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Absorption of grapiprant in red-tailed hawks (*Buteo jamaicensis*) is decreased when administered with food

Paula Rodriguez, DVM[1]; Joanne R. Paul-Murphy, DVM[2]*; Heather K. Knych, DVM, PhD[3]; Tracy L. Drazenovich, DVM[2]; Michelle G. Hawkins, VMD[2]

[1]William R. Pritchard Veterinary Medical Teaching Hospital, School of Veterinary Medicine, University of California-Davis, Davis, CA
[2]Department of Medicine and Epidemiology, School of Veterinary Medicine, University of California-Davis, Davis, CA
[3]K. L. Maddy Equine Analytical Pharmacology Laboratory, School of Veterinary Medicine, University of California-Davis, Davis, CA

*Corresponding author: Dr. Paul-Murphy (paulmurphy@ucdavis.edu)

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OBJECTIVE
Describe the pharmacokinetics of grapiprant administered orally with food to red-tailed hawks (RTHAs; *Buteo jamaicensis*) and compare the results with previously described grapiprant pharmacokinetics administered without food in this species.

ANIMALS
6 healthy adult RTHA (3 males, 3 females) under human care.

PROCEDURES
A single dose of grapiprant (30 mg/kg) was given orally to RTHAs, followed by force-feeding. Blood samples were obtained at 14 time points for 120 hours postgrapiprant administration. Plasma concentrations of grapiprant were measured via tandem liquid chromatography-mass spectrometry. Nonparametric superimposition using pharmacokinetic modeling software used plasma concentrations to calculate simulations of grapiprant plasma concentrations for 30 mg/kg administered orally with food every 12 hours.

RESULTS
The arithmetic mean maximum plasma concentration was 405.8 ng/mL, time to maximum plasma concentration was 16 hours, and harmonic mean terminal half-life was 15.6 hours. Simulations determined 30 mg/kg every 12 hours could attain minimum effective concentrations (> 164 ng/mL) reported in dogs for a sustained period of approximately 20 hours.

CLINICAL RELEVANCE
Grapiprant plasma concentrations were achieved above the canine therapeutic concentrations within 16 hours postmedication. Mean concentrations were maintained for approximately 20 hours. Simulations support a dosing frequency of 12-hour intervals with food reaching minimum effective concentrations established for canines, although it is unknown whether these plasma concentrations are therapeutic for birds. Bioaccumulation was not noted on simulations secondary to increased grapiprant administration. Further research including multidose assessments at this current dose with food, in vitro pharmacological characterization, and pharmacodynamic studies in this species are warranted.

Red-tailed hawks (RTHAs; *Buteo jamaicensis*) are widely distributed in the wild and in captive settings. For this reason, this species is commonly used as a raptor model for evaluating medications. Trauma is one of the most common presentations for birds of prey to wildlife centers.[1] Osteoarthritis (OA) is a common finding of captive raptors and has also been reported in wild raptors;[1–4] one study[4] identified a prevalence of 2.8% OA of the intertarsal joint from postmortem examinations of over 2,000 free-ranging hawks. Osteoarthritis is characterized by the degeneration of the cartilage and soft tissues, hypertrophy of the bone at the margins, and changes in the synovial membrane.[5]

NSAIDs with their nonselective or preferential cyclooxygenase (COX) isoform inhibition are the most common treatments for inflammation and musculoskeletal pain in many species, including birds.[6] Grapiprant (Galliprant; Elanco Animal Health) is a non–COX enzyme–inhibiting, nontraditional NSAID approved for dogs.[6–10] It belongs in the piprant class of drugs that preserves the functions associated with COX enzymes pathways by directly binding to the prostaglandin E_2 receptor 4 (EP4), blocking the sensitization of sensory neurons and stimulation of inflammation that is mediated by prostaglandin E2 (PGE_2).[6,8] Based on a recent study, a single oral dose of 30 mg/kg grapiprant administered to fasted

RTHAs achieved plasma concentrations much higher than the canine minimum effective concentration (MEC) of 164 ng/mL.[9,11–13] To the authors' knowledge, the previous report was the first and only study to evaluate grapiprant in any avian species.[13]

The oral bioavailability of grapiprant is affected by food intake in mammals.[14] The canine grapiprant MEC was elected for comparison due to extensive research on this subject and similarities of frequency of feeding strategy of 1 or 2 meals per day. Administration of food decreased bioavailability of grapiprant by 52% in dogs compared with dogs receiving the same oral dose with food withheld, yet plasma concentrations were reported above the MEC for both groups.[14] The drug composition and the meal offered to the evaluated species are important to predict food-drug interactions.[15]

The purpose of the study reported here was to identify whether 30 mg/kg grapiprant administered orally with food to RTHAs would attain plasma concentrations considered therapeutic in dogs (164 ng/mL) and to compare with the pharmacokinetics of the same grapiprant dose administered to RTHAs when food was withheld for 24 hours.[13] We hypothesized that grapiprant administered orally with food to RTHAs would achieve lower plasma concentrations than the previous RTHA study and maintain plasma concentrations above 164 ng/mL with minimal adverse effects.[13]

Materials and Methods

Animals

The 6 adult RTHAs (3 males, 3 females) used in this study are permanent residents of the California Raptor Center, School of Veterinary Medicine University of California-Davis. Their estimated ages ranged between 6 and 18 years. These same birds were involved in a previous grapiprant study, and inclusion criteria were previously described.[13]

Housing and feeding

During the study period, birds were housed in 2 rooms in individual plastic kennels (121.9 cm wide X 81.2 cm high X 88.9 cm deep) with cage fronts and sides covered with cardboard to reduce visual stress from human activities in the rooms. Birds underwent 2 weeks of acclimation, had a light cycle of 12 to 14 hours light and 10 to12 hours darkness, and were returned to their permanent outdoor enclosures after the final phlebotomy at 120 hours after drug administration, as previously described.[13]

The daily diet consisted of 4- to 5-day-old chicks/RTHA, based on their resting energy requirement. Water was provided ad libitum. Force-feeding was implemented if no food was eaten over a 24-hour period.

Monitoring for adverse effects

The RTHAs were monitored for mentation changes, regurgitation, or decreased appetite. The presence and characteristics of urofeces were monitored daily for noticeable diarrhea, melena, hemorrhage, or bright green appearance. Body weights were obtained daily during cage cleaning and before feeding to minimize capturing.

Single-dose study

All study procedures were approved by the Institutional Animal Care and Use Committee of the University of California (No. 21492). Based on a previous study, the single oral dosage of 30 mg/kg grapiprant was selected.[13] The 6 RTHAs were randomly[16] assigned to the administration order for the drug. Grapiprant was prepared for oral administration as described previously.[13] Each RTHA was manually restrained, and oral administration was completed by digitally placing the capsule into the crop and massaging it past the thoracic inlet, immediately followed by force-feeding the daily meal of day-old chicks cut into multiple pieces. Because birds were force-fed on the initial day of the study, food was offered ad libitum on the remaining days.

During phlebotomy, the RTHAs were manually restrained while their heads were covered with a light cloth hood to mitigate stress. Blood was collected immediately before grapiprant administration (time 0) and then at 0, 10, 15, and 30 minutes and 1, 2, 4, 6, 10, 16, 24, 48, 96, and 120 hours after grapiprant administration and force-feeding. To minimize stress from repeated capture, each RTHA was restrained and hooded for the first 30 minutes during the initial collection time points that were in close succession. Phlebotomy methods have been previously described,[13] with the amount collected from each RTHA for the entire study ≤ 1% of its body weight.

Grapiprant concentrations and pharmacokinetic parameters

Plasma calibrators, calibration curves, negative control samples, and grapiprant quality control samples were prepared as described.[13] Also, as previously described,[13,17] samples were extracted and grapiprant concentrations were determined with liquid chromatography-tandem mass spectrometry.

Commercially available software (Phoenix WinNolin version 8.0; Certara) was used for pharmacokinetic analysis of plasma grapiprant concentrations. Visual inspection of the concentration-time data was used[11,14,18] to identify plasma grapiprant maximum concentration (C_{max}), time to maximum concentration (t_{max}), and the duration of time that plasma concentrations were maintained above 164 ng/mL.[11,14,18] The terminal half-life ($t_{1/2\lambda}$) was calculated with the formula: $t_{1/2\lambda} = 0.693/_{\lambda z}$, where λ_z is the log-transformed terminal rate constant. Standard pharmacokinetic equations (Phoenix WinNonlin version 8.0; Certara) were used to determine the area under the concentration-versus-time curve from time 0 to infinity ($AUC_{0-\infty}$). With the use of confidence intervals for significance, results for pharmacological parameters of the previous study[13] in which food was withheld were compared with results of the present study in which food was not withheld.

Determination of grapiprant concentrations and pharmacokinetic parameters via simulations

Nonparametric superimposition using pharmacokinetic modeling software (Phoenix WinNonlin version 8.0; Certara), the assumption of linear kinetics, and the plasma concentrations measured in this single-dose study were utilized to generate simulation curves to determine the concentrations with oral administration of 30 mg/kg grapiprant at a frequency of every 12 hours. The canine grapiprant MEC of 164 ng/mL was used.[9,14,17–19]

Results

Animals

All 6 RTHAs were healthy and completed the single dose with food administration as planned with no changes in urofeces or mentation. Mean body weight was 1.06 kg (range, 0.93 to 1.22 kg) at T0 for this study.

Liquid chromatography with tandem mass spectrometry analysis

The liquid chromatography with tandem mass spectrometry (LC-MS/MS) instrument responses for the grapiprant were linear and yielded a correlation coefficient of 0.99 or better. The precision and accuracy of the assay were determined by assaying quality control samples in replicates (n = 6). Accuracy of the assay (reported as percent nominal concentration) was 98%, 105%, and 105% for plasma grapiprant concentrations of 500, 10, and 0.3 ng/mL, respectively; precision (reported as percent relative SD) was 4%, 4%, and 9% for plasma grapiprant concentrations of 500, 10, and 0.3 ng/mL, respectively. The precision of the assay was 9%, 4%, and 4% for 0.3, 10, and 500 ng/mL, respectively. The technique was optimized to provide a limit of quantitation of 0.1 ng/mL and a limit of detection of approximately 0.05 ng/mL for grapiprant.

Single-dose study

At 16 hours after administration of 30 mg/kg grapiprant orally with food, the mean ± SD plasma grapiprant concentration was 178.1 ± 201.7 ng/mL **(Figure 1)**, which exceeded the canine MEC of 164 ng/mL. The overall mean ± SD $t_{1/2}$ was 27.2 ± 27.9 hours (range, 8.47 to 81.7 h). Results for λ_z, $t_{1/2\lambda}$, t_{max}, C_{max}, total area under the first moment curve from time 0 to the last measured concentration (AUC_{0-last}), $AUC_{0-\infty}$, total area under the first moment curve from time 0 to the last measured concentration ($AUMC_{0-last}$), total area under the first moment curve from time 0 to infinity ($AUMC_{0-\infty}$), mean residence time from time 0 to the last measured concentration (MRT_{0-last}), and mean residence time from time 0 to infinity ($MRT_{0-\infty}$) were compiled **(Table 1)**. After oral administration of grapiprant to RTHAs with food, there was a delay in absorption, although this varied between RTHAs. Compared with findings of a previous study[13] in which food was withheld from RTHAs after administration of grapiprant (30 mg/kg, PO and advanced into the crop), the mean C_{max} was lower and median t_{max} was longer in RTHAs that received food immediately after drug administration. Means of pharmacokinetic parameters were compared for statistical significance using the 95% CIs of their means **(Table 2)**. The harmonic terminal half-life ($t_{1/2\lambda}$) was similar in both groups.

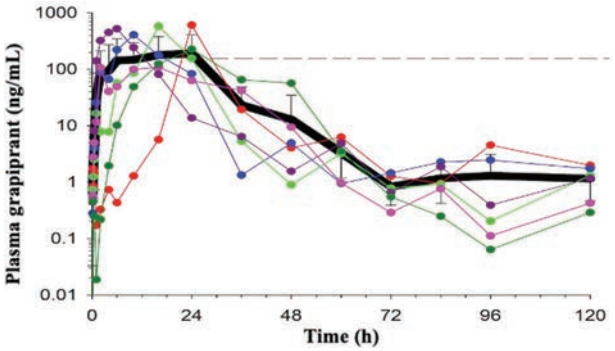

Figure 1—Log-transformed plasma grapiprant concentration measurements following administration of a single dose of grapiprant (30 mg/kg, PO and advanced into the crop) followed immediately with food force-fed at time 0 for 6 healthy red-tailed hawks (RTHAs; *Buteo jamaicensis*) from which food was not withheld before or after treatment. The black bold solid line represents the mean plasma grapiprant concentrations of all 6 RTHAs. The dashed horizontal line represents the plasma grapiprant concentration of 164 ng/mL (minimum effective concentration in dogs with osteoarthritis).

Table 1—Pharmacokinetic results for a single dose of grapiprant (30 mg/kg) administered PO and advanced into the crop followed by food to 6 healthy adult red-tailed hawks (*Buteo jamaicensis*).

Parameter	Mean (range)
AUC_{0-last} (h·ng/mL)	5,194.4 (2,924.6–6,579.1)
$AUC_{0-\infty}$ (h·ng/mL)	5,254.4 (2,932.1–6,670.8)
$AUMC_{0-last}$ (h·h·ng/mL)	102,241 (50,425–173,597)
$AUMC_{0-\infty}$ (h·h·ng/mL)	114,384 (53,861–188,839)
MRT_{0-last} (h)	19.6 (10.4–28.3)
$MRT_{0-\infty}$ (h)	21.5 (9.77–27.5)
C_{max} (ng/mL)	405.8 (108.3–604.2)
t_{max} (h)*	16 (6–24)
λ_Z (h^{-1})	0.048 (0.008–0.082)
$t_{1/2\lambda}$ (h)†	15.6 (8.47–81.7)

Data are reported as arithmetic mean and range, except where indicated.

λ_Z = Terminal slope of the concentration-versus-time curve. $AUC_{0-\infty}$ = Area under the concentration-versus-time curve from time 0 to infinity. AUC_{0-last} = Area under the concentration-versus-time curve from time 0 to the last measured concentration. $AUMC_{0-\infty}$ = Total area under the first moment curve from time 0 to infinity. $AUMC_{0-last}$ = Total area under the first moment curve from time 0 to the last measured concentration. C_{max} = Maximum observed concentration. MRT_{0-last} = Mean residence time from time 0 to the last measured concentration. $MRT_{0-\infty}$ = Mean residence time from time 0 to infinity. $t_{1/2\lambda}$ = Terminal half-life. T_{max} = Time to maximum concentration.

*The median and range are reported. †The harmonic mean and range are reported.

Table 2—Comparison of the means and 95% CIs of results for pharmacokinetic parameters for a single dose of grapiprant (30 mg/kg, PO and advanced into the crop) administered and followed immediately by food having been either withheld (previous study[13]) or force fed (present study) to the 6 red-tailed hawks described in Table 1.

	With food		Without food[13]	
Pharmacokinetic parameter	**Mean**	**95% CI of the mean**	**Mean**	**95% CI of the mean**
C_{max} (ng/mL)	405.8 ± 200.9 (108.3–604.2)	(245.02–566.5)[a]	3,625.7 ± 1,631.8 (1,013.3–5,298.8)	(2,319.73–4,931.67)[a]
t_{max} (h)	16 ± 7.27 (6–24)	(10.18–21.82)[b]	3.33 ± 2.07 (2–6)	(1.68–4.98)[b]
$t_{1/2\lambda}$ (h)	27.2 ± 27.9 (8.47–81.7)	(2.8–49.6)	21.9 ± 20.6 (9.62–63.3)	(5.42–38.38)
$t_{1/2\lambda}$ (h)*	15.6	—	14.7	—

Data are reported as arithmetic mean ± SD and range, except where indicated.
— = Not evaluated.
*The harmonic means are reported. [a,b]Values with the same superscripts differ significantly in that their 95% CIs do not overlap.
See Table 1 for the rest of the key.

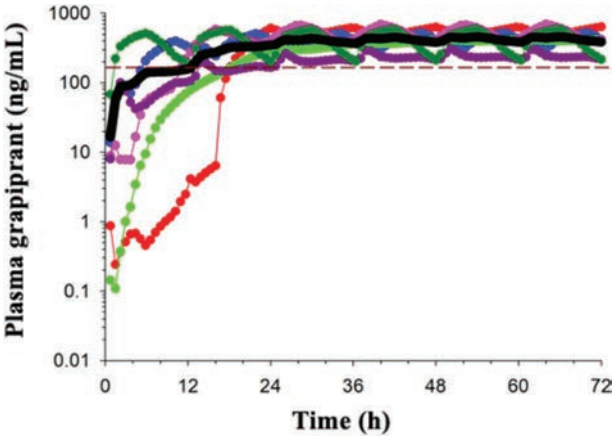

Figure 2—Results of simulations for log-transformed plasma grapiprant concentrations for grapiprant (30 mg/kg, PO and advanced into the crop, q 12 h) administration based on data gathered during the single-dose study performed in 6 healthy adult RTHAs administered a single dose of grapiprant (30 mg/kg, PO) with food. The black bold solid line represents the simulation concentrations of all 6 RTHAs. The dashed horizontal line represents the plasma grapiprant concentration of 164 ng/mL (the minimum effective concentration in dogs with osteoarthritis).

Simulations

Simulations of grapiprant plasma concentrations assuming linear elimination kinetics suggested that 30 mg/kg grapiprant administered every 12 hours with food should maintain plasma concentrations above the canine MEC for up to 20 hours **(Figure 2)**.

Adverse effects

Minimal adverse effects were noted in this study. Two episodes of regurgitation occurred: one bird regurgitated immediately after administration of the grapiprant capsule and food; both were immediately readministered without incident, and in the second episode only food was regurgitated 30-minute post-administration; the regurgitated food was force-fed again. Two birds were force-fed on other days of the study as these birds did not show evidence of an appetite after day 1. The mean weight of the birds over the first 48 hours was stable (mean of 1.06 kg) with a slight decrease (1.05 kg) at the 120-hour time point. The RTHA weights increased above the initial weight (mean, 1.15 kg) once they returned to their regular enclosures.

Discussion

Our findings indicated that after administration of a single dose of grapiprant (30 mg/kg) orally followed by force-feeding, the RTHAs of the present study achieved mean plasma grapiprant concentrations > 164 ng/mL at 16 hours postadministration and maintained up to 24 hours. This is equivalent to the plasma grapiprant concentration considered therapeutic in dogs with OA.[13,14,18,20] As hypothesized, RTHA plasma grapiprant concentrations were decreased when grapiprant was administered with food in the present study, compared a previous study[13] in which food was withheld. In canine studies, using the same group of dogs in the fed versus non fed studies, the absorption of grapiprant decreased by approximately 50% when dogs were fed prior to administration.[14] Similarly, the same RTHAs were used for evaluation of grapiprant administered with food (present study) or without food (previous study[13]), and the arithmetic mean ± SD plasma grapiprant C_{max} was significantly lower for the RTHAs in the fed study (405.8 ± 200.9 ng/mL), compared with the earlier study where food was withheld (3,625.7 ± 1,631.8 ng/mL; Table 2). In the present study, grapiprant plasma concentrations were reduced by 88% when the RTHAs were fed compared with not fed,[13] a greater change than reported in dogs comparing administration with food versus without food.[14]

In the present study, the median t_{max} was 16 hours. This is greater than the 2 hours identified when food was withheld from the hawks, illustrating that the presence of food in the gastrointestinal tract delayed t_{max} (Table 2). This is quite different from the t_{max} of 3 hours in fed dogs.[14] This is not surprising given the differences in gastrointestinal tract anatomy and physiology between hawks and dogs. Additionally, the effects on hawk crop emptying and gastrointestinal motility need to be considered.[21,22] Delayed crop emptying occurred in hooded RTHAs compared with those without a hood.[21] In the present study, the hawks were hooded for the initial blood collections possibly affecting the rate of crop

emptying, absorption of the medication, and the digestion of food. Other potential factors causing delayed crop emptying and gastrointestinal transit include systemic illness, diet, and size of the dietary item.[21,22] Different types of food can produce various effects on a drug's metabolism; however, these hawks are fed a uniform diet, reducing this concern.[15] These results support that the presence of food in the crop when administering grapiprant lowers the drug absorption. This is critical information, directly applicable to the clinical care and welfare of captive RTHAs requiring long-term treatment because the administration of medications in food is the standard of care to decrease daily handling.

The harmonic mean half-life of grapiprant administered to RTHAs with food versus without food was 15.6 hours and 14.7 hours, respectively, with similar variability.[13] The similarity of the harmonic mean half-life with and without food indicated that increasing the administration frequency could maintain the MEC for 8 hours or longer. Simulation plots of the pharmacokinetic data from the present study supported that plasma concentration would be maintained above the canine MEC of 164 ng/mL, which is therapeutic for dogs, with little to no accumulation over time with repeated doses.[14,18,20,23]

Even though the plasma concentrations noted in the previous RTHA study[13] with food withheld were high, no substantial adverse effects were reported. In the present study, the 2 episodes of regurgitation of food with or without a drug capsule occurred within 30 minutes after force-feeding could be attributed to handling or the volume of food as both episodes occurred while the hawks were being held for initial blood collections. In the present study, the RTHAs had better appetites and stable weights compared with the previous study.[13] This could have been attributed to the different study area environment, including fewer birds per room and reduced human activity.[13] Administering the single dose of grapiprant with food may have facilitated normal appetites in some of the hawks; however, the stress of the study presumably affected the hawk's appetites and weights because when returned to their regular outdoor enclosure, their weights increased.

Limitations of the present study included a low sample size, reducing the power of the study and increasing the margin of error. The RTHAs of the present study were the same as used in the previous grapiprant study,[13] and large individual variability in plasma concentrations occurred in both studies. Individual variability might be higher in a group of previously wild animals currently under human care when compared with a uniform population of laboratory animals commonly used in research studies. The variance of data acquired is expected to have been large because pharmacokinetic properties of drugs administered orally are often associated with higher variability than parental administration.[24] The final formulation administered to the birds was not evaluated to confirm the actual concentration; therefore, a potential lack of homogeneity in the doses administered to the 6 birds could have contributed to the variability of the results. However, the entire grapiprant tablet was finely ground and mixed prior to aliquoting the required powder for each bird's dose into gel capsules to minimize variation.[13,25]

The results of the present study confirmed our hypothesis that oral administration of a single dose of grapiprant (30 mg/kg) administered with food to adult RTHAs resulted in significantly lower grapiprant plasma concentrations when compared with findings of a previous study[13] in which the RTHAs were administered this same dose but had food withheld for 24 hours. Increasing the frequency of administration to every 12 hours with food may achieve plasma concentrations similar to the canine MEC determined to be effective in treating OA, for a longer period with minimal to no accumulation based on the simulations. However, this does not assure the dose can be considered therapeutic in RTHAs without pharmacodynamic data. These pharmacokinetic results provide a foundation for future pharmacodynamic studies and/or clinical trials for using grapiprant in birds. Additional safety monitoring with a multidose study and pharmacodynamic data collection is warranted on the use of grapiprant in RTHAs.

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