

Pharmacokinetics of penciclovir in healthy cats following oral administration of famciclovir or intravenous infusion of penciclovir

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Objective—To investigate the pharmacokinetics of penciclovir in healthy cats following oral administration of famciclovir or IV infusion of penciclovir.

Animals—6 cats.

Procedures—Cats received famciclovir (40 [n = 3] or 90 [3] mg/kg, PO, once) in a balanced crossover-design study; the alternate dose was administered after a ≥ 2 -week washout period. After another washout period (≥ 4 weeks), cats received an IV infusion of penciclovir (10 mg/kg delivered over 1 hour). Plasma penciclovir concentrations were analyzed via liquid chromatography–mass spectrometry at fixed time points after drug administration.

Results—Mean \pm SD maximum plasma concentration (C_{\max}) of penciclovir following oral administration of 40 and 90 mg of famciclovir/kg was 1.34 ± 0.33 $\mu\text{g/mL}$ and 1.28 ± 0.42 $\mu\text{g/mL}$ and occurred at 2.8 ± 1.8 hours and 3.0 ± 1.1 hours, respectively; penciclovir elimination half-life was 4.2 ± 0.6 hours and 4.8 ± 1.4 hours, respectively; and penciclovir bioavailability was $12.5 \pm 3.0\%$ and $7.0 \pm 1.8\%$, respectively. Following IV infusion of penciclovir (10 mg/kg), mean \pm SD penciclovir clearance, volume of distribution, and elimination half-life were 4.3 ± 0.8 mL/min/kg, 0.6 ± 0.1 L/kg, and 1.9 ± 0.4 hours, respectively.

Conclusions and Clinical Relevance—Penciclovir pharmacokinetics following oral administration of famciclovir were nonlinear within the dosage range studied, likely because of saturation of famciclovir metabolism. Oral administration of famciclovir at 40 or 90 mg/kg produced similar C_{\max} and time to C_{\max} values. Therefore, the lower dose may have similar antiviral efficacy to that proven for the higher dose. (*Am J Vet Res* 2012;73:1092–1099)

Penciclovir is a nucleoside deoxyguanosine analogue with a mechanism of action similar to that of acyclovir and with potent antiviral activity against human herpesviruses (ie, HSV-1, HSV-2, and varicella zoster virus).¹ Several investigators have studied the in vitro

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ABBREVIATIONS

AUC	Area under the plasma concentration-time curve
AUC _{0–τ}	Area under the plasma concentration-time curve during the dosing interval at steady state
AUC _{0–∞}	Area under the plasma concentration-time curve extrapolated from time 0 to infinity
Cl	Total body clearance
C_{\max}	Maximum observed plasma concentration
FHV-1	Feline herpesvirus type 1
GGT	γ -Glutamyl transpeptidase
HSV	Herpes simplex virus
k_{el}	Elimination rate constant
T_{\max}	Time to maximum observed plasma concentration
TP	Total protein
$t_{1/2(\lambda_2)}$	Apparent elimination half-life
VAP	Vascular access port

activity of penciclovir against FHV-1. The half maximal inhibitory concentration of penciclovir against FHV-1 was first determined in vitro to be 13.9 μM (3.5 $\mu\text{g/mL}$).² This is similar to that of idoxuridine and cidofovir, which are clinically useful when applied topically for the treatment of FHV-1 infection.^{3,4} However,

subsequent studies⁵⁻⁷ investigating the in vitro efficacy of penciclovir against FHV-1 have reported a wide range of half maximal inhibitory concentrations against FHV-1 (1.2 to 130 μ M [0.3 to 33 μ g/mL]). Regardless, penciclovir is consistently more potent than acyclovir, which is the only other drug used systemically to treat cats infected with FHV-1.^{2,3,8-10} In humans, penciclovir has poor bioavailability following oral administration, and the penciclovir prodrug famciclovir is used instead. Following absorption in humans, famciclovir is metabolized to penciclovir by di-deacetylation and oxidation.¹¹

Although oral administration of 9 to 18 mg of famciclovir/kg every 8 or 12 hours in cats was not associated with toxic effects,¹² the C_{max} achieved was approximately one fifth (0.68 μ g/mL) to one tenth (0.33 μ g/mL) that of the target plasma concentration suggested by in vitro data available at that time (3.5 μ g of penciclovir/mL).² Thus, a dose of 90 mg of famciclovir/kg administered orally 3 times daily (8:00 AM, 2:00 PM, and 8:00 PM) was used in cats experimentally inoculated with FHV-1.¹³ Although this dose resulted in significantly improved systemic, ophthalmic, clinicopathologic, virologic, and histologic variables in famciclovir-treated cats than in placebo-treated cats, the approximate C_{max} of penciclovir (2 to 2.1 μ g/mL) was again less than the target concentration, according to analysis of in vitro data (3.5 μ g of penciclovir/mL).² In addition, subjective comparison of pharmacokinetic data from the 2 in vivo studies^{12,13} revealed that in the second study,¹³ a 90 mg/kg dose of famciclovir (approx 6 times the dose used in the first study [mean value, 15 mg/kg]),¹² resulted in a penciclovir C_{max} value only approximately 3 times that of cats in the first study (2 μ g/mL, compared with 0.68 μ g/mL). Following evaluation of these data, we hypothesized that famciclovir absorption or metabolism, penciclovir elimination, or some combination of these processes was nonlinear in cats. Therefore, the purpose of the study reported here was to further evaluate the pharmacokinetics of famciclovir and penciclovir in cats. Specifically, our goals were to better understand the absorption and metabolism of famciclovir and the distribution and excretion of penciclovir by determining the disposition of famciclovir and penciclovir following an oral dose of 40 or 90 mg of famciclovir/kg, and the disposition of penciclovir following an IV infusion of 10 mg of penciclovir/kg over 1 hour. In addition, the safety of a single IV infusion of penciclovir was investigated.

Materials and Methods

Cats—Three neutered male and 3 sexually intact female domestic shorthair cats (mean \pm SD body weight and age, 4.2 \pm 0.7 kg and 1.3 \pm 0.7 years, respectively) were included in the study. These 6 cats had no known history of ocular or systemic illness. Cats were assessed as healthy on the basis of results of physical examination, CBC, serum biochemical analysis, and urinalysis performed prior to the start of the study (ie, baseline). Ambient temperature (21 \pm 2°C) and light-to-dark cycle ratio (ie, 14 hours of light to 10 hours of darkness) of the housing area were controlled throughout the study period.

Penciclovir formulation and testing—The drug product was prepared according to strict aseptic compounding technique in a laminar airflow hood in a clean room by personnel trained in aseptic manipulation and procedures. Penciclovir^a was first suspended in saline (0.9% NaCl) solution, and sodium hydroxide aqueous solution was added with stirring until complete dissolution of penciclovir occurred at 25°C (pH, 11.0). The resultant solution was diluted with saline solution to a concentration of 2 mg of penciclovir/mL and filtered through a 0.22- μ m sterilizing filter into sterile vials and sealed. An FDA-approved *Limulus* amoebocyte lysate test method¹⁴ was used to detect endotoxins. This test satisfied the US Pharmacopeia bacterial endotoxins test chapter.¹⁵ A validated sterility test conducted by means of membrane filtration within an International Organization for Standardization class-5 environment under the standards specified in US Pharmacopeia¹⁶ was also used to test the drug product for evidence of microbial contamination.

Experimental design—The study was divided into 2 phases. In phase I, a balanced crossover design was used with 3 cats each assigned to receive 1 orally administered dose of 40 or 90 mg of famciclovir^b/kg. Cats were grouped according to sex, but because of the crossover design, all cats received both doses. At least 2 weeks separated administration of each orally administered dose of famciclovir. In phase II, all 6 cats received 1 IV infusion of 10 mg of penciclovir/kg delivered over 1 hour through a jugular catheter via a syringe pump.^c At least 4 weeks separated phase I from II. All aspects of the study were approved by the Institutional Animal Care and Use Committee of the University of California-Davis.

Placement of VAPs and indwelling catheters—Prior to entering the study and to facilitate collection of multiple blood samples, a VAP¹⁷ was placed surgically in 1 jugular vein of each cat. Briefly, food was withheld from all cats for 12 hours prior to premedication with acepromazine (0.02 mg/kg, SC) and butorphanol (0.2 mg/kg, SC). General anesthesia was induced via IV administration of ketamine (6 mg/kg) and diazepam (0.3 mg/kg) and maintained with isoflurane in oxygen delivered via an endotracheal tube until VAP placement was complete. Cats were positioned in right or left lateral recumbency for access to the contralateral jugular vein, and the surgical site was prepared aseptically. A subcutaneous pocket was created by blunt dissection, the VAP was placed in the pocket, and the base plate was sutured to the underlying fascia of the cervical musculature with 4-0 nylon suture. A 2-cm skin incision then was made parallel and dorsal to the external jugular vein in the midcervical region, the vein was isolated, and two 4-0 polydioxanone stay sutures were placed around it. The vein was incised between the 2 ligatures, and a 5F silicone catheter was introduced into it and advanced to approximately the level of the right atrium. The catheter was flushed with heparinized saline solution and secured in place by tightening the caudal stay suture. The cranial stay suture was tightened to occlude the jugular vein. The proximal end of the catheter then was passed via a subcutaneous tunnel and attached to the VAP. The unit was flushed to verify patency prior to

closure of the incision. The surgical site was bandaged for 24 hours. During the first week after the procedure, VAPs were flushed approximately every 24 hours with saline solution (3 mL) injected through a Huber needle^d by use of aseptic technique. One milliliter of locking solution (1 U of heparin/mL of saline solution) was slowly injected as the Huber needle was removed. Thereafter, the ports were flushed once weekly in a similar fashion. Famciclovir administration and blood collection began ≥ 2 weeks after VAP placement.

For IV infusion of penciclovir during phase II, a 5.5F, 13-cm triple-lumen catheter^e was placed percutaneously into the jugular vein contralateral to that used for VAP placement. To complete this procedure, all cats were anesthetized by use of the same protocol as described for VAP placement.

Sample collection and analysis—In phase I, blood samples (2.5 to 3 mL/sample) were obtained from the VAP prior to and 0.5, 1, 2, 4, 6, 9, 12, 15 and 24 hours following oral administration of famciclovir. In phase II, blood samples (2.5 to 3 mL/sample) were obtained from the VAP prior to and 0.25, 0.5, 0.75, 1, 1.083, 1.167, 1.5, 2, 4, 6, 9, and 12 hours following initiation of the penciclovir infusion. All samples were collected into heparinized glass tubes. During both phases, each blood sample volume was replaced with an equal volume of lactated Ringer's solution administered through the VAP. Blood samples were centrifuged for 10 minutes at 2,000 \times g, and the resulting plasma was collected and stored at -20°C for subsequent determination of plasma concentrations of penciclovir and famciclovir via a liquid chromatography–mass spectrometry method described elsewhere.¹² During spectrometric analysis, the responses for penciclovir and famciclovir were linear and had correlation coefficients (r^2) ≥ 0.99 . The technique was optimized to provide a minimum limit of quantification of 25 ng/mL.

To assess the safety of IV penciclovir administration, a CBC, serum biochemical analysis, and analysis of urine obtained via cystocentesis were performed for each cat prior to beginning phase I of the experiment and again 24 hours after the penciclovir infusion.

Data analysis—Analysis of pharmacokinetic data was performed with a commercial software program,^f and plasma penciclovir and famciclovir concentration-time data following oral administration were assessed via noncompartmental analysis.¹⁸ Values of C_{\max} and T_{\max} were estimated from the data. Linear trapezoidal areas were used in calculating the $\text{AUC}_{0 \rightarrow \tau}$, and other pharmacokinetic parameters were determined by use of standard noncompartmental equations. Specifically, the k_{el} was calculated as the slope of the terminal phase of the log plasma-concentration curve that included a minimum of 3 points, and $t_{1/2(\lambda_2)}$ was calculated as $0.693/k_{\text{el}}$. Compartmental open mammillary models were fitted to the plasma famciclovir concentration-versus-time data following IV infusion by means of nonlinear least squares regression implemented in the

computer software.^f The error variance model weighted residual errors by the square of the predicted penciclovir concentration. The appropriate model was selected by use of the Akaike information criterion, and standard compartmental equations were used to estimate pharmacokinetic variables for each cat.¹⁹ The penciclovir $\text{AUC}_{0 \rightarrow \infty}$ was used to estimate bioavailability following a single dose of oral famciclovir (40 or 90 mg/kg) by calculating the ratio of dose-normalized penciclovir $\text{AUC}_{0 \rightarrow \infty}$ after oral famciclovir and IV penciclovir administration. This ratio was multiplied by 1.268 to address the difference in molecular weights between famciclovir (321.33 g/mol) and penciclovir (253.26 g/mol).

To assess whether dose had a significant effect on famciclovir pharmacokinetic variables, a paired difference t test with a Hochberg correction for multiple tests was used to compare C_{\max} , T_{\max} , and $\text{AUC}_{0 \rightarrow \tau}$ between the 40 and 90 mg/kg doses of orally administered famciclovir. To assess whether dose had a significant effect on penciclovir pharmacokinetic variables, a paired difference t test with a Hochberg correction for multiple tests was used to compare C_{\max} , T_{\max} , $\text{AUC}_{0 \rightarrow \infty}$, $t_{1/2(\lambda_2)}$, and bioavailability between the 40 and 90 mg/kg doses of orally administered famciclovir. Least squares linear regression was used to evaluate the relationship between relative bioavailability of famciclovir and penciclovir.

To determine whether the penciclovir infusion affected the clinicopathologic values measured, data obtained before and after drug administration were compared via paired difference t test with a Bonferroni correction for multiple t tests. Significance was set at $P < 0.05$ for all analyses. All data are reported as mean \pm SD.

Results

Following a single orally administered dose of 40 or 90 mg of famciclovir/kg to 6 cats, plasma famciclovir

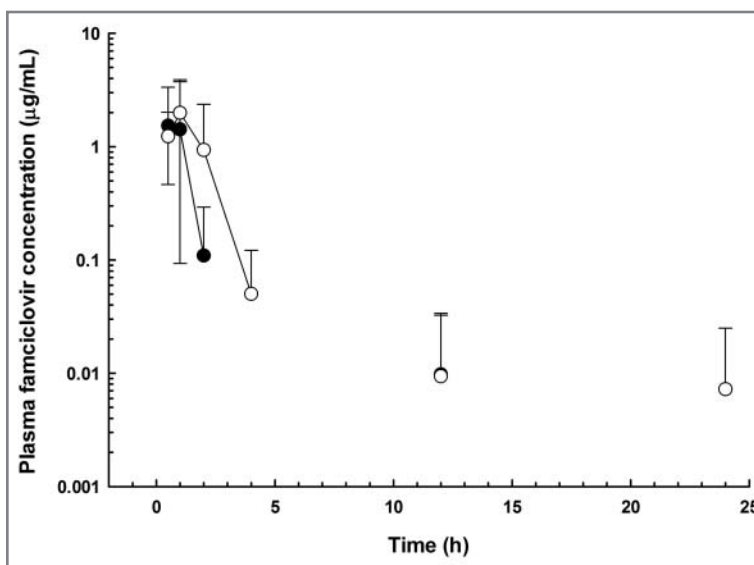


Figure 1—Mean \pm SD plasma famciclovir concentrations at various time points following oral administration of a single dose of 40 (black circles) or 90 (white circles) mg of famciclovir/kg to 6 cats. A balanced crossover design was used in which 3 cats, grouped according to sex, received 1 of the 2 orally administered doses of famciclovir. After a ≥ 2 -week washout period, the alternate treatment was administered to the same cats. Regardless of dose, famciclovir was detected in only 6 of 72 samples at any time ≥ 4 hours after drug administration.

Table 1—Mean \pm SD values for pharmacokinetic variables of famciclovir determined via noncompartmental analysis following oral administration of a single dose of famciclovir (40 or 90 mg/kg) to 6 healthy cats.

Variable	Famciclovir dose (mg/kg)		P value
	40	90	
C_{\max} ($\mu\text{g/mL}$)	2.70 ± 2.23	2.98 ± 1.30	0.83
T_{\max} (h)	0.8 ± 0.3	1.1 ± 0.5	0.11
$AUC_{0 \rightarrow \infty}$ ($\mu\text{g}\cdot\text{h/mL}$)	1.32 ± 0.61	3.49 ± 1.64	0.06

A balanced crossover design was used in which 3 cats, grouped according to sex, received 40 or 90 mg of famciclovir/kg. After a \geq 2-week washout period, the alternate treatment was administered to the same cats. Values of $P < 0.05$ were considered significant.

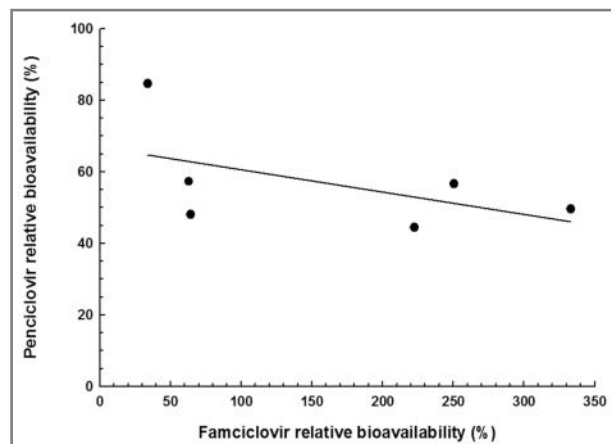


Figure 2—Scatterplot of relative bioavailability of famciclovir versus penciclovir (black circles) in the same 6 cats in Figure 1. A balanced crossover design was used in which 3 cats, grouped according to sex, received a single orally administered dose of 40 or 90 mg of famciclovir/kg. After a \geq 2-week washout period, the alternate treatment was administered to the same cats. Values were not significantly ($P = 0.28$) correlated (black line).

concentrations rapidly increased and declined (Figure 1). Regardless of dose, famciclovir was detected in only 6 of 72 plasma samples at any time \geq 4 hours following drug administration. The C_{\max} , T_{\max} , and $AUC_{0 \rightarrow \infty}$ of famciclovir were not significantly different between the 2 doses (Table 1). Relative bioavailability of famciclovir following dose escalation from 40 to 90 mg of famciclovir/kg was highly variable among cats and was not significantly correlated with relative bioavailability of penciclovir (Figure 2). Because of the paucity of data that could be used to determine k_{cl} , a meaningful famciclovir $t_{1/2(\lambda_z)}$ could not be calculated for most cats, irrespective of dose.

Plasma penciclovir concentration-versus-time profiles following a single orally administered dose of 40 or 90 mg of famciclovir/kg were similar (Figure 3). The C_{\max} , T_{\max} , $AUC_{0 \rightarrow \infty}$, and $t_{1/2(\lambda_z)}$ of penciclovir were not significantly different between the 2 doses (Table 2). Penciclovir bioavailability was significantly ($P = 0.002$) lower in cats that received the 90 mg/kg dose ($7.0 \pm 1.8\%$), compared with those that received the 40 mg/kg dose ($12.5 \pm 3.0\%$) of famciclovir.

Oral administration of 40 or 90 mg of famciclovir/kg to cats in the present study resulted in apparently higher $AUC_{0 \rightarrow \infty}$ values (11.3 or $13.8 \mu\text{g}\cdot\text{h/mL}$, respectively) for penciclovir, compared with those in a pre-

Table 2—Mean \pm SD values for pharmacokinetic variables of penciclovir determined via noncompartmental analysis following oral administration of a single dose of famciclovir (40 or 90 mg/kg) to the same 6 cats in Table 1.

Variable	Famciclovir dose (mg/kg)		P value
	40	90	
C_{\max} ($\mu\text{g/mL}$)	1.34 ± 0.33	1.28 ± 0.42	0.67
T_{\max} (h)	2.8 ± 1.8	3.0 ± 1.1	0.77
$AUC_{0 \rightarrow \infty}$ ($\mu\text{g}\cdot\text{h/mL}$)	11.3 ± 3.9	13.8 ± 3.2	0.06
$t_{1/2(\lambda_z)}$ (h)	4.2 ± 0.6	4.8 ± 1.4	0.41
Bioavailability (%)	12.5 ± 3.0	7.0 ± 1.8	0.002
Relative bioavailability (%)	NA	57 ± 15	NA

NA = Not applicable.

vious study¹² ($2.5 \mu\text{g}\cdot\text{h/mL}$) in which cats of similar health status were administered 9 to 18 mg of famciclovir/kg (Figure 4). However, the increase in penciclovir concentrations was nonlinear, as indicated by C_{\max} values of $0.33 \pm 0.12 \mu\text{g/mL}$, $1.34 \pm 0.33 \mu\text{g/mL}$, and $1.28 \pm 0.42 \mu\text{g/mL}$ following administration of 9 to 18,¹² 40, and 90 mg of famciclovir/kg, respectively.

Following IV infusion of 10 mg of penciclovir/kg over 1 hour to 6 cats, a C_{\max} of $18.6 \pm 6.5 \mu\text{g/mL}$ was detected at 0.9 ± 0.2 hours after initiation of infusion. Penciclovir concentrations then decreased rapidly but exceeded the target concentration² of $3.5 \mu\text{g}$ of penciclovir/mL from 0.25 to 4 hours after initiation of infusion (Figure 3). A 2-compartment model best described the decrease in plasma penciclovir concentrations over time (Table 3).

Transient fine muscle tremors were detected in 1 cat during IV infusion of penciclovir; no other clinical signs of potential adverse effects were observed in the remaining cats during either phase of the study. Following IV administration of penciclovir and coincident frequent blood sample collection, TP concentration decreased significantly ($P = 0.02$) from a baseline value of 6.8 ± 0.2 g/dL to 5.8 ± 0.4 g/dL 24 hours after initiation of the infusion. This change was partially attributable to a significant ($P = 0.03$) decrease in albumin concentration from 3.4 ± 0.2 g/dL to 2.8 ± 0.1 g/dL 24 hours after initiation of the penciclovir infusion. Mean platelet concentration determined via automated counts also decreased significantly ($P = 0.02$) from $294,000 \pm 89,000$ platelets/ μL at baseline to $137,000 \pm 47,000$ platelets/ μL 24 hours after initiation of penciclovir administration. The automated platelet count after IV infusion of penciclovir was decreased below the reference range in 6 cats; however, review of a blood smear confirmed thrombocytopenia in only 2 cats (with values of 79,000 and 162,000 platelets/ μL). Following penciclovir infusion, mean GGT activity decreased significantly ($P = 0.02$) from 1.3 ± 0.5 U/L to 0.2 ± 0.4 U/L. Mean platelet and TP concentrations after penciclovir infusion were below the reference ranges (170,000 to 60,000 platelets/ μL and 5.9 to 8.5 g/dL, respectively),⁸ but mean values for albumin concentration and GGT activity remained within the reference ranges. No significant changes for other variables evaluated via CBC, serum biochemical analysis, and urinalysis were detected after penciclovir infusion, and the cats appeared behaviorally normal at the completion of the study.

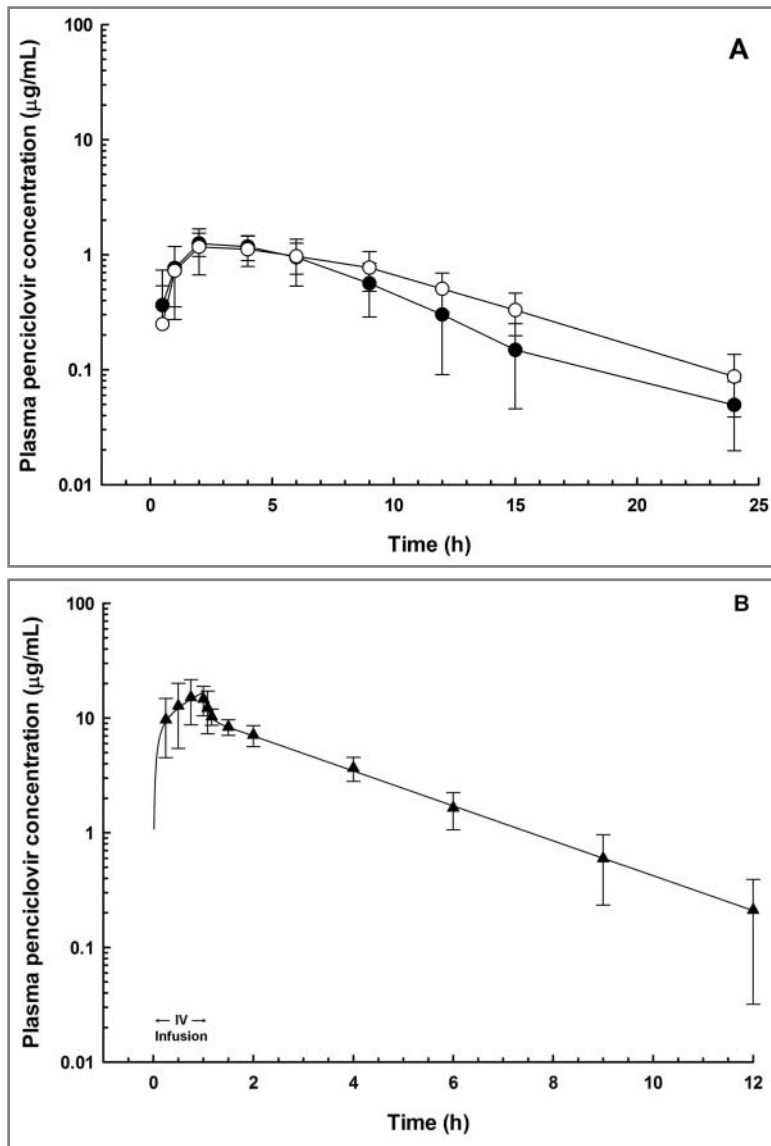


Figure 3—Mean \pm SD plasma penciclovir concentrations at various time points following oral administration of a single dose of 40 (black circles) or 90 (white circles) mg of famciclovir/kg (A) or IV infusion of 10 mg of penciclovir/kg (black triangles) over 1 hour (B) to the same 6 cats in Figure 1. A washout period of ≥ 4 weeks was allowed between administration of the last dose of famciclovir and IV infusion of penciclovir. In panel B, predicted plasma penciclovir concentrations (black line) were derived from a 2-compartment IV infusion model.

Discussion

In all species studied to date, absorption and conversion of the prodrug famciclovir to its active metabolite, penciclovir, is complex. In the study reported here, we determined that famciclovir absorption was rapid, as evidenced by a famciclovir T_{max} of approximately 1 hour following oral administration of a single 40 or 90 mg/kg dose. However, famciclovir absorption was highly variable among cats, as evidenced by the wide range of relative bioavailability of famciclovir observed (34% to 333%). In contrast, relative bioavailability of penciclovir following dose escalation from 40 to 90 mg of famciclovir/kg was only 57% and a significant correlation between the relative bioavailability of famciclovir and penciclovir was not detected. In humans, dogs,

and rats, famciclovir undergoes extensive first-pass metabolism by di-deacetylation to the intermediate metabolite BRL 42359.^{1,20} These deacetylation processes are thought to take place predominantly in the blood but may also occur within intestinal tissue or the liver.^{11,20} Subsequently, in humans and rats, BRL 42359 is converted to penciclovir by hepatic aldehyde oxidase-catalyzed 6-oxidation.^{11,21} In cats, the precise mechanism by which famciclovir is converted to penciclovir is unknown. However, assuming the same metabolic processes occur, we have previously hypothesized that, because hepatic aldehyde oxidase activity is nearly absent in cats,²² metabolism of famciclovir to penciclovir in cats may be slowed or reduced by saturation of hepatic aldehyde oxidase. This hypothesis is supported by data from the present study. First, in the present study, our analysis revealed that penciclovir bioavailability is very low following oral administration of 40 (12.5%) or 90 (7%) mg of famciclovir/kg. Second, we detected rapid disappearance of famciclovir following oral administration of 40 or 90 mg/kg, which suggests that the initial step of famciclovir metabolism in cats (presumably di-deacetylation of famciclovir to BRL 42359) is efficient and complete. Taken together, these data support saturation of the process by which BRL 42359 is converted to penciclovir. However, other possible mechanisms exist, including production of other metabolites from famciclovir or BRL 42359 or elimination of BRL 42359 prior to its conversion to penciclovir in cats. Measurement of BRL 42359 in the present study would have helped elucidate which step of metabolism is being saturated in cats. However, BRL 42359 quantification was not possible because a reference standard for this metabolite was not commercially available.

Intravenous infusion of penciclovir (10 mg/kg over 1 hour) in phase II of the present study provided further insight into the distribution and elimination of penciclovir in cats. Our results indicate that the penciclovir volume of distribution in cats approximates total body water, which is typically 60% of body weight in this species,²³ and that penciclovir Cl (4.3 mL/kg/min) was rapid and resulted in linear elimination with a half-life of 1.9 hours. Importantly, IV infusion of 10 mg of penciclovir/kg to cats resulted in a penciclovir C_{max} nearly 15 times that achieved following oral administration of 40 or 90 mg of famciclovir/kg. Taken together, these results support the hypothesis that low bioavailability of penciclovir after oral administration of famciclovir (relative to IV administration of penciclovir) in cats is attributable to incomplete or slow famciclovir metabolism. Another hypothesis is that rapid penciclovir disposition or elimination is responsible for the low relative bioavailability

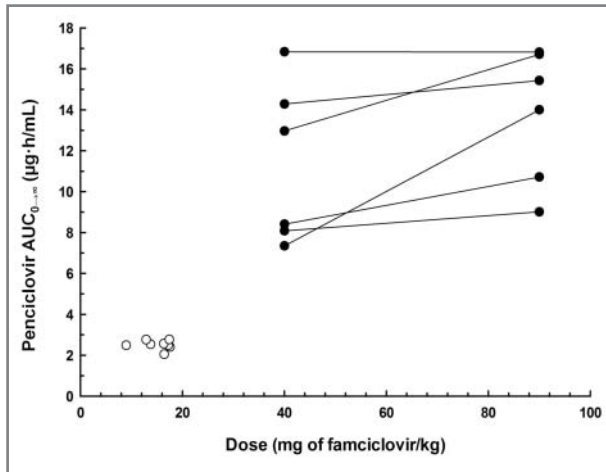


Figure 4—Penciclovir $AUC_{0-\infty}$ values following oral administration of a single dose of 40 or 90 mg of famciclovir/kg administered to 6 cats in the present study (black circles) or following oral administration of a single dose of 9 to 18 mg of famciclovir/kg (white circles) to 8 cats in a previous study.¹² For each cat, $AUC_{0-\infty}$ values for the 40 mg/kg and 90 mg/kg dose are connected by a solid line.

Table 3—Mean \pm SD values for pharmacokinetic variables of penciclovir determined via compartmental analysis after IV administration of a single infusion of penciclovir (10 mg/kg over 1 hour) to the same 6 cats in Table 1.

Variable	Value
Extrapolated time zero plasma drug concentration ($\mu\text{g/mL}$)	17.4 ± 3.8
Intercept of distribution phase* ($\mu\text{g/mL}$)	107 ± 70
Intercept of elimination phase* ($\mu\text{g/mL}$)	12.1 ± 1.1
Distribution half-life (min)	3.4 ± 2.3
Elimination half-life (min)	115 ± 22
Apparent volume of the central compartment (L/kg)	0.11 ± 0.05
Apparent volume of distribution at steady state (L/kg)	0.57 ± 0.11
Cl (mL/min/kg)	4.3 ± 0.75
$AUC_{0-\infty}$ ($\mu\text{g}\cdot\text{h/mL}$)	41.1 ± 7.6
Mean residence time (min)	138 ± 34

*Intercepts were normalized to dose.
An IV infusion of penciclovir was administered to each cat ≥ 4 weeks after the previous oral administration of famciclovir.

of famciclovir; this alternative hypothesis is less likely true, given the results of the IV infusion of penciclovir.

This raises the question as to whether penciclovir could be administered IV as a treatment for cats infected with FHV-1, as has been done for humans infected with herpesviruses. For example, IV infusion of 5 mg of penciclovir/kg every 12 hours was safe and as efficacious as administration of 5 mg of acyclovir/kg every 8 hours for treatment of mucocutaneous HSV infections in immunocompromised human patients.²⁴ Results of the present study revealed that IV infusion of 10 mg of penciclovir/kg maintained plasma penciclovir concentrations above the target concentration for efficacy against FHV-1² for ≥ 4 hours following initiation of infusion. Therefore, IV infusion of penciclovir would be potentially useful for cats with severe FHV-1 infections, especially those that are anorexic or do not tolerate orally administered medications.

The present study also investigated the safety of a single IV infusion of 10 mg of penciclovir/kg. The only adverse clinical effect detected was transient muscle

tremors in 1 of 6 cats during IV administration of penciclovir. This is in agreement with studies^{24,25} assessing the safety of IV infusions of penciclovir in healthy and immunocompromised human patients in which investigators found a low incidence of adverse effects. The only CBC or serum biochemical values that changed significantly following IV infusion of penciclovir in the present study were TP, albumin, and platelet concentrations and GGT activity; all of these were decreased at the end of the present study. Although the decrease in TP and albumin concentration could have resulted from drug administration, they would also be expected as a result of the frequent blood sample collection required to accurately determine plasma famciclovir and penciclovir concentrations.¹² In the present study, between 32.5 and 39 mL of blood was collected with equal volume replacement over a 24-hour period from cats receiving the penciclovir infusion. Blood sample collection and volume replacement could also have contributed to the significant decrease in absolute platelet concentration observed in 2 cats in the present study. Alternatively, the platelet concentration could have been spuriously low in these 2 cats because of a clot within the sample. Regardless, it seems unlikely that a single IV dose of penciclovir would cause bone marrow suppression and a circulating thrombocytopenia within 24 hours after drug administration, given that no clinical or clinicopathologic adverse effects were observed in FHV-1 infected cats following oral administration of 90 mg of famciclovir/kg 3 times daily (8:00 AM, 2:00 PM and 8:00 PM) for 21 days.¹³ In addition, neutropenia secondary to bone marrow suppression was not detected in FHV-1-infected cats that received the pharmacologically related antiviral agent valacyclovir until the drug had been administered for 5 days.¹⁰ However, this treatment was only evaluated in a small number of healthy cats and was only administered once; if IV infusion of penciclovir were to become a potential treatment for cats, further investigation of effects on blood cell counts and other physiologic effects is warranted in cats not undergoing frequent blood sample collection.

Subjective comparison of data from the present study with those from a previous study¹² determining the pharmacokinetics of orally administered famciclovir in cats permits some interesting observations. For example, a mean famciclovir dose of 15 mg/kg resulted in a mean penciclovir C_{max} of $0.33 \pm 0.12 \mu\text{g/mL}$ and $AUC_{0-\infty}$ of $2.5 \pm 0.2 \mu\text{g}\cdot\text{h/mL}$,¹² whereas in the present study, a 40 mg/kg dose of famciclovir (approx 2.7 times that used in the earlier study) resulted in mean penciclovir C_{max} ($1.34 \mu\text{g/mL}$) and $AUC_{0-\infty}$ ($11.3 \mu\text{g}\cdot\text{h/mL}$) values approximately 4 times those achieved at the lower dose. In addition, T_{max} in the previous study¹² (4.6 hours) was considerably longer than in the present study (approx 3 hours). Coadministration of a small amount of food with the famciclovir may have contributed to the low C_{max} and delayed T_{max} observed in the previous study.¹² In humans, administration of famciclovir 0.5 hours after ingestion of food significantly decreased penciclovir C_{max} by 53% and delayed T_{max} from 0.9 to 2.25 hours.²⁶ Although food was available at all times for cats in the previous study¹² and the present study, food was not specifically administered with fam-

ciclovir in the present study. Elimination half-life also varied among cats in the previous study¹² that received approximately 15 mg of famciclovir/kg (3.1 hours) and those in the present study that received 40 (4.2 hours) or 90 (4.8 hours) mg of famciclovir/kg. This apparent difference was most likely attributable to differences in sample collection time points, considering that blood was collected at various times up to 12 hours in the previous study,¹² whereas in the present study, blood samples were obtained for 24 hours following drug administration.

Despite low bioavailability and C_{\max} in cats, orally administered famciclovir remains a very efficacious treatment for cats infected with FHV-1. Reported doses and dose frequencies have ranged widely (from 8 mg/kg once daily²⁷ to 90 mg/kg 3 times daily^{13,28}). In the only study,¹³ to the authors' knowledge, to assess famciclovir pharmacokinetics and efficacy in cats, 90 mg of famciclovir/kg administered 3 times daily (8:00 AM, 2:00 PM, and 8:00 PM) was highly efficacious and associated with C_{\max} values of approximately 2.0 to 2.1 μg of penciclovir/mL. In the present study, we determined that penciclovir pharmacokinetic variables were similar whether cats received a single orally administered dose of 40 or 90 mg of famciclovir/kg. These data indirectly suggest that antiviral efficacy would be similar in cats administered 40 or 90 mg of famciclovir/kg, which is important because the use of famciclovir may be limited in some situations because of its expense. Because famciclovir pharmacokinetics in cats are nonlinear, it seems likely that oral administration of < 40 mg but > 15 mg of famciclovir/kg 3 times daily could also result in pharmacokinetic variables and antiviral efficacy similar to those achieved with thrice-daily oral administration of 90 mg of famciclovir/kg. Thus, further investigation of famciclovir pharmacokinetics and efficacy at doses between 15 and 40 mg/kg 2 or 3 times daily is warranted to determine the ideal dosage for this drug in cats.

Disposition of famciclovir and penciclovir following oral administration of famciclovir differs markedly in cats, compared with other species; however, penciclovir disposition following IV infusion appears to be similar among species.^{1,29} It is intriguing to try to determine whether this represents differences in the way cats absorb, metabolize, or excrete famciclovir and its metabolites. Comparison of famciclovir absorption among cats and other species is difficult because in humans, dogs, and rats, famciclovir was detectable at only low concentrations and only at 0.25 or 0.5 hours after administration of single orally administered doses that ranged from approximately 5 to 4,000 mg of famciclovir/kg.^{1,29} However, famciclovir absorption and metabolism are likely to be more or less complete in humans, given that bioavailability of penciclovir is 77% following oral administration of 500 mg of famciclovir.³⁰ In addition, humans have linear increases in $\text{AUC}_{0 \rightarrow \infty}$ and C_{\max} of penciclovir when famciclovir dose is increased 6-fold from 125 to 750 mg,³¹ whereas cats in the present study had no significant increase in penciclovir AUC and C_{\max} following a 2.25-fold increase in famciclovir dose from 40 to 90 mg/kg. Pharmacokinetics of famciclovir in dogs are also nonlinear, with 2- or 10-fold increases in famciclovir dose from 25 to 50 or 250 mg/

kg resulting in only 1.3- or 3-fold increases in penciclovir C_{\max} from 4.4 $\mu\text{g}/\text{mL}$ to 5.7 or 14 $\mu\text{g}/\text{mL}$.¹ This may be attributable to saturation of famciclovir metabolism because dogs also have low hepatic aldehyde oxidase activity, compared with that in humans and rats.²² However, dogs that received 25 mg of famciclovir/kg had a penciclovir C_{\max} (4.4 $\mu\text{g}/\text{mL}$)¹ approximately 3 times that of cats of the present study that received either 40 or 90 mg of famciclovir/kg (1.34 or 1.28 $\mu\text{g}/\text{mL}$, respectively). It is possible that dogs and perhaps cats metabolize BRL 42359 to penciclovir differently than do humans and rats, which have been described as having good and moderate hepatic aldehyde oxidase activities, respectively.²² For example, dogs have high xanthine oxidase activity in liver tissue, and this enzyme may play a role in the conversion of BRL 42359 to penciclovir.³² Intravenous infusion of 10 mg of penciclovir/kg over 1 hour to cats in the present study and to humans in an earlier study²⁴ resulted in C_{\max} values of 18.6 and 12.1 $\mu\text{g}/\text{mL}$, respectively. The apparently greater C_{\max} detected in cats, compared with that in humans after IV administration of penciclovir, is interesting given that an orally administered dose of 40 mg of famciclovir/kg resulted in a penciclovir C_{\max} of only 1.3 $\mu\text{g}/\text{mL}$ in cats of the present study, whereas 10 mg of famciclovir/kg resulted in a penciclovir C_{\max} of 5.1 $\mu\text{g}/\text{mL}$ in humans.³¹ The apparently higher C_{\max} of penciclovir following IV infusion in cats, compared with that in humans, is likely attributable to the combination of a smaller volume of distribution in cats (0.57 L/kg) than in humans (1.31 L/kg) and slower Cl rates in cats (4.3 mL/min/kg) than in humans (5.9 mL/min/kg).²⁴ The volume of distribution in cats approximates the volume of total body water, which is typically 60% of body weight, and suggests that penciclovir may be distributed less widely in tissues of cats than of humans.^{23,24} Despite these differences, the elimination half-life of penciclovir following IV infusion in cats in the present study was nearly identical to that determined in humans (1.9 hours).²⁴ Interestingly, penciclovir elimination half-life following oral administration of famciclovir and IV infusion of penciclovir is identical in humans (1.9 hours), but cats in the present study had a penciclovir elimination half-life of approximately 4.5 hours following oral administration of famciclovir. The prolonged elimination half-life of penciclovir in cats that received famciclovir may reflect a slow elimination half-life of BRL 42359 or another intermediate metabolite. These results reinforce that the marked differences in penciclovir pharmacokinetics following oral administration of famciclovir to cats and other species are likely attributable to variations in famciclovir metabolism rather than penciclovir disposition or elimination.

- a. Penciclovir, Novartis Pharmaceuticals Corp, East Hanover, NJ.
- b. Famvir, Novartis Pharmaceuticals Corp, East Hanover, NJ.
- c. Medfusion 2010i, Medex, Watford, Hertfordshire, England.
- d. Access Technologies, Skokie, Ill.
- e. Arrow International Inc, Reading, Pa.
- f. WinNonlin, version 5.0.1, Pharsight, Palo Alto, Calif.
- g. IDEXX Laboratories, Sacramento, Calif.

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