

Concentration-effect relationship of dapagliflozin in healthy Beagle dogs

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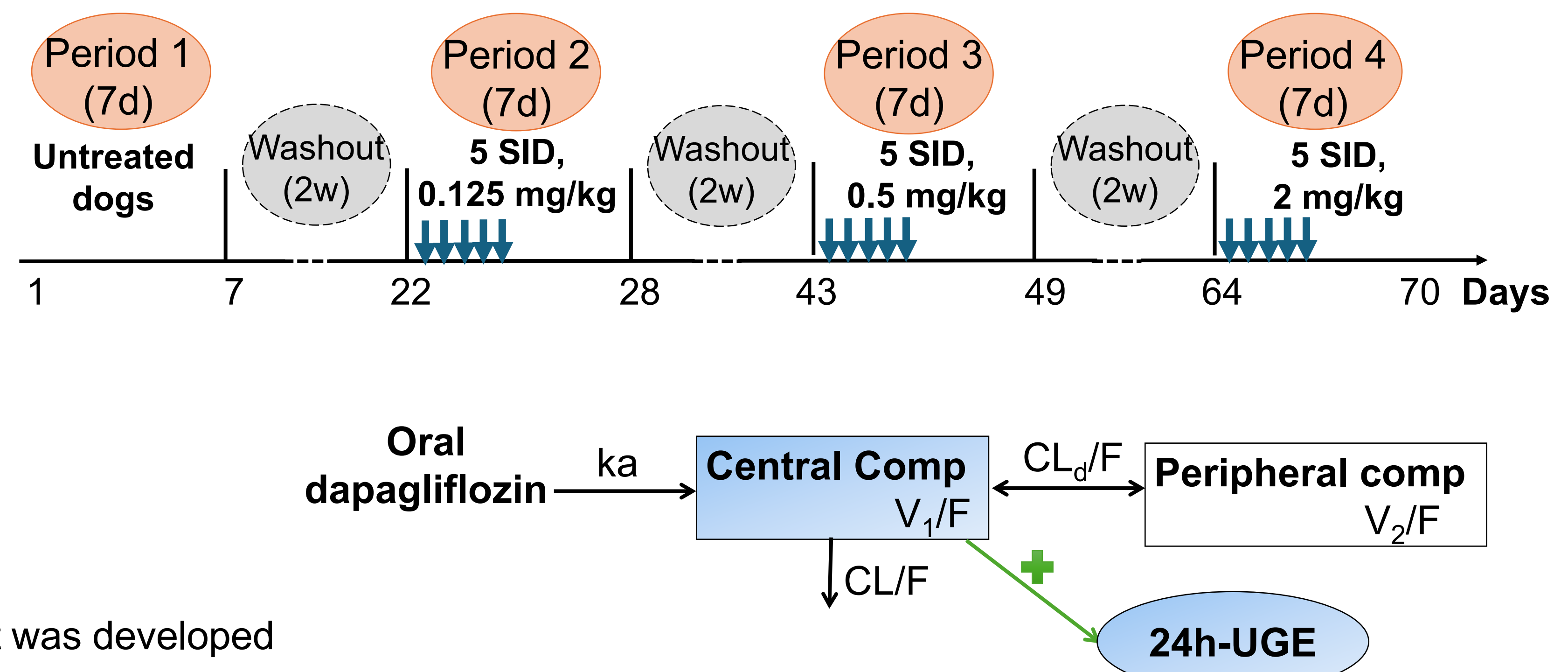
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Background and objectives

- Dapagliflozin is approved for human patients with diabetes, cardiac and renal disease.
- Daily dose of dapagliflozin capable of inducing 75% of the maximum 24-hours urinary glucose excretion (24h-UGE) has previously been shown to be predictive of clinical cardio-renal efficacy in human [1].
- The objectives of this study were to investigate the pharmacokinetics (PK) of dapagliflozin, and the relationship between dapagliflozin concentrations and 24h-UGE in healthy dogs to compute an effective dosage of dapagliflozin in the treatment of different altered conditions in dogs.

Materials and methods

- Sequential design study (i.e. four periods).
- 12 male healthy Beagle dogs were assessed.
- Dapagliflozin was administered to dogs in fasted state.
- The order of magnitude of dosages to be tested were estimated using an allometric approach based on the respective clearances in humans and dogs (i.e. dose of 0.1 mg/kg/day in dogs).
- Dapagliflozin plasma concentrations were measured 9 and 12 times, respectively, after administration of the first and last dose of each treatment period, and 2 times between days 2 and 4 of each treatment period.
- Urine was collected three times daily after each administration, and glucose concentration was measured.
- Nonlinear mixed-effects modeling using Monolix Suite 2021R1.
- A two-compartment model with a first-order absorption rate constant was developed to model the pharmacokinetic data.
- A direct Emax PK-PD model was developed to model the 24h-UGE data.



Results

Tab 1. Parameter estimates (final PK-PD model)

Parameter (unit)	Estimate (rse%)	CV (%)
Fixed effects		
k_a (h ⁻¹)	3.63	
V_1/F (mL.kg ⁻¹)	536.48 (3.85)	
CL/F (mL.h ⁻¹ .kg ⁻¹)	67 (3.74)	
CL_d/F (mL.h ⁻¹ .kg ⁻¹)	47.32 (5.68)	
V_2/F (mL.kg ⁻¹)	322.61 (8.00)	
E_{max} (g/day)	29.44 (4.90)	
AUC_{tau50} (ng.h.mL ⁻¹)	879.41 (14.30)	
SD of the Random Effects		
ω_{ka}	1	131.1
$\omega_{CL/F}$	0.12 (20.6)	12.0
$\omega_{V2/F}$	0.24 (22.7)	24.3
$\omega_{E_{max}}$	0.14 (24.4)	14.0
Residual variability		
$\sigma_{add PK}$ (ng.mL ⁻¹)	1.44 (28.5)	
$\sigma_{prop PK}$ (%)	18 (3.73)	
$\sigma_{prop UGE}$ (%)	27 (5.77)	

Abbreviations: AUC_{tau50} , 24h-dapagliflozin exposure associated with half maximal effect; E_{max} , maximum possible response (24h-UGE).

$V_{ss}/F = V_1/F + V_2/F = 859$ mL.kg⁻¹;

Considering $F = 83\%$ [1], $V_d = 713$ mL.kg⁻¹;

Distribution half-life = 2.32 h; Elimination half-life = 11.29 h.

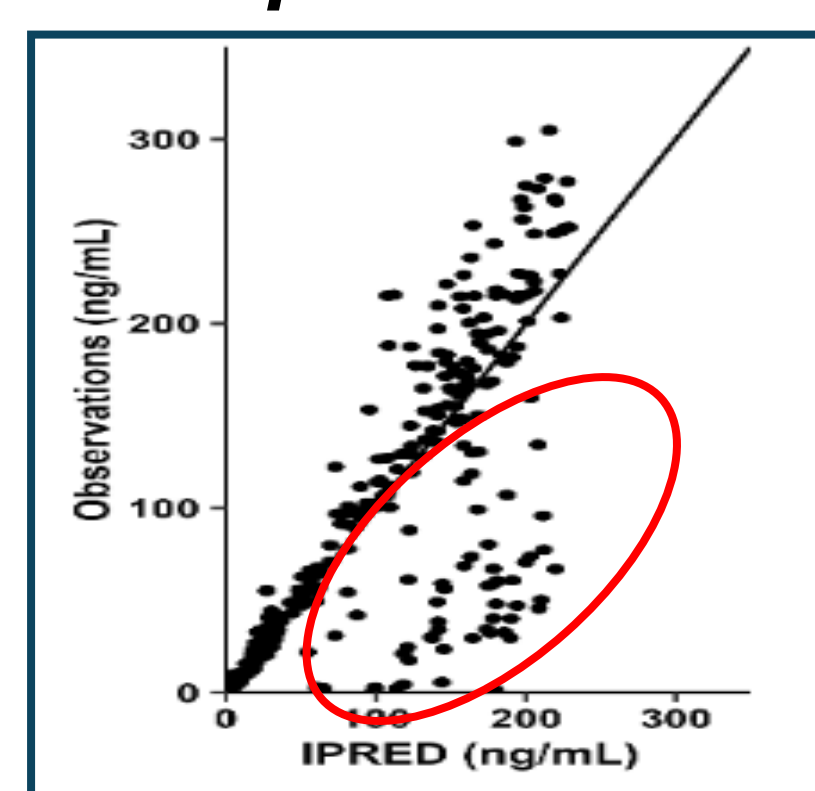
$Dose (daily) = Apparent\ clearance\ per\ hour \times target\ 24h\ exposure$
 $Target\ 24h\ exposure (AUC_{tau75}) = AUC_{tau50} \times 3$ (i.e. from E_{max} model)

$$Dose (daily) = 0.18 \text{ mg/kg}$$

Dose determination using simulation

- The dose that covers 90% of dogs was determined to be 0.21 mg/kg.
- Considering a variability of 30% or 50% in PK parameters (i.e. CL/F and AUC_{tau50}) the oral dose that covers 99% of dogs was determined to be 0.46 mg/kg/day and 0.85 mg/kg/day, respectively.

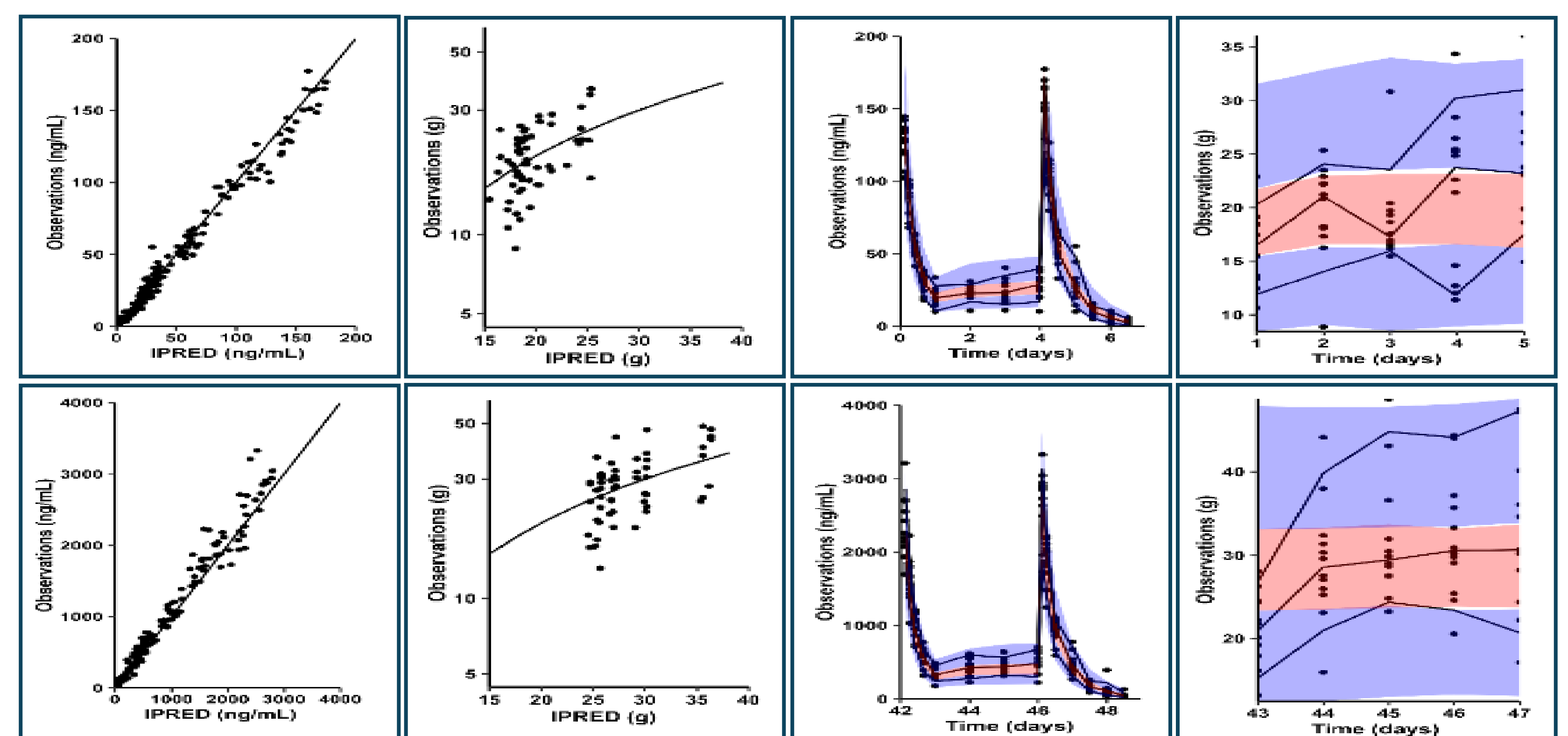
Fig 1. Impact of Interdigestive Migrating Myoelectric Currents (IMMCs) on dapagliflozin absorption. Plot of observed vs model-predicted of dapagliflozin concentrations in period 2 (left).



- In fasted state, gastrointestinal motility is organized as IMMCs with four phases (I, II, III, IV) that pass approximately every 60-100 min through the antral area of the stomach.
- During phase III of the IMMC (lasts ≈ 5 -15 min), gastric emptying occurs as a complete sweep (housekeeper peristaltic wave) [2, 3].
- Temporal aspect of duodenal absorption of dapagliflozin is random: depend on whether the time of administration coincides with phase III of the IMMC.
- Each administration becomes a unique occasion, and it is impossible to fit, for each dogs, the 15 absorption events with a single k_a value (see left plot).

- The adopted solution:** (i) to estimate a unique k_a value for each dog taking into account only the first administration, (ii) to fix this value of k_a as well as its random effect, (iii) to adjust the data collected over the 3 periods considering plasma concentrations before 90 min as missing observations.

Fig 2. Diagnostic plots of the final PK-PD model. Observed vs model-predicted, and visual predictive check of dapagliflozin concentrations and UGEs (from left to right), in period 2 and 4 (from top to bottom). In VPC plots, dots are data, solid lines are low (10th), median (50th) and up (90th) percentiles of observed data, and shaded areas are 10%, 50%, and 90% prediction intervals. The time of the first administration is considered the start time.



Conclusions

- First study describing the pharmacokinetics (PK) and the concentration-effect relationship of oral dapagliflozin in healthy dogs using a population PK-PD modeling approach.
- The PK of dapagliflozin was well described using a two-compartment model with a first-order absorption rate constant; and the 24h-UGE was well described using a direct E_{max} PK-PD model.
- The oral daily dose of dapagliflozin that induces 75% of the maximum glucosuria in healthy dogs was determined to range between 0.18-0.85 mg/kg/day.

References

- [1] European public assessment reports. Forxiga, dapagliflozin. Procedure No. EMEA/H/C/002322
- [2] Martinez MN, Papich MG. J Pharm Sci. 2009. PMID: 18661535.
- [3] Dressman JB. Pharm Res. 1986. PMID: 24271517.