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Bioavailability of suppository acetaminophen in healthy and hospitalized ill dogs

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To determine the plasma pharmacokinetics of suppository acetaminophen (APAP) in healthy dogs and clinically ill dogs. This prospective study used six healthy client-owned and 20 clinically ill hospitalized dogs. The healthy dogs were randomized by coin flip to receive APAP orally or as a suppository in crossover study design. Blood samples were collected up to 10 hr after APAP dosing. The hospitalized dogs were administered APAP as a suppository, and blood collected at 2 and 6 hr after dosing. Plasma samples were analyzed by ultra-performance liquid chromatography with triple quadrupole mass spectrometry. In healthy dogs, oral APAP maximal concentration (C_{MAX}=2.69 μg/ml) was reached quickly (T_{MAX}=1.04 hr) and eliminated rapidly (*T1/2* = 1.81 hr). Suppository APAP was rapidly, but variably absorbed (C_{MAX}=0.52 μg/ml T_{MAX}=0.67 hr) and eliminated ($T_{1/2}$ = 3.21 hr). The relative (to oral) fraction of the suppository dose absorbed was 30% (range <1%–67%). In hospitalized ill dogs, the suppository APAP mean plasma concentration at 2 hr and 6 hr was 1.317 μg/ml and 0.283 μg/ml. Nonlinear mixed-effects modeling did not identify significant covariates affecting variability and was similar to noncompartmental results. Results supported that oral and suppository acetaminophen in healthy and clinical dogs did not reach or sustain concentrations associated with efficacy. Further studies performed on different doses are needed.

1 | INTRODUCTION

Hospitalized patients frequently are unable to take medications orally (e.g., sedation, regurgitation, vomiting). A wide array of illnesses or conditions can contribute to nausea or vomiting, some of which include chemotherapy, abdominal surgery, anesthesia, esophagitis, megaesophagus, gastric surgery, or ulceration. Patients with such conditions may be unlikely to tolerate oral medications. Also, oral food, water, and medications may be withheld prior to anesthesia or because of esophageal or gastric disease. Veterinarians and pet owners would benefit from additional options to provide pain management using suppository APAP as an alternative pain medication, or a contribution to multimodal canine pain management. In contrast to NSAIDs, APAP at clinically relevant dosages is not associated with adverse gastrointestinal effects such as ulceration and APAP does not impair kidney function in people at clinical dosages (Hörl, 2010). Older patients are more likely to have preexisting renal insufficiency, which may preclude them from using NSAIDs (Behrend et al., 1996).

The bioavailability and kinetics of oral APAP have been previously determined; APAP maximal concentration (C_{MAX} = 6.74 μg/ml) was reached quickly (T_{MAX} = 0.86 hr) and eliminated rapidly (T½ = 0.96 hr) (KuKanich, 2009; Savides, Oehme, Nash, & Leipold, 1984). Formulations for intravenous administration of APAP are available, but costly. Suppository APAP is approximately 3% the cost of the injectable formulation. The bioavailability and pharmacokinetics of suppository APAP in dogs have not been determined. Our aim was to determine the bioavailability and pharmacokinetics of suppository APAP in dogs. We hypothesize that suppository APAP will have acceptable bioavailability and duration allowing this agent to provide analgesia in dogs.

2 | MATERIAL AND METHODS

2.1 | Subjects

Two groups of dogs were recruited. The first group consisted of six healthy dogs weighing between 25 and 35 kg owned by staff and students of the University of Wisconsin-Madison (UW-Madison) Veterinary Medical Teaching Hospital (VMTH). They were healthy based on an evaluation of past medical history, vaccine status, exclusion of any concurrent diseases, complete physical examination, and normal PCV/TP and liver parameters on biochemical profile. Additionally, the subject's age, weight, body condition score, and estimation of ideal body weight were recorded.

The second group consisted of twenty clinically ill hospitalized patients, weighing between 25 and 35 kg that were hospitalized at the UW-Madison critical care unit (CCU) and receiving suppository APAP. The clinical decision for patient to be administered suppository APAP was at the primary clinician's discretion. Suppository APAP was regularly prescribed in the CCU at the time of this study. Twenty subjects were selected as a sample size that could be feasibly fulfilled during the study period. The hospitalized patient's age and primary disease process were recorded; any evidence of hypotension or organ dysfunction as well as body condition score and ideal weight estimation was also recorded. Client consent was obtained prior to study enrollment. All animals were treated humanely and under an animal care and use protocol.

2.2 | Design and sample handling

The healthy group had a sampling catheter placed aseptically in the lateral saphenous vein prior to drug administration. In a cross over design, the dogs received 325 mg (9.3–13 mg/kg) APAP orally (Plus Pharma, Commack, NY) or rectally (G&W Laboratories, South Plainfield, NJ). The route of admission was randomized via coin flip. There was a minimum washout period of 7 days between treatments. Blood samples (2 ml each) were collected at baseline (T = 0) and at 10, 20, 30, 45, min and 1, 2, 3, 4, 6, and 8 hr following APAP administration. An additional blood sample was obtained at 10 hr in the suppository group to document potential delayed absorption or sustained drug release. The saphenous catheters were flushed with 3 ml of sterile 0.9% saline after each collection to maintain patency. Blood samples were kept on ice, and plasma removed following centrifugation at 2000 *g* for 10 min; plasma was stored frozen at −70°C until batch analysis.

In the hospitalized dogs, blood samples were collected at two time points: 2 hr and 6 hr following rectal APAP drug administration as whole suppositories, 325 or 650 mg per dog, at a targeted dose of 10 mg/kg. Plasma was removed following blood sample centrifugation at 2000 *g* for 10 min; plasma was stored frozen at −70°C until batch analysis.

2.3 | Sample analysis

Acetaminophen concentrations were determined with ultra-performance liquid chromatography (Waters Acquity, Waters Corporation, Milford, MA, USA) with triple quadrupole mass spectrometry (Waters TQD, Waters Corporation, Milford, MA, USA). Acetaminophen d4 (200 ng/ml in acetonitrile) was used as an internal standard. Plasma standards, quality controls in plasma, and plasma samples were processed in an identical manner. Plasma, 50 µl, was added to 50 µl of deionized water in pass-through sample preparation plates (Ostro Pass-through Sample Preparation Plate, Waters Corporation, Milford, MA, USA) followed by 100 µl of internal standard solution and then the plates were vortexed and positive pressure applied. The liquid that passed through was then directly injected with an injection volume of 2 µl. The mobile phase consisted water with 0.1% formic acid and acetonitrile and separation was achieved with a C18 column (Waters CSH C18, 1.7 µm, 50 mm × 2.1 mm, Waters Corporation, Milford, MA, USA). The qualifying ions for acetaminophen and acetaminophen d4 were *m/z* (mass:charge) 152.15 and 156.16, respectively. The quantifying ions for acetaminophen and acetaminophen d4 were *m/z* 110.05 and 114.07, respectively. The standard curves in canine plasma were linear from 0.05 to 10 µg/ml. The accuracy of the assay on replicates of 5 each at 0.05, 0.5, and 5 µg/ml was 99, 94 and 96% of the actual concentration, respectively. The coefficient of variation of the assay on replicates of 5 each at 0.05, 0.5, and 5 µg/ml was 11, 3, and 1%, respectively. Stability of acetaminophen in canine plasma was assessed daily for 5 days with spiked plasma stored refrigerated (4°C) and at room temperature (20°C) on replicates of 3 each at 0.05, 0.5, and 5 µg/ml.

Noncompartmental pharmacokinetic analysis was performed with computer software (Phoenix 64, Winnonlin 7.0 Certara, Princeton NJ, USA). The variables calculated included the area under the curve from time 0 to infinity (AUCINF) using the linear trapezoidal rule, plasma clearance per fraction of the dose absorbed (Cl/F), apparent volume of distribution of the area during the elimination phase per fraction of the dose absorbed (V_z/F), first-order rate constant (λ_z), terminal half-life ($T_{1/2}$ λ_z), and mean residence time extrapolated to infinity (MRT). The maximum plasma concentration (C_{MAX}) and time to maximum plasma concentration (T_{MAX}) were directly determined from the data (KuKanich, 2009).

The nonlinear mixed-effects approach as implemented in Phoenix NLME™ (version 7.0, Certara USA, Inc., Cary, NC) was used to fit the plasma acetaminophen concentration data to a compartmental pharmacokinetic model for both the healthy (n = 6) and hospitalized (n = 20) dogs (Li et al., 2014; Lin et al., 2016; Mould & Upton, 2012; Upton & Mould, 2014). In brief, the extended least-squares, first-order conditional estimation (FOCE-ELS) algorithm with interaction was used to fit the data to the model and to calculate the population pharmacokinetic parameters. Typical population pharmacokinetic parameter values, interindividual variability (IIV), and residual error were calculated. Exponential models were employed to describe between-individual variability, while residual variability was tested with additive, proportional, poisson, and combined error models. The choice of the number of compartments was guided by goodness-of-fit plots (e.g., observed vs. predicted plasma concentrations, weighted residuals vs. predicted concentrations, and weighted residuals vs. time), the −2 log-likelihood (−2LL), Akaike

information criterion (AIC), as well as the Bayesian information criterion (BIC). The model was selected based on the following considerations: superior goodness-of-fit plots, better precision of estimates, less model complexity, less uncertainty of parameter values, and/or smaller values of AIC and BIC.

To identify possible associations between the values of the pharmacokinetic parameters and individual characteristics, the following potential covariates were tested: body weight, surgical operation, age, breed, sex, and values the serum chemistry profile including glucose, blood urea nitrogen (BUN), albumin (Alb), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin (tBili), and cholesterol (Chol). The breed, sex, and surgical operation were set as categorical variables, while others were set as continuous variables. A covariate was identified in an intermediate model if addition of the covariate resulted in a decrease in AIC or BIC of 2, which is often a threshold for considering one model, is better over another (Mould & Upton, 2012). A covariate was retained in the model only when its influence was statistically significant and relevant.

The performance and stability of the final pharmacokinetic model were evaluated with both graphical methods by comparing observed vs. model-predicted concentrations visually, and by a bootstrap analysis. The bootstrap samples were collected through random resampling by replacing the original dataset to generate another dataset with the same sample size as the original but with a different combination of subjects. The bootstrap resampling analysis was repeated 100 times using Phoenix NLME™. If the parameter estimates fell into the 95% confidence intervals (CIs) from the bootstrap analysis, the model was considered unbiased and stable.

The final model was used to conduct Monte Carlo simulations using a dosage regimen of 325 mg/dog per rectum in Phoenix NLME™. The population mean value and the interindividual variability (IIV) of each parameter from Table 3 were used in the Monte Carlo simulations. The Monte Carlo simulations generated plasma time–concentration profiles of acetaminophen in dogs for 100 replicates. The predicted 5%, 50%, and 95% quantiles of plasma acetaminophen concentrations were compared to the observed individual animal plasma concentrations, as well as to the 5%, 50%, and 95% quantiles of observed plasma concentrations.

3 | RESULTS

Acetaminophen was stable in canine plasma when stored at room temperature or refrigerated for 5 days. The mean concentrations were 99%, 107%, 105%, 103%, 104%, and 102% of the actual concentration on days 0, 1, 2, 3, 4, and 5, respectively, when stored at room temperature. The mean concentrations were 99%, 104%, 104%, 100%, 101%, and 99% of the actual concentration on days 0, 1, 2, 3, 4, and 5, respectively, when stored refrigerated. The lowest single accuracy was 86% of the 108 stability samples assessed across the 5 days which is still within the acceptable variability of the assay.

Oral and suppository APAP treatments were tolerated well by both the healthy and hospitalized dogs. The healthy group breeds included two Labrador Retrievers and one each Golden Retriever, Doberman Pinscher, Staffordshire Terrier, German Shorthair Pointer. The mean age was 6.3 years (3.5–12.0 years), mean weight was 28.8 kg (27.1–34.4 kg), and a mean body condition score was 5/9. Their PCV/TP was within normal limits (range PCV 37%–55%, TP 5.5–7.5 g/dl). Biochemistry values (glucose, BUN, albumin, AST, ALT, ALP, GGT, tBili, and Chol) were normal in four dogs. One dog had a mildly elevated ALP of 313U/L (reference interval (RI): 20–157U/L). Another subject with historically elevated liver enzymes had the following liver enzyme elevations [AST 56U/L (RI: 21–53U/L), ALT 265U/L (RI: 20–157U/L), ALP 984U/L (RI: 20–157U/L)].

Twenty hospitalized dogs were recruited from the UW-Madison VMTH CCU. Each dog was administered 325 mg or 650 mg of suppository APAP to approximate a 10 mg/kg dosage. Blood

TABLE 1 Acetaminophen pharmacokinetic parameters after a single oral dose in six healthy dogs using noncompartmental analysis

		Geometric Mean	Min	Median	Max
AUC Extrapolated	%	4.9	1.1	3.1	29.4
AUC LAST	hr*µg/ml	7.04	5.78	6.92	9.58
AUCINF	hr*µg/ml	7.83	6.09	7.88	9.81
Cl/F	ml min^{-1} kg^{-1}	24.4	17.2	22.4	35.4
C_{MAX}	µg/ml	2.69	1.18	2.98	5.87
$T_{1/2}$ λ_z	hr	1.81	0.87	1.78	4.01
λ_z	1/hr	0.383	0.173	0.392	0.798
MRT INF	hr	2.69	1.46	2.10	6.44
T_{MAX}	hr	1.04	0.75	0.75	4.00
V_z/F	L/kg	3.82	2.25	3.76	8.28

AUC extrapolated, percent of AUC extrapolated to infinity; AUC last, AUC to the last time point above the analytical lower limit of quantification; AUC INF, AUC extrapolated to infinity; Cl/F, clearance per fraction of the dose absorbed; C_{MAX}, maximum plasma concentration; $T_{1/2}$ λ_z, terminal half-life; λ_z, terminal rate constant; MRT INF, mean residence time extrapolated to infinity; T_{MAX}, time of C_{MAX}; V_Z/F, volume of distribution per fraction of the dose absorbed.

samples were collected at 2 hr and 6 hr following suppository APAP administration. The dog breeds included Labrador Retrievers (*n* = 4), Golden Retrievers (*n* = 4), English Springer Spaniels (*n* = 3), German Shepherds (*n* = 2), German Pointers (*n* = 2), and one each of the following: Vizsla, Old English Sheepdog, Staffordshire Terrier, Collie, Doberman Pinscher. The hospitalized dogs primary diagnosis leading to CCU admission included gastric dilatation and volvulus (*n* = 3), left arytenoid lateralization (*n* = 2), gastrointestinal foreign body (*n* = 2), fungal rhinitis (*n* = 2), and one each of the following: pyometra, pyothorax, chylothorax, gastrointestinal perforation, bilateral anal sacculectomy, forelimb amputation, hemoperitoneum with splenectomy, sialocele, septic peritonitis, septic arthritis, and septic cholangitis. The hospitalized dogs mean weight was 29.9 kg (range: 21.8–43.5 kg); their mean age was 7.5 years (range: 3–12 years), and mean body condition score was 4/9.

In total, 25 different medications were administered in addition to acetaminophen. The average number of medications per patient was 3.4 ± 2.2 (range: 0–8). The most commonly administered drugs were fentanyl (14/20 dogs), maropitant (8/20), ampicillin/sulbactam (6/20), pantoprazole (5/20), and ketamine (5/20) with the remaining drugs administered to 3 or less dogs. The effect of these medications on acetaminophen elimination or rectal absorption is undetermined. The remaining concurrent drugs included enrofloxacin, amoxicillin/clavulanate, piperacillin, metronidazole, sucralfate, misoprostol, mirtazapine, dolasetron, gabapentin, lidocaine, hydromorphone, carprofen, acepromazine, trazodone, metoclopramide, famotidine, diphenhydramine, ursodiol, butorphanol, and erythromycin. Due to the large variability in the number and specific concurrent drugs, lack of documented interactions on glucuronidation in dogs, acetaminophen's primary mechanism of metabolism, and relatively

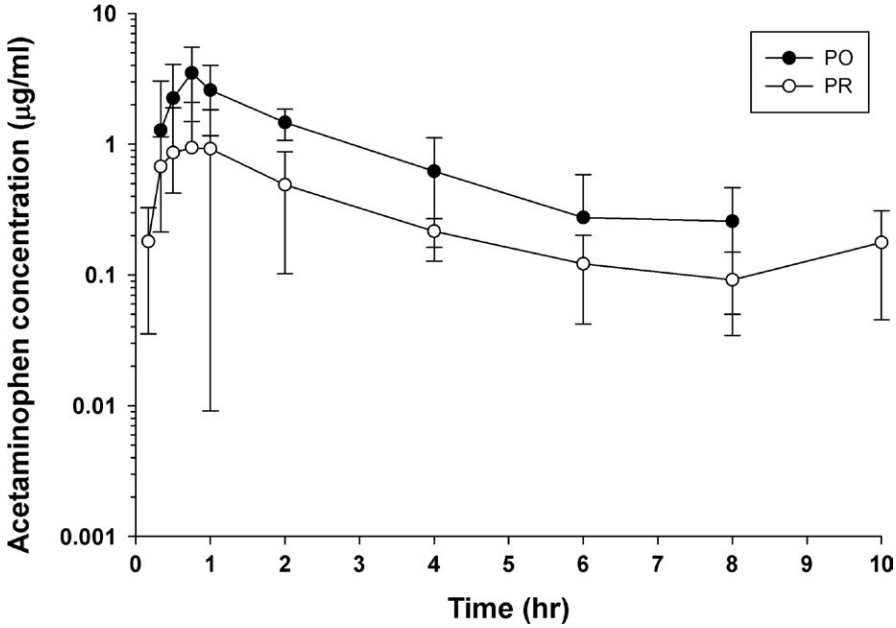

FIGURE 1 Plasma concentrations (mean and standard deviation) of acetaminophen after oral (PO) tablet administration or rectal (PR) suppository administration to healthy dogs

TABLE 2 Acetaminophen pharmacokinetic parameters after a single suppository dose in six healthy dogs using noncompartement analysis

		Geometric Mean	Min	Median	Max	*n*
AUC Extrapolated	%	13.2	2.6	25.6	62.5	5
AUC LAST	hr*µg/ml	1.05	0.03	1.91	4.93	6
AUCINF	hr*µg/ml	3.06	1.02	4.05	6.68	5
Cl/F	ml min^{-1} kg^{-1}	60.0	29.3	48.9	166.6	5
C_{MAX}	µg/ml	0.52	0.07	0.54	2.58	6
$T_{1/2}$ λ_z	hr	3.21	1.12	3.41	10.69	5
λ_z	1/hr	0.216	0.065	0.203	0.618	5
MRT INF	hr	4.70	1.79	4.41	17.59	5
T_{MAX}	hr	0.67	0.33	0.75	2.00	6
V_z/F	L/kg	16.67	4.56	27.11	49.23	5
Relative F (to PO)		30%	<1%	33%	67%	6

The number of dogs included for each pharmacokinetic parameter (*n*) is included as one of the animals only had plasma concentrations detected at three time points and as such could have full pharmacokinetic analysis. Relative F, fraction of the dose absorbed relative to p.o administration; also see Table 1.

small number of dogs (n = 20), evaluation of concurrent drugs in the mixed-effects modeling was not performed.

In the healthy group, the median APAP dose was 11.8 mg/kg (range: 9.5–14.0 mg/kg). Results of pharmacokinetic parameters following administration of oral acetaminophen are reported in Table 1 and Figure 1. Results of pharmacokinetic parameters following administration of suppository acetaminophen are reported in Table 2 and Figure 1.

In the hospitalized group, the median dose of suppository APAP was 11.9 mg/kg (range: 9.3–14.9 mg/kg). The suppository acetaminophen plasma concentration at 2 hr had a mean of 1.317 μg/ml (range 0.1453–3.7736 μg/ml), Figure 2. The suppository acetaminophen plasma concentration mean in the clinical group at 6 hr was 0.283 μg/ml (range <0.05–0.8538 μg/ml), Figure 2.

Overall for the nonlinear mixed-effects model, a one-compartment model without lag time and first-order absorption and first-order elimination adequately characterized the plasma acetaminophen concentration data (Table 3). None of the potential covariates was found to be statistically significant and relevant. Therefore, the base model without covariates was used for subsequent analyses. The bootstrap analysis results showed that the 95% CIs of all parameters were generally centered around the parameter mean estimates. The mean values obtained from the bootstrap analysis were comparable to the estimates of the typical population values in the final model and to the values of the noncompartmental analysis in the healthy dogs. However, noncompartmental or compartmental analysis was not possible in the clinical patient due to the sparse sampling. Using the final model parameter estimates, the simulated plasma time–acetaminophen concentration profiles for the 5th to the 95th percentiles of the population covered almost all the observed concentrations in the samples collected from individual animals and correlated with the 5th to the 95th percentiles of the observed data well (Figure 3).

4 | DISCUSSION

Results revealed that the 325 mg dosage of suppository APAP had a much lower bioavailability than orally administered APAP. It is unclear why the

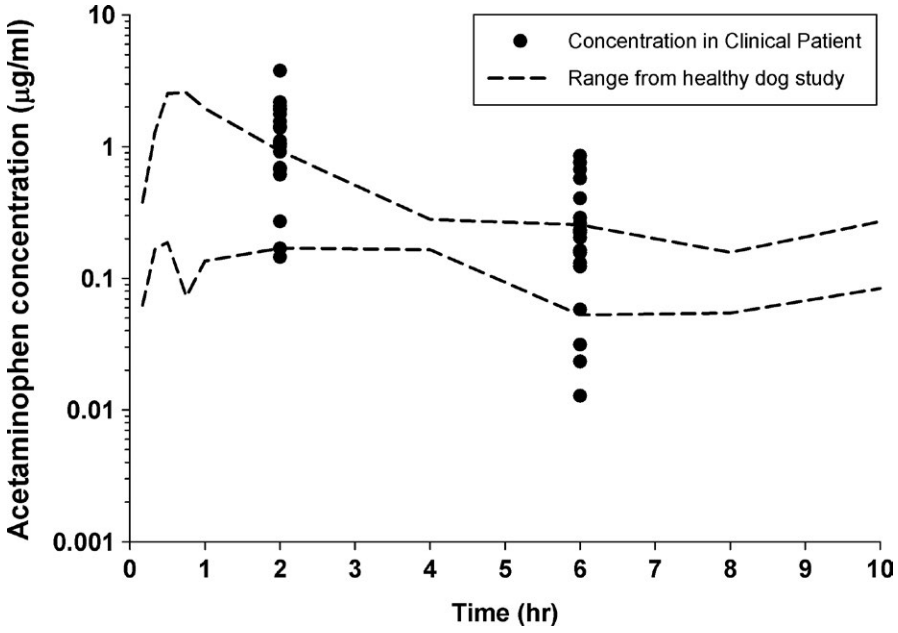

FIGURE 2 Plasma concentrations of acetaminophen from clinical patients and ranges (min-max) from healthy dogs after per rectum administration of acetaminophen as a suppository

TABLE 3 Typical population values for the one-compartment pharmacokinetic model parameters for plasma acetaminophen following rectal administration in dogs

Parameter	Units	Typical value for the population	IIV	Bootstrap mean	2.5% CI	97.5% CI
K_a	1/hr	2.169	2.398	2.128	0.534	4.558
V/F	L	273.09	0.794	240.71	112.96	420.87
K_{el}	1/hr	0.327	0.251	0.374	0.222	0.554
stdev0		0.464	NA	0.464	0.296	0.624
Cl/F	ml/min	1488	NA	1371	950	2087

These values are not weight normalized.

CI, confidence interval; IIV, interindividual variability; K_a, absorption rate constant; K_{el}, elimination rate constant; NA, not available or not applicable; stdev0, residual error; also see Table 1.

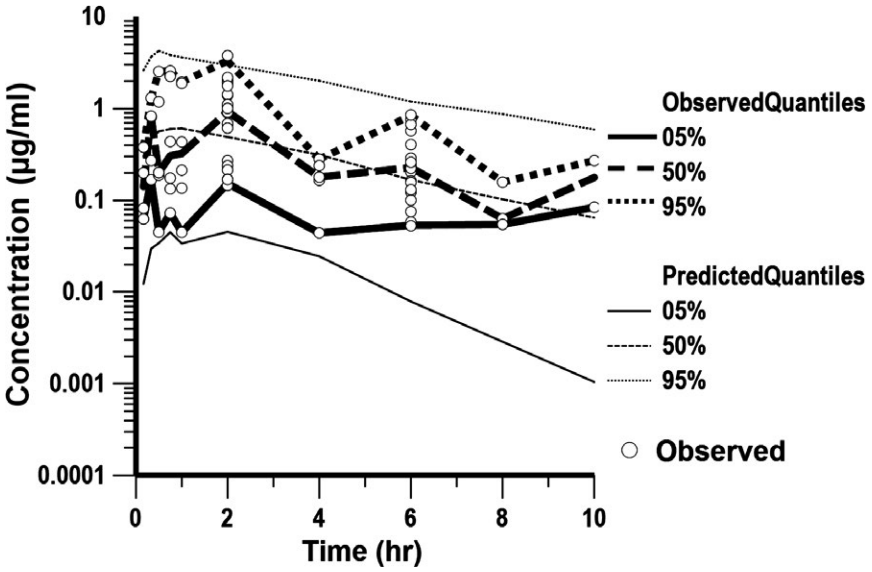

FIGURE 3 Monte Carlo simulation result. Comparisons of simulated 5%, 50%, and 95% percentiles of plasma acetaminophen time–concentration profiles vs. the observed concentrations in individual animals and the 5%, 50%, and 95% percentiles of the observed time–concentration profiles

relative fraction for suppository APAP was so low. In healthy dogs, suppository APAP was rapidly absorbed and eliminated (Table 2) but did not reach the previously described antinociception concentrations in humans, 4 µg/ml (Gelotte, Auiler, Lynch, Temple, & Slattery, 2007).

An additional and unexpected finding in this study was that the oral bioavailability of APAP was lower (Table 1) than has been previously reported (C_{MAX} 6.74 µg/ml; AUC 13.78 h*µg/ml) for a similar dose (KuKanich, 2009). The previous study administered the combination product containing APAP with codeine, but our study administered APAP as a sole ingredient tablet. The presence of codeine could slow intestinal motility allowing for greater absorption. It is not known why such differences in bioavailability occurred.

In the hospitalized dogs, mean plasma concentrations following suppository APAP were low at 2 hr and at 6 hr (Figure 2). The elimination half-life based on the Kel as determined by NLME was 2.1 hr within the range reported for both oral and rectal administration in healthy dogs. The plasma concentrations of some animals in the clinical group were slightly higher than those of the healthy group, but were variable.

Antinociception was not assessed in our study. In humans, antinociception is reported at plasma APAP levels of 4 µg/ml or greater (Pickering et al., 2006). Antinociception was not detected with use of an electronic von Frey device with APAP C_{MAX} of 7.95 µg/ml in Greyhounds (KuKanich, 2016) when administered with codeine. Given the low bioavailability of suppository APAP and antinociception evidence, it is doubtful that suppository APAP at current dosages is of clinical benefit.

A study performed by Yong et al. (2004); examined the enhanced rectal bioavailability of ibuprofen, a poorly water-soluble drug, in rats using poloxamer 188 and menthol. It was found that the poloxamer gel with menthol gave significantly higher initial plasma concentrations, C_{MAX}, than the solid suppository, indicating that using poloxamer 188 and menthol was more effective on absorption rates for ibuprofen. Acetaminophen, also a poorly water-soluble drug, may benefit from the addition of absorption enhancers to improve rectal absorption, which could be investigated in the future.

Our study had some limitations. The healthy dogs fasting times were not standardized or recorded; variable fasting times could alter gastrointestinal transit times and absorption rates. When subjects had last defecated was not recorded prior to starting the trial, and the amount of fecal matter palpated in the rectum was not quantified in either group. Greater focus on patients' fasting, defecation, and rectal fecal material may have altered the results. However, such factors are unlikely to account for such low bioavailability (and plasma concentrations) following suppository APAP.

We conclude that the suppository APAP dose of 9.5–14 mg/kg resulted in low plasma concentrations which are unlikely to be therapeutic or beneficial in canine patients. Oral APAP administered as a sole agent without codeine achieves much lower plasma concentrations than previously reported. Further investigation is needed.

CONFLICT OF INTEREST

None of the authors have any professional or financial conflicts of interest that would affect this works outcome.

AUTHORS' CONTRIBUTIONS

ES, JB, and BK contributed to study design. ES and JB performed the experiments. ZL, RG, and BK performed data analysis. ES composed the manuscript with contributions from JB, ZL, RG, and BK. All authors have read and approved of the final manuscript.

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REFERENCES

Behrend, E. N., Grauer, G. F., Mani, I., Groman, R. P., Salman, M. D., & Greco, D. S. (1996). Hospital-acquired acute renal failure in dogs: 29 cases (1983-1992). *Journal of the American Veterinary Medical Association*, *208*, 537–541.

Gelotte, C. K., Auiler, J. F., Lynch, J. M., Temple, A. R., & Slattery, J. T. (2007). Disposition of acetaminophen at 4, 6, and 8 g/day for 3 days in healthy young adults. *Clinical Pharmacology and Therapeutics*, *81*, 840–848. https://doi.org/10.1038/sj.clpt.6100121

Hörl, W. (2010). Nonsteroidal anti-inflammatory drugs and the kidney. *Pharmaceuticals*, *3*, 2291–2321.

KuKanich, B. (2009). Pharmacokinetics of acetaminophen, codeine, and the codeine metabolites morphine and codeine-6-glucuronide in healthy Greyhound dogs. *Journal of Veterinary Pharmacology and Therapeutics*, *33*, 15–21.

KuKanich, B. (2016). Pharmacokinetics and pharmacodynamics of oral acetaminophen in combination with codeine in healthy Greyhound dogs. *Journal of Veterinary Pharmacology and Therapeutics*, *39*, 514–517. https://doi.org/10.1111/jvp.12299

Li, M., Gehring, R., Tell, L., Baynes, R., Huang, Q., & Riviere, J. E. (2014). Interspecies mixed-effect pharmacokinetic modeling of penicillin G in cattle and swine. *Antimicrobial Agents and Chemotherapy*, *58*, 4495–4503. https://doi.org/10.1128/AAC.02806-14

Lin, Z., Cuneo, M., Rowe, J. D., Li, M., Tell, L. A., Allison, S., … Gehring, R. (2016). Estimation of tulathromycin depletion in plasma and milk after subcutaneous injection in lactating goats using a nonlinear mixed-effects pharmacokinetic modeling approach. *BMC Veterinary Research*, *12*, 258. https://doi.org/10.1186/s12917-016-0884-4

Mould, D. R., & Upton, R. N. (2012). Basic concepts in population modeling, simulation, and model-based drug development. *CPT: Pharmacometrics & Systems Pharmacology*, *1*, 1–14.

Pickering, G., Loriot, M. A., Libert, F., Eschalier, A., Beaune, P., & Dubray, C. (2006). Analgesic effect of acetaminophen in humans: First evidence of a central serotonergic mechanism. *Clinical Pharmacology and Therapeutics*, *79*, 371–378. https://doi.org/10.1016/j.clpt.2005.12.307

Savides, M. C., Oehme, F. W., Nash, S. L., & Leipold, H. W. (1984). The toxicity and biotransformation of single doses of acetaminophen in dogs and cats. *Toxicology and Applied Pharmacology*, *15*, 74.

Upton, R. N., & Mould, D. R. (2014). Basic concepts in population modeling, simulation, and Model-Based drug development: Part 3—Introduction to pharmacodynamic modeling methods. *CPT: Pharmacometrics & Systems Pharmacology*, *3*, 1–16.

Yong, C. S., Yang, C. H., Rhee, J. D., Lee, B. J., Kim, D. C., Kim, D. D., & Choi, H. G. (2004). Enhanced rectal bioavailability of ibuprofen in rats by poloxamer 188 and menthol. *International Journal of Pharmaceutics*, *269*, 169–176. https://doi.org/10.1016/j.ijpharm.2003.09.013

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