Penciclovir pharmacokinetics after oral and rectal administration of famciclovir in African elephants (*Loxodonta africana*) shows that effective concentrations can be achieved from rectal administration, despite lower absorption

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**OBJECTIVE**

To evaluate the pharmacokinetics of famciclovir and its metabolite penciclovir following a single dose administered orally and rectally in African elephants (*Loxodonta africana*).

**ANIMALS**

15 African elephants (6 males and 9 females) of various ages.

**METHODS**

Famciclovir (15 mg/kg) was administered orally or per rectum once, with at least a three-week washout period between administrations. Blood was collected at 13 different timepoints per administration for 6 elephants, occurring between February and March 2020. An additional 9 elephants were sampled at variable timepoints per administration utilizing a sparse sampling design between July 2020 and January 2021. Plasma famciclovir and penciclovir levels were measured via HPLC and fluorescence detection. Pharmacokinetic analysis was completed in the summer of 2021 using noncompartmental analysis and nonlinear mixed-effects modeling.

**RESULTS**

Famciclovir was not detected in any sample, suggesting complete metabolism. Key pharmacokinetic parameters for penciclovir following oral administration were time to maximum concentration (*t*\(_{\text{max}}\); 2.12 hours), area under the concentration-versus-time curve (AUC; 33.93 μg·h/mL), maximum observed concentration (C\(_{\text{max}}\); 3.73 μg/mL), and absorption half-life (*t*\(_{1/2}\); 0.65 hours). Following rectal administration, the values were: *t*\(_{\text{max}}\), 0.65 hours; AUC, 15.62 μg·h/mL; C\(_{\text{max}}\), 2.52 μg/mL; and absorption *t*\(_{1/2}\), 0.13 hours.

**CONCLUSIONS**

Famciclovir was rapidly metabolized to penciclovir. Oral administration resulted in slower absorption but higher maximum plasma concentration and higher AUC compared to rectal administration.

**CLINICAL RELEVANCE**

African elephants administered famciclovir via oral and rectal routes resulted in measurable serum penciclovir, and these findings may be utilized by clinicians treating viral infections in this species.

**Keywords:** African elephant, elephant endothelial herpesvirus, penciclovir, famciclovir, *Loxodonta africana*
in wild elephants. Multiple strains of EEHV have been identified, with associations between virus strain and elephant species. Initially, African elephants were believed to be asymptomatic carriers; however, a number of clinical cases of EEHV-hemorrhagic disease have been documented in recent years. Clinical signs are variable and include lethargy, anorexia, colic, leg stiffness, hyperemia, and discoloration (cyanosis) of mucous membranes, lingual vesicles, focal to generalized edema (particularly of the head and trunk), and internal hemorrhage. Clinical disease due to EEHV-hemorrhagic disease has been documented in both young and adult animals, and progression is often rapid and has been fatal within days of the first observation of clinical signs in several cases. However, early detection and treatment prior to or at the immediate onset of clinical signs has resulted in survival of some clinically affected animals. As sick elephants often become hyporexic or anorexic, there is a need and desire to be able to deliver medications rectally. Rectal administration has been successful in producing drug plasma concentrations in a presumptive therapeutic range for metronidazole, levofloxacin, and penciclovir/penciclovir in Asian elephants.

Recommended standard treatment for EEHV includes a combination of antiviral therapy, oral and/or rectal fluids, and plasma and whole-blood transfusions, with analgesics and antibiotics utilized as needed. Penciclovir has been the antiviral of choice in the majority of clinical cases in both Asian and African elephants in North America, although route (oral, rectal), dose (4.06 to 16.3 mg/kg), and frequency (every 8 to 12 hours) have varied. Because penciclovir has poor oral absorption, it is delivered as famciclovir, which is a prodrug that is metabolized to the active antiviral form of penciclovir. In humans and mice, oral penciclovir undergoes rapid deacetylation followed by oxidation of the purine structure to form the active metabolite penciclovir, which occurs in both the intestinal wall and liver in humans. Penciclovir is subsequently phosphorylated in herpesvirus-infected cells in a manner superior to acyclovir, another herpesvirus-selective drug. Administration of famciclovir to young Asian elephants by oral (5 mg/kg) and rectal (5 and 15 mg/kg) routes produced plasma drug concentrations similar to other mammalian studies: penciclovir was the predominant metabolite, with no measurable famciclovir in any of the samples. This finding supports rapid metabolism of famciclovir to penciclovir in Asian elephants. Differences in pharmacokinetic parameters between African and Asian elephants have been observed for several drugs, including trimethoprim-sulfamethoxazole, phenylbutazone, flunixin meglumine, and ibuprofen. Intestinal length varies between Asian and African elephants, which can have a profound effect on the absorption and distribution of some classes of oral drugs. Considering that the metabolism of famciclovir occurs at least partially in the intestinal wall of other mammals, there may be variability in famciclovir metabolism between these 2 species. Because of this, clinicians should use caution with extrapolation of oral pharmacokinetic data between Asian and African elephants.

The objective of this study was to evaluate the pharmacokinetic parameters of famciclovir and its active metabolite penciclovir following single oral and rectal dose administration in African elephants. We hypothesized that a single dose of oral or rectal famciclovir at 15 mg/kg would result in rapid metabolism to penciclovir and produce concentrations above the threshold of detection. We also hypothesized that penciclovir disposition would be different from that previously reported in Asian elephants because of differences in anatomy and physiology.

Methods

Elephants

All elephants were managed under human care at 6 different Association of Zoos and Aquariums-accredited facilities, with 1 to 6 elephants participating per facility. Fifteen elephants (6 male, 9 female) participated in total, with one bull only participating in the oral administration phase. Ages were variable ranging from 4 to 51 years old (median, 20 years old), and weights ranged from 1,336 to 4,864 kg (median, 3,452 kg). Elephants were eligible for inclusion if the following parameters were deemed unremarkable by the attending veterinarian: physical exam, complete blood count, serum biochemistry, and EEHV quantitative PCR performed on whole blood (Smithsonian Conservation Biology Institute). All elephants were housed in accordance with Association of Zoos and Aquariums elephant care requirements and otherwise managed according to their typical daily care routine. The study and animal use were approved by the Indianapolis Zoo research review committee as well as individual participating facilities’ research review committees or institutional animal care and use committees as applicable.

Drug administration

Elephants were administered famciclovir at a target dosage of 15 mg/kg body weight based on their individual weight and rounded to the nearest 500-mg increment based on tablet size (500-mg tablets). Fasting was not required prior to either route of administration, but access to concentrate diet items and other medications were restricted for 1 hour prior to and following famciclovir administration. All elephants received oral administration first, followed by rectal administration after a minimum of a three-week washout period. For oral administration, famciclovir was administered as entire intact tablets per os, and time of administration was recorded as the time the last tablet was administered and swallowed. Prior to rectal administration, animal care staff manually removed fecal boluses from the distal rectum. Famciclovir tablets were then crushed into a powder using a mortar and pestle. The powder was then mixed with water at a rate of 1.6 to 1.75 mL per tablet to create a thick paste and then loaded into 60-mL catheter-tip syringes and applied to the rectal...
mucosa by animal care staff as far proximally as they were able to reach. The time of administration was recorded once the final syringe of paste was applied. Any volume lost from adhering to gloves or mixing equipment was then measured to calculate a more precise dose administered.

**Sample collection and processing**

Serial 10-mL whole-blood samples were collected from each animal utilizing auricular veins and a winged infusion set attached to a 12-mL syringe. Total blood volume sampled for each animal was well below the accepted maximum blood collection volume for all animals (approx 1% total body weight). The initial blood sample was collected immediately prior to administration (time 0) and again at regular time intervals: 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 8 hours, 12 hours, and 24 hours as described for Asian elephants. Blood samples were immediately transferred to lithium heparin tubes and gently inverted to mix the sample and anticoagulant. Samples were centrifuged (approx 2,400 X g) to harvest plasma. Plasma was transferred to cryovials for storage at ~80°C until the time of analysis. The ability to obtain complete sample sets (13 samples per administration route) was dependent on voluntary participation of each elephant in the requested behaviors (both administration and blood sample collection), resulting in partial sample sets for 9 of the 15 elephants.

**Plasma drug analysis**

Plasma samples were analyzed for both the parent drug, famciclovir, and the active metabolite, penciclovir. No penciclovir was detected in any samples, so no further steps were possible for this drug. Plasma penciclovir was quantified with HPLC paired with fluorescence detection using a validated method developed in the Clinical Pharmacology Laboratory at North Carolina College of Veterinary Medicine. This laboratory uses the International Council for Harmonisation of Technical Requirements for Pharmaceuticals validation guidelines for analytical methods and the guidelines published in Chapter 1225 of the United States Pharmacopeia.

Samples were processed by thawing at room temperature, extracting penciclovir from 400 µL of plasma with solid phase extraction, and reconstituting with mobile phase. The samples were injected into an HPLC system that consisted of a quaternary solvent delivery system (flow rate, 0.5 mL/min), an autosampler (Agilent 1200 Series solvent delivery system, Agilent Technologies), and a fluorescence detector (Agilent 1200 Series Fluorescence Detector, Agilent Technologies) with an excitation wavelength of 260 nm and an emission wavelength of 380 nm. Chromatograms were integrated with a computer program (Agilent OpenLAB software, Agilent Technologies). The column was a reverse-phase 4.6 mm X 15-cm C8 column (Zorbax Rx-C1, MAC-MOD Analytical Inc) kept at a constant temperature of 40°C. The mobile phase for HPLC analysis consisted of 75% acetonitrile and 25% distilled water with trifluoroacetic acid added as a mobile phase modifier. Fresh mobile phase was prepared, filtered (0.45 µm), and degassed for each daily run.

The incurred samples were quantified using a calibration curve that consisted of fortified blank elephant plasma with 7 calibration standards ranging from 0.1 µg/mL to 10 µg/mL and included a blank (0 µg/mL). The limit of quantitation for the assay was 0.1 µg/mL, determined by the lowest point on the linear calibration curve that met our criteria for acceptance. Fresh calibration standards and quality control samples were prepared daily for each run.

**Pharmacokinetic analysis**

The pharmacokinetic analysis was conducted in 2 phases. In the first phase, samples from elephants at facility #1 were analyzed together because complete sample sets for both oral and rectal administration were available. Following the steps noted above, the concentrations from these samples were analyzed using noncompartmental pharmacokinetic analysis and nonlinear mixed-effects (NLME) modeling software (Phoenix NLME, Certara, version 8.4). The noncompartmental analysis uses the trapezoidal method (linear trapezoidal, linear interpolation) to calculate the area under the curve (AUC), with the final portion of the curve estimated from the terminal slope.

The second phase of the analysis included the remaining samples from the other 5 facilities, for a total of 9 additional elephants. The study protocol was identical, but it was not possible to sample each elephant at all timepoints; therefore, a sparse-sampling design was used. Each elephant was sampled at least 3 times, with a median of 5 times. Two elephants were sampled 12 times, but samples after rectal administration from one elephant were not collected. Because the sparse sampling design does not allow for traditional standard two-stage pharmacokinetic analysis, samples from this phase were analyzed using naïve averaged sample analysis and noncompartmental pharmacokinetic analysis with the NLME modeling software.

The pharmacokinetic analysis from phase 1 and phase 2 were used as input to obtain pharmacokinetic estimates (Tables 1 and 2). These initial estimates were used as input for the pharmacokinetic parameters for all 15 elephants (both phases), combined and calculated with population pharmacokinetic methods and NLME modeling. This analysis produces the typical value for the population parameters (fixed effects) as well as estimates for the between-subject variability (random effects) and allows for exploration of the sources of variation. From these initial estimates, the NLME model was fitted to these data (Phoenix NLME, version 8.4). Compartmental analysis of the data from penciclovir levels following famciclovir administration was calculated using a one-compartment model according the following formula:

\[
C(T) = \frac{D \times K_{01}}{V_d(K_{01} - K_{10})} \times \left[ e^{(-K_{10} \times t)} - e^{(-K_{01} \times t)} \right]
\]
Table 1—Penciclovir pharmacokinetic parameters from 6 African elephants (Loxodonta africana) from a single facility following administration of famciclovir at approximately 15 mg/kg body weight.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Oral dose</th>
<th>Rectal dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Geo mean</td>
<td>Geo CV%</td>
</tr>
<tr>
<td>AUC % extrapolated</td>
<td>7.41</td>
<td>59.15</td>
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<tr>
<td>AUC (0 to Cn)</td>
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<td>AUC (0 to infinity)</td>
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<td>20.94</td>
</tr>
<tr>
<td>CI/F</td>
<td>318.99</td>
<td>20.83</td>
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<tr>
<td>C_{\text{max}}</td>
<td>8.70</td>
<td>39.67</td>
</tr>
<tr>
<td>Lambda-Z 1/2</td>
<td>7.66</td>
<td>32.52</td>
</tr>
<tr>
<td>Lambda-Z</td>
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<td>32.52</td>
</tr>
<tr>
<td>MRT</td>
<td>8.59</td>
<td>27.66</td>
</tr>
<tr>
<td>t_{\text{max}}</td>
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<td>76.42</td>
</tr>
<tr>
<td>Vd/F</td>
<td>3,523.10</td>
<td>52.54</td>
</tr>
<tr>
<td>F% (relative)</td>
<td>8.87</td>
<td>—</td>
</tr>
</tbody>
</table>

The table includes data for both oral administration and rectal administration. Pharmacokinetic analysis was performed using noncompartmental pharmacokinetics. Note that without an accompanying IV dose, the CL and VD are expressed as fraction absorbed.

AUC = Area under the concentration-versus-time curve. AUC % extrapolated = The percent of the total AUC estimated from the terminal slope. AUC (0 to Cn) = The AUC from time zero to the last measured point (Cn). AUC (0 to infinity) = The AUC from zero to infinity. CI/F = Clearance per fraction absorbed. C_{\text{max}} = Peak concentration observed. CV% = Coefficient of variation (standard deviation divided by the mean and multiplied by 100). F% (relative) = The percent of penciclovir absorbed from the rectal dose relative to the oral dose. Lambda-Z = Terminal rate constant. Lambda-Z 1/2 = Terminal rate constant and accompanying half-life. MRT = Mean residence time. t_{\text{max}} = Time to peak concentration. Vd/F = Volume of distribution per fraction absorbed.

where C is the penciclovir concentration at time T, D is the dose, Vd is the apparent volume of distribution, K10 is the elimination rate constant, and K01 is the absorption rate constant. Secondary parameters calculated include the elimination and absorption half-life, AUC, peak concentration (C_{\text{max}}), time to peak concentration (t_{\text{max}}), and systemic clearance. Because these doses were non-IV, the values of Vd and clearance are reported as per fraction absorbed – volume of distribution per fraction absorbed and clearance per fraction absorbed, respectively.

Various models were tested with different error structures to determine the best-fit base model. Final model selection was based on goodness-of-fit plots, diagnostic plots of residuals, scatter plots of predicted versus observed values, and statistical significance between models using the minimum value of the objective function.

Interindividual (between-subject) variability (variance of a parameter among different subjects) was expressed using an exponential error model according to the equation:

\[ Pi = \theta P \times \exp(\eta_i P) \]

where P is the pharmacokinetic parameter of interest for the individual i; \( \theta P \) is \( \theta \) (theta), or the typical value (fixed effect) for the population estimate of the parameter of interest; and \( \eta_i P \) is the \( \eta \) (eta, random effect) for the interindividual (between-subject) differences of the parameter of interest. The \( \eta \) values were assumed to be independent and have a normal distribution with a mean of zero and variance of \( \omega^2 \). A multiplicative model described the residual random variability (\( \epsilon \)) of the data, where \( \epsilon \) is the residual intrasubject (within subject) variability with a mean of zero and a variance of \( \alpha^2 \) according to the equation:

\[ C_{\text{obs}} = C_{\text{true}} \times (1 + \epsilon_i) \]
where $C_{\text{obs}}$ is the observed concentration for the individual and $C_{\text{pred}}$ is the model-predicted concentration plus the error value ($\varepsilon$).

**Results**

Compliance with drug administration was considered excellent, with dose ranges very close to the target dose of 15 mg/kg when accounting for rounding due to tablet size and potential loss during administration. Final doses ranged from 13.97 to 15.15 mg/kg (median, 15.01 mg/kg) for oral administration and 13.97 to 15.38 mg/kg (median, 15.04 mg/kg) for rectal administration. Seven elephants had all 26 sample timepoints collected, 1 elephant had 18 timepoints, 1 elephant had 16 timepoints, 3 elephants had 12 timepoints, and 1 elephant had 8 timepoints. The final elephant had all 13 samples collected for the

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**Figure 1**—A—Plots of penciclovir plasma concentrations over time in 6 African elephants (*Loxodonta africana*) from one facility following oral (red circles) and rectal (blue squares) administration of famciclovir at a dose of approximately 15 mg/kg body weight. Each solid point (circle, square) represents the mean concentration $\pm$ SD. B—Plots of penciclovir plasma concentrations in African elephants from 9 elephants representing 5 facilities following oral (red circles) and rectal (blue squares) administration of famciclovir at a dose of approximately 15 mg/kg body weight. Each solid point (circle, square) represents the mean concentration $\pm$ SD. Each point represents 3 to 8 elephants (median, 5), and each elephant was sampled a median of 5 times.

**Figure 2**—Penciclovir plasma concentrations in a population of 15 African elephants (*L. africana*) detailed in Figure 1 following an oral dose of famciclovir at approximately 15 mg/kg body weight. Each open point represents a single sample. The solid line represents the fitted line according to the pharmacokinetic model. A—The left panel is the spaghetti plot of each individual elephant fitted to the model. B—The right panel represents the fitted curve to the model after accounting for random variation (between-subject variability) in the model. Notice the improved population model fit on the right after adjusting for between-subject variability.
oral administration phase but did not participate in the rectal administration component.

Plasma concentrations from both phases of the study are represented graphically (Figure 1). The individual points from each phase of the study are also represented graphically with spaghetti plots for each individual elephant (open points representing each sample) and collectively as a fitted curve for the population after accounting for between-subject variation (Figure 2 [oral dose]; Figure 3 [rectal dose]). The pharmacokinetic values from the initial non-compartmental analysis from both phases of the study are summarized (Table 1 [first phase]; Table 2 [second phase]). More data is available regarding variability for the first phase because a full pharmacokinetic analysis could be performed on each of the 6 elephants. In the analysis for phase 2, there is an indication of the variability for only 2 parameters because of the sparse sampling design and naïve averaged analysis.

A high degree of variability was observed in this study as seen in the spaghetti plots (Figures 2 and 3) and parameter summaries (Table 1, Table 2, and Table 3). Exploration of the source of the variability

![Figure 3](image_url) — Penciclovir plasma concentrations in a population of 14 African elephants (*L. africana*) detailed in Figure 1 following a rectal dose of famciclovir at approximately 15 mg/kg body weight. Each open point represents a single sample. The solid line represents the fitted line according to the pharmacokinetic model. A—The left panel is the spaghetti plot of each individual elephant fitted to the model. B—The right panel represents the fitted curve to the model after accounting for random variation (between-subject variability) in the model. Notice the improved population model fit on the right after adjusting for between-subject variability.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Units</th>
<th>Oral dose</th>
<th>Rectal dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>θ Ka</td>
<td>1/h</td>
<td>1.073</td>
<td>5.388</td>
</tr>
<tr>
<td>θ V/F</td>
<td>L/kg</td>
<td>2.91</td>
<td>5.27</td>
</tr>
<tr>
<td>θ Ke</td>
<td>1/h</td>
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<td>0.182</td>
</tr>
<tr>
<td>t_{max}</td>
<td>h</td>
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<td>0.65</td>
</tr>
<tr>
<td>AUC</td>
<td>μg·h/mL</td>
<td>33.93</td>
<td>15.62</td>
</tr>
<tr>
<td>C_{max}</td>
<td>μg/mL</td>
<td>3.73</td>
<td>2.52</td>
</tr>
<tr>
<td>Cl/F</td>
<td>L/kg/h</td>
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<td>0.96</td>
</tr>
<tr>
<td>Ka</td>
<td>h</td>
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<td>0.13</td>
</tr>
<tr>
<td>Ke</td>
<td>h</td>
<td>4.56</td>
<td>3.81</td>
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<tr>
<td>%F (relative)</td>
<td>%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
| %F = Fraction of the rectal dose absorbed relative to the oral dose. AUC = Area under the drug concentration curve. Cl/F = Systemic clearance. C_{max} = Peak plasma penciclovir concentration. CV% = coefficient of variation (standard deviation divided by the mean and multiplied by 100). θ t_{1/2} = Absorption rate and respective t_{1/2}. Ke t_{1/2} = Elimination rate constant and respective t_{1/2}. t_{max} = Time to peak concentration. V/F = Volume of distribution.
was attempted using a covariate analysis. One of the potential sources of variability explored was the different zoo locations used for sample collection because it appeared that the rectal dose was absorbed better in the elephants from facility #1 than the other 5 facilities. These were entered as categorical covariates in the analysis, but the contribution to the random source variability (n) did not reach the threshold of significance. All facilities utilized the same procedures and dose. We were unable to identify any other sources (covariates) of unexplained variation in our population analysis.

Discussion

The administration of famciclovir tablets was successful via oral delivery and via the application of a paste applied rectally, resulting in measurable plasma levels of the active metabolite penciclovir, supporting our hypothesis that famciclovir would be metabolized to penciclovir in an amount quantifiable in plasma. Consistent with previous findings in Asian elephants, famciclovir was rapidly metabolized to the active metabolite penciclovir, with no detectable famciclovir in the plasma, even at 15 minutes postadministration. 

In comparing oral and rectal administration in this study, oral administration exhibited a longer $t_{\text{max}}$ (2.12 hours) compared to rectal administration (0.65 hours), consistent with more rapid absorption through the rectal mucosa and into the bloodstream. The $C_{\text{max}}$ was also higher with oral administration (3.73 μg/mL) compared to rectal administration (2.52 μg/mL), indicating that despite slower absorption, oral administration resulted in higher maximum concentrations in the plasma. The AUC after oral administration (33.93 μg·h/mL) was more than twice that of rectal administration (15.62 μg·h/mL).

Previous investigation in Asian elephants is difficult to directly compare to this study given differences in study protocol and methodology. For instance, oral administration in Asian elephants was administered at 5 mg/kg compared to 15 mg/kg in this study. It was expected that a higher dose will produce higher values for AUC and $C_{\text{max}}$ in African elephants compared to Asian elephants but does not explain the differences we observed for $t_{\text{max}}$ and elimination and absorption half-life. 

The same study in Asian elephants evaluated a 15-mg/kg rectal dose, allowing closer comparison of pharmacokinetic data between the 2 species. In comparing population-derived values (Table 3), African elephants exhibit a similar $t_{\text{max}}$ (0.65 hours) to Asian elephants (0.66 hours). African elephants in our study had a higher AUC (15.62 μg·h/mL compared to 8.50 μg·h/mL) and $t_{1/2}$ (3.81 hours compared to 2.60 hours). Asian elephants showed a higher $C_{\text{max}}$ (3.60 μg/mL) compared to African elephants (2.52 μg/mL). Taken together, this suggests that both species absorb rectal administration of famciclovir at a similar rate, with higher maximum concentrations of penciclovir achieved in Asian elephants and longer elevations of penciclovir plasma concentrations in African elephants, supporting our secondary hypothesis that pharmacokinetic parameters would vary by species.

No published data exists for other antiviral medications in these 2 species. Previous work with other drug class pharmacokinetic comparisons between species show variable results. Similar to this study, African elephants exhibited higher elimination $t_{1/2}$ and a lower $C_{\text{max}}$ for trimethoprim administered orally and IV but dissimilarly a higher $t_{\text{max}}$ and a lower AUC. 

For sulfamethoxazole administered orally and IV, AUC, $C_{\text{max}}$, and elimination $t_{1/2}$ were all lower for African elephants, while $t_{\text{max}}$ was higher. 

Phenylbutazone administered orally was similar to sulfamethoxazole, except $t_{\text{max}}$ was also lower for African elephants. Oral administration of both ibuprofen and flunixin meglumine had trends that varied between species depending on dose administered, but for all doses, AUC was lower in African elephants. 

Our study, and the data from these other studies, highlights the importance of utilizing species-specific pharmacokinetic data, as available, for African and Asian elephants.

The minimum effective concentration (MEC) of penciclovir for inactivation of EEHV remains unknown, which prevents establishing a target therapeutic dose in elephants. However, several MECs have been proposed for other herpesviruses, including feline herpesvirus-1, human herpesvirus-1 and -2, and equine herpesvirus-1. Establishing a clear MEC is challenging, with reports conflicting for feline herpesvirus-1, with proposed MECs ranging from 0.3 to 1.2 μg/mL. 

For human herpesvirus-1, the MEC ranges from 0.2 to 1.8 μg/mL and from 0.3 to 2.4 μg/mL for human herpesvirus-2. 

A MEC value of 1.64 μg/mL has been proposed for penciclovir against equine herpesvirus-1. As the equine is often a model for extrapolation in elephant medicine, a cutoff of 1.64 μg/mL is considered a hypothetical proxy for discussion regarding the potential of reaching therapeutic levels in elephants. Plasma concentrations remained above this value for approximately 3.5 to 4.5 hours following rectal administration and 6.5 to 8 hours following oral administration. Multidose administration was not evaluated in this study, and further research is required to determine the effect of repeated famciclovir dosing. As such, dosing recommendations cannot be made on the data provided in this study alone but can be a guide to future studies.

The data in this study shows notable differences between the first phase (facility #1) and the second phase (facilities 2 through 6) (Tables 1 and 2; Figures 1–3). The cause for these differences is undetermined. The second phase of the study produced variable results, which may be attributed to differences among the 5 facilities in methods, diet of the animals, and husbandry. All facilities were provided with identical instruction regarding preparation, drug administration, and blood sample collection. As the second phase of the study utilized sparse sampling and had less complete sample collection, this may have contributed to the observed
variation between phase 1 and 2 as well as the variability within phase 2. Administration of the medication varied (eg, administrator arm length, exact consistency of paste, etc) by facility, and even within facility, which may have also contributed to increased variability, but such variability in dose administration mimics typical management challenges with clinical case management. Because the underlying cause of difference among facilities was unable to be identified, a population approach was appropriate (Figures 2 and 3; Table 3). Variability was high but is considered within reason, with a coefficient of variation of less than 40% for key parameters. Rectal absorption was the most variable (71% coefficient of variation), which is not unexpected given the inherent nature of medication preparation and technique required for per rectum administration.

A limitation of the study is the relatively small number of elephants included. However, compared to previous pharmacokinetic research in elephants, the population size in this study is similar to or exceeds that of previous studies. Given the relatively small African elephant population in North America, variably aged animals were necessary to provide adequate population size, but the impact of age on drug metabolism and excretion should be considered.

In conclusion, this study provides the first pharmacokinetic data for penciclovir in African elephants following oral and rectal administration of famciclovir. Famciclovir was rapidly and completely metabolized to the active metabolite penciclovir regardless of administration route. Oral administration resulted in a higher Cmax, tmax, absorption t1/2, and AUC compared to rectal administration. Plasma concentrations of penciclovir remained above a hypothetical proxy MEC of 1.64 μg/mL for approximately 3.5 to 4.5 hours following rectal administration and 6.5 to 8 hours following oral administration. Additional research is needed to determine the pharmacokinetics of repeated famciclovir dosing in elephants and to establish a MEC for EEHV to better guide antiviral therapeutic use.

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Disclosures

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