. Sams, R.A. *et al*. 1985, Am J Vet Res,46(677-683). 2. Court, M.H. *et al*. 1999, Vet Clin North Am Small Anim Pract,43:5. 3. Rodgers, T. & Rowland M. 2006, Journal of Pharmaceutical Sciences,95(6). 4. https://pubchem.ncbi.nlm.nih.gov 5. Mazoit, J.X. & Samil 1999, K. J Clin Pharmacol,47(35-42). 6. Lee, S-H *et al*. 2009, British Journal of Pharmacology,158(1982-1995). 7. Gaohua, L. & Kimura, H. 2007, Theoretical Biology and Medical Modelling,4:46. 8. Nolan, A. & Reid, J. Bristish Journal of Anaesthesia,70:5(546-551). 9. Zoran *et al*. 1993, AM J Vet Res,54:5. 10. Daidoxicz, A.L. *et al*. 2006, Chemico-Biological Interactions, 159(149-155).