

Effect of topical ophthalmic application of cidofovir on experimentally induced primary ocular feline herpesvirus-1 infection in cats

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Objective—To evaluate the efficacy of twice-daily ophthalmic application of 0.5% cidofovir solution in cats with experimentally induced primary ocular feline herpesvirus-1 (FHV-1) infection.

Animals—Twelve 6-month-old sexually intact male cats.

Procedures—Cats were randomly assigned to either a treatment or control group. Ocular infection with FHV-1 was induced (day 0) in all cats via inoculation of both eyes with 10^4 plaque-forming units of a plaque-purified FHV-1 field strain. Twice daily for 10 days beginning on day 4 after virus inoculation, the treatment group received 1 drop of 0.5% cidofovir in 1% carboxymethylcellulose in both eyes, and the control group received 1 drop of 1% carboxymethylcellulose in both eyes. A standardized scoring method was used to evaluate clinical signs of FHV-1 infection in each cat once daily for 24 days. The amount of ocular viral shedding was assessed by use of a quantitative real-time PCR procedure every 3 days during the study period. Clinical scores and viral quantification were averaged over the pretreatment (days 0 to 3), treatment (days 4 to 14), and posttreatment (days 15 to 24) periods for each cat.

Results—During the treatment period, clinical scores and amount of viral ocular shedding were significantly lower in the treatment group, compared with findings in the control group.

Conclusions and Clinical Relevance—Twice-daily application of 0.5% cidofovir solution in both eyes significantly decreased the amount of viral shedding and the severity of clinical disease in cats with experimentally induced ocular FHV-1 infection. (*Am J Vet Res* 2008;69:289–293)

Feline herpesvirus-1 infection is one of the most common infectious diseases of cats and is probably the most common cause of ocular disease.¹ Feline herpesvirus-1 is a cytopathic DNA virus that replicates in the respiratory, nasal, pharyngeal, and conjunctival epithelia of cats. The virus is transmitted among cats via direct contact with infected ocular and respiratory tract secretions. As with other alphaherpesviruses, neuronal latency develops after primary infection with FHV-1 in as many as 80% of cats.^{2–4} Spontaneous and stress-related recrudescence of the virus occurs in approximately 50% of cats with latent infections.⁵ Many cats that shed FHV-1 develop clinical disease with recurrent conjunctivitis and keratitis being the most common ocular signs.⁶

Topical ophthalmic antiviral medications commonly used for the treatment of FHV-1 are vidarabine,

ABBREVIATIONS

FHV-1	Feline herpesvirus-1
GAPDH	Glyceraldehyde-3-phosphate dehydrogenase
HSV	Herpes simplex virus

trifluridine, and idoxuridine. The current recommendation is to administer these drugs at least 4 to 6 times daily for 2 to 3 weeks. Trifluridine and idoxuridine are the most efficacious against different FHV-1 strains¹ but may be highly irritating. The combination of frequent application and accompanying ocular discomfort often leads to poor owner compliance and inadequate treatment of affected cats. A nonirritating antiviral drug that is effective and long-acting (thereby reducing the frequency of administration) would be a major improvement over what is currently available for treatment of FHV-1 ocular disease. The purpose of the study reported here was to evaluate the efficacy of twice-daily application of 0.5% cidofovir solution in eyes of cats with experimentally induced primary ocular FHV-1 infection.

Materials and Methods

Study population—Twelve 6-month-old sexually intact male specific-pathogen-free kittens were purchased from a commercial breeder. The cats were allowed to become adapted to their new surroundings

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for 1 month prior to beginning the study. To confirm that the cats were not previously infected with FHV-1, conjunctival swabs from each eye were tested via virus isolation^a and PCR assay⁷; results of an ELISA indicated that the cats were seronegative for anti-FHV-1 antibodies.^{8,b} A CBC and serum biochemical analyses were performed on each cat during the adaptation period and 10 days after initiation of medical treatment. Cats were randomly assigned to either the treatment ($n = 6$) or control group (6) prior to viral inoculation. Ocular infection with FHV-1 was induced in all cats via inoculation of both eyes with 10^4 plaque-forming units of a plaque-purified FHV-1 field strain, as previously described.^{9,10} This study was conducted with approval of the Animal Care and Use Committee of the Colorado State University.

Drugs—Cidofovir^c is commercially available only for IV use but has been formulated as an ophthalmic solution (0.2% to 1%).^{11–14} For use in the study, 0.2 mL of the commercially available concentration of cidofovir (75 mg/mL) was diluted in 2.8 mL of 1% carboxymethylcellulose^d to achieve the desired concentration of 0.5% cidofovir (5 mg/mL); the solution was stored in plastic bottles at 4°C. The placebo solution (1% carboxymethylcellulose) was handled and stored in the same manner. The cats in the treatment group were administered 1 drop of 0.5% cidofovir solution topically in each eye, and the cats in the control group were administered 1 drop of the placebo solution topically in each eye; both groups were treated twice daily for 10 days, beginning on day 4 after inoculation.

Clinical score—For 24 days after inoculation, each cat was evaluated by use of a previously described clinical scoring system¹⁵ with a modification of the blepharospasm score (**Appendix**). A blepharospasm score of 0 (representing no eye closure) through 4 (> 75% eyelid closure) was assigned to each cat. Assessments were performed daily by 1 of 2 trained evaluators (JPF or CCP) who were unaware of the group assignments. Conjunctivitis, blepharospasm, and ocular discharge were grouped together as the ocular score. The total clinical score also included the respiratory clinical signs (sneezing and nasal discharge). Higher clinical scores represented more severe clinical signs.

Real-time PCR assay—To obtain cells and ocular fluid samples, standard cotton-tipped wooden applicators were gently rolled in the ventral conjunctiva of both eyes (1 swab/eye) of all cats on days 0, 3, 6, 9, 12, 15, 18, 21, and 24 after inoculation with FHV-1. Swabs were placed in 1 mL of sterile 0.01M PBS solution and allowed to remain at room temperature (approx 25°C) for 2 to 3 hours before being stored at –70°C until analyzed. The DNA was extracted by use of a commercial kit^e and assayed for FHV-1 and GAPDH. Quantitation of FHV-1 DNA by use of a real-time PCR assay was adapted from a previously published protocol.¹⁶ Briefly, the 25- μ L real-time PCR reaction contained 12.5 μ L of a supermix,^f 0.5 μ L (400nM) of each primer, 0.2 μ L (80nM) of double-labeled probe (6-carboxyfluorescein/carboxytetramethylrhodamine [FAM/TAMRA]), 1.3 μ L of sterile water, and 10 μ L of extracted template DNA. All reactions were carried out on a thermal cycler^g by

use of the following conditions: 2 minutes at 50°C; 10 minutes at 95°C; and then 40 cycles consisting of a 15-second, 95°C denaturation step followed by a 1-minute 60°C annealing step. By use of a previously published protocol,¹⁷ parallel reactions for feline GAPDH were performed on the same plate to account for variations in DNA quantity (secondary to different yields of cells during swab sample collection) in each sample. The GAPDH reaction conditions were the same as those for FHV-1 with the exception that only 5 μ L of template DNA was used with a corresponding increase in the volume of sterile water (6.3 μ L). Data were analyzed with the instrument software. Signals were considered positive if the fluorescence intensity exceeded 10 times the SD of the baseline fluorescence (threshold cycle). All test sample reactions were run in duplicate.

A standard curve for GAPDH-cell equivalent was generated by use of RNA isolated from Crandell-Rees feline kidney cells in the same manner as the test samples. The standard curve for FHV-1 was generated by use of a 10-fold dilution series with plasmid-generated DNA. The FHV-1 plasmid-generated DNA was prepared by use of a commercially available vector^h after purificationⁱ of product obtained from a conventional PCR reaction involving the primers used in the real-time assay. All standard curve samples were run in duplicate. The log of FHV-1 DNA copy numbers per cell equivalent was determined for each sample. Because of technical difficulties, DNA extracted from samples collected on day 15 was not available for analysis.

Statistical analysis—Mean ocular and total clinical scores were calculated for the pretreatment (days 0 to 3), treatment (days 4 to 14), and posttreatment (days 15 to 24) periods for each cat. A repeated-measures ANOVA^j was used to evaluate a statistical model containing treatment group, period, and the period by group interaction. If the interaction was significant ($P < 0.05$), the treatment effects within periods were evaluated. If the interaction was not significant, the main effect of treatment was evaluated. Median ocular and total clinical scores were also evaluated, with similar results. Least squares means for treatment effects within time periods are reported.

The statistical methods used for the viral quantification were the same as those used for the clinical scores, with the exception that the pretreatment values (days 0 to 3) were included in the statistical model as a covariate, as there were differences in the quantity of FHV-1 DNA between the treatment and control groups prior to initiation of treatment. The mean viral quantification for the 2 eyes was used in the statistical analysis. A value of $P < 0.05$ was considered significant for all analyses.

Results

Clinical scores—Clinical signs of conjunctivitis were noticeable by day 3 after inoculation in all cats, and treatment with cidofovir or placebo solution was initiated on day 4. The interaction between treatment period and group was significant for both ocular ($P = 0.032$) and total clinical scores ($P = 0.03$). Evaluation of the within-period treatment effects revealed no significant ($P > 0.05$) difference in the pre- or posttreatment

periods for either of these 2 outcomes. However, during the treatment period, cats in the cidofovir-treated group had significantly lower ocular ($P = 0.028$) and total clinical scores ($P = 0.026$), compared with the placebo-treated control group (Figure 1).

Real-time PCR assay—In the pretreatment period (after viral inoculation but prior to initiation of either treatment), the treatment group had a significantly ($P < 0.05$) lower viral load, compared with the control group. To account for these differences in viral load, the pretreatment values were included in the statistical model as a covariate. As determined for the clinical signs evaluation, the time-by-treatment interaction was significant ($P = 0.011$) for the quantification of FHV-1 DNA. Within-period evaluations revealed that dur-

ing the treatment period, cats in the treatment group had significantly ($P = 0.003$) lower amounts of FHV-1 DNA, compared with findings in the control group (Figure 2). During the posttreatment period, there was no difference in the amount of FHV-1 DNA between the groups ($P = 0.724$), and the amount of FHV-1 DNA was not significantly different from 0 for either group. Shedding of FHV-1 from the eyes treated with cidofovir ceased between days 7 and 9 after inoculation, whereas virus shedding in the placebo-treated eyes reached non-detectable levels between days 12 and 18.

Discussion

Cidofovir is a nucleoside monophosphate analog of cytosine that acts as a competitive inhibitor and chain terminator during DNA synthesis. It is a broad-spectrum antiviral medication with proven efficacy against a large number of DNA viruses including HSV types 1 and 2, human herpesvirus type 6, varicella-zoster virus, cytomegalovirus, Epstein-Barr virus, and equine and bovine herpesviruses.¹⁸ Recently, it was determined that cidofovir is also highly effective at reducing in vitro replication of FHV-1.¹⁹ Nucleoside monophosphate analogs differ from nucleoside analogs, such as acyclovir, in that they require 2 rather than 3 phosphorylation steps to be activated. Therefore, cidofovir is not reliant on the initial phosphorylation step that is typically mediated by the virus-encoded thymidine kinase for activation within cells. However, cidofovir does require the 2 additional phosphorylation steps to be completed by the host's cellular enzymes. Both of these steps occur in uninfected cells but are accentuated in cells infected with a virus.²⁰ Although currently only available for IV administration, cidofovir has been formulated as an ophthalmic solution (0.2% to 1%)^{10,12-14} and used in studies^{11,12,21} of rabbits with experimentally induced HSV-1 keratitis and for treatment of adenoviral keratoconjunctivitis in humans in clinical pilot studies.^{13,14}

Although effective, antiviral medications that are currently administered topically for FHV-1 infection in cats are often irritating and require frequent administration. Systemic administration of antiviral medications may be even less suitable for treatment of FHV-1 infection. For example, acyclovir has poor bioavailability in cats and may cause toxic effects (eg, leukopenia and anemia) in some cats at subtherapeutic dosages.²² Valacyclovir, an acyclovir prodrug, is comparatively more bioavailable in cats²² but can cause severe adverse effects including bone marrow suppression, renal necrosis, and liver necrosis in that species.²³ The in vitro ef-

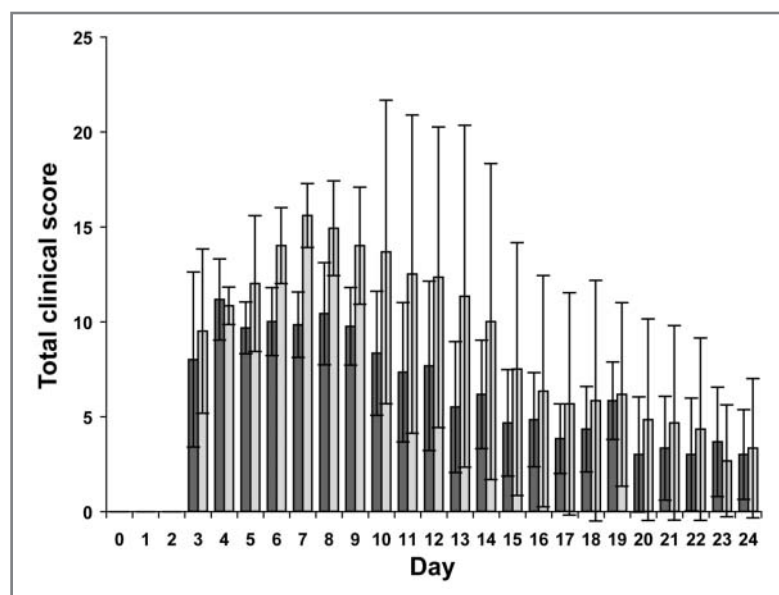


Figure 1—Mean \pm SD total clinical scores determined for cats with experimentally induced primary ocular FHV-1 infection that were treated with 0.5% cidofovir solution ($n = 6$; dark gray bars) or 1% carboxymethylcellulose solution (6; light gray bars) in both eyes twice daily. Total clinical scores were calculated daily for 21 days beginning on day 3 after viral inoculation (day 0). Higher scores were associated with more severe clinical signs.

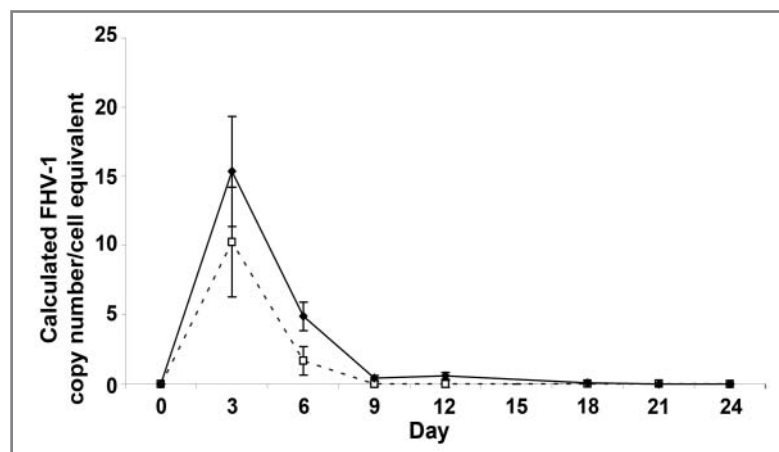


Figure 2—Mean \pm SD FHV-1 viral quantity determined in cats with experimentally induced primary ocular FHV-1 infection that were treated with 0.5% cidofovir solution ($n = 6$; white squares) or 1% carboxymethylcellulose solution (6; black diamonds) in both eyes twice daily. Assessments were performed at intervals during a 24-day period after viral inoculation (day 0).

efficacy against FHV-1 of other systemic antiviral medications has been investigated,¹⁹ although *in vivo* studies with these medications are lacking in the veterinary medical literature, to our knowledge. However, a recent study^k revealed that the oral administration of famciclovir 3 times/d was safe and effective in cats with primary FHV-1 infection.

The goal of the present study was to assess the efficacy of twice-daily topical application of 0.5% cidofovir on experimentally induced primary ocular FHV-1 infection in cats via subjective (clinical scoring) and objective (viral quantification) methods. Despite random assignment of these cats into either the treatment or control group, the treatment group had a lower viral load, compared with the control group, in the period after inoculation but prior to initiation of treatment with cidofovir or placebo solution (pretreatment period). Although there was a difference between the amounts of virus detected between these groups, there was no difference in the severity of clinical signs during this same period. To account for these differences in viral load, the pretreatment (viral quantity) values were included in the statistical model as a covariate. Inclusion of the pretreatment values as a covariate in the statistical model adjusted the outcomes for each individual cat as if all cats had the same pretreatment value; thus, subsequent adjusted values for cats with lower pretreatment values were increased, and subsequent adjusted values for those individuals with higher pretreatment values were decreased. By use of this statistical model, twice-daily application of 0.5% cidofovir solution significantly decreased the amount of viral shedding during the treatment period. This finding combined with a significant decrease in severity of clinical disease in the cats treated with cidofovir (compared with the placebo-treated control cats) during the treatment period lead to our conclusion that twice-daily application of 0.5% cidofovir solution to both eyes of cats was effective against experimentally induced primary ocular FHV-1 infection.

Some of the most intriguing characteristics of cidofovir include its long half-life and extended persistence in ocular tissues.^{11,21,24} These unique qualities allow less frequent administration and shorter duration of treatment, compared with other antiviral medications. In a study²¹ of rabbits with HSV-1-associated keratitis, administration of 0.5% and 1% cidofovir topically twice daily for only 7 days significantly decreased viral titers, severity of keratitis, and time to resolution of clinical signs, compared with other antiviral medications that were administered as many as 5 times/d. The long intracellular half-life of cidofovir seemed to translate to its prolonged antiviral activity in the cats treated in the present study. After only 9 days of treatment with cidofovir, virus was not detected in any of the treated eyes, and there was no rebound of FHV-1 replication or increase in severity of clinical signs of conjunctivitis after cessation of treatment on day 10. Shedding of FHV-1 from eyes treated with cidofovir ceased between day 7 and 9 after inoculation, whereas amounts of virus in the placebo-treated eyes reached nondetectable levels between day 12 and 18. Whether this difference is

attributable to cidofovir's antiviral effect or to the initial difference in viral load cannot be determined.

To the authors' knowledge, there have been no reports of systemic adverse effects associated with application of cidofovir in eyes; however, several local adverse effects have been described.^{12,13,24,25} Although administration of 1% cidofovir solution has resulted in superficial punctate keratitis in some rabbits, no adverse effects were detected after administration of a 0.5% cidofovir solution.¹² In another study,²⁴ some rabbits developed punctal stenosis with delayed onset of lacrimation 10 to 20 days after administration of cidofovir. Although other topically applied antiviral medications (idoxuridine, trifluridine, and vidarabine) have been reported to cause punctal stenosis,²⁶ specific anatomic and physiologic features of rabbits (ie, single punctum, slow tear turnover, and low blink rate) may have also contributed to the development of this adverse effect.²⁴ Frequent and prolonged ophthalmic application of cidofovir (2.5 mg/mL, q 2 h for 2 weeks, then q 4 to 8 h for 4 additional weeks) in a human with conjunctival squamous cell carcinoma resulted in cicatrization of the inferior punctum 6 months after treatment.²⁷ The possible relationship between topical administration of cidofovir and nasolacrimal duct obstruction cannot be determined from these isolated reports; however, further investigation into this possible adverse effect in cats is indicated. A specific cause-and-effect relationship may be difficult to determine in cats infected with FHV-1 because severe conjunctivitis has also been implicated as a cause of cicatrization of the nasolacrimal puncta in cats.⁶ Topical application of cidofovir can cause decreased intraocular pressure in guinea pigs²⁵; however, it does not affect the intraocular pressure of rabbits.¹⁰ Major ocular or systemic toxic effects associated with administration of 0.2% cidofovir in humans were not detected,¹⁴ but in a subsequent study,¹³ a dose-dependent local toxic effect (conjunctivitis and erythematous eyelids) was evident when 1% cidofovir was administered. To reduce potential adverse effects in the present study, we chose to administer 0.5% cidofovir solution in both eyes of cats in the treatment group twice daily for 10 days. No systemic or local adverse effects were detected, although the eyes were not evaluated for changes in intraocular pressure or development of corneal ulcers. All of the cats were monitored for at least 1 year after the conclusion of our study, and although nasolacrimal patency was not confirmed with a Jones test in all cats, none of them developed chronic epiphora indicative of nasolacrimal duct obstruction.

Presently, FHV-1 conjunctivitis often goes untreated because the treatment is perceived by the owners and veterinarians to be worse than the disease. On the basis of the findings of our experiment, cidofovir appears to be an effective antiviral agent against experimentally induced primary ocular infection with FHV-1 in cats and requires less frequent administration than many other medications. However, its potential local adverse effects such as ocular hypotonia and nasolacrimal duct obstruction have not been investigated in cats, and the efficacy of the drug in cats with naturally occurring primary or recrudescing FHV-1-associated disease has yet to be elucidated. We believe that such investigations in cats are warranted.

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- b. Veterinary Diagnostic Laboratory, Heska Corp, Loveland, Colo.
- c. Cidofovir, Vistide, Gilead, Foster City, Calif.
- d. Carboxymethylcellulose, Veterinary Pharmacy, James L. Voss Veterinary Teaching Hospital, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, Colo.
- e. QIAamp DNA minikit, Qiagen Inc, Valencia, Calif.
- f. iQ Supermix, Bio-Rad Laboratories, Hercules, Calif.
- g. Bio-Rad iCycler, Bio-Rad Laboratories, Hercules, Calif.
- h. TA cloning vector, Invitrogen Corp, Carlsbad, Calif.
- i. Qiaquick PCR purification kit, Qiagen Inc, Valencia, Calif.
- j. MIXED procedure of SAS, version 9, SAS Institute, Cary, NC.
- k. Thomasy SM, Maggs DJ, Lim CC, et al. Safety and efficacy of famciclovir in cats infected with feline herpesvirus 1 (abstr). *Vet Ophthalmol* 2006;9:419.

Appendix

Clinical scoring system used to monitor cats for clinical evidence of disease induced by ocular inoculation with FHV-1.

Clinical sign of FHV-1 infection	Score
Conjunctivitis	0 = None 1 = Mild conjunctival hyperemia 2 = Moderate to severe conjunctival hyperemia 3 = Moderate to severe conjunctival hyperemia and chemosis
Blepharospasm	0 = None 1 = Eye < 25% closed 2 = Eye 25%–50% closed 3 = Eye > 50%–75% closed 4 = Eye > 75% closed
Ocular discharge	0 = None 1 = Minor serous discharge 2 = Moderate mucoid discharge 3 = Marked mucopurulent discharge
Sneezing	0 = None 1 = Observed
Nasal discharge	0 = None 1 = Minor serous discharge 2 = Moderate mucoid discharge 3 = Marked mucopurulent discharge

References

1. Nasissé MP, Guy JS, Davidson MG, et al. In vitro susceptibility of feline herpesvirus-1 to vidarabine, idoxuridine, trifluridine, acyclovir, or bromovinyldeoxyuridine. *Am J Vet Res* 1989;50:158–160.
2. Nasissé MP, Davis BJ, Guy JS, et al. Isolation of feline herpesvirus 1 from the trigeminal ganglia of acutely and chronically infected cats. *J Vet Intern Med* 1992;6:102–103.
3. Gaskell RM, Dennis PE, Goddard LE. Isolation of feline herpesvirus 1 from the trigeminal ganglia of latently infected cats. *J Gen Virol* 1985;66:391–394.
4. Ohmura Y, Ono E, Matsuura T, et al. Detection of feline herpesvirus 1 transcripts in trigeminal ganglia of latently infected cats. *Arch Virol* 1993;129:341–347.
5. Gaskell RM, Povey RC. Experimental induction of feline viral rhinotracheitis re-excretion in FVR recovered cats. *Vet Rec* 1977;100:128–133.
6. Stiles J. Feline herpesvirus. *Vet Clin North Am Small Anim Pract* 2000;30:1001–1014.
7. Burgesser KM, Hotaling S, Schiebel A, et al. Comparison of PCR, virus isolation, and indirect fluorescent antibody staining in the detection of naturally occurring feline herpesvirus infections. *J Vet Diagn Invest* 1999;11:122–126.
8. Lappin MR, Andrews J, Simpson D, et al. Use of serologic tests to predict resistance to feline herpesvirus 1, feline calicivirus, and feline parvovirus infection in cats. *J Am Vet Med Assoc* 2002;220:38–42.
9. Maggs DJ, Nasissé MP, Kass PH. Efficacy of oral supplementation with L-lysine in cats latently infected with feline herpesvirus. *Am J Vet Res* 2003;64:37–42.
10. Stiles J, Townsend WM, Rogers QR, et al. Effect of oral administration of L-lysine on conjunctivitis caused by feline herpesvirus in cats. *Am J Vet Res* 2002;63:99–103.
11. Kaufman HE, Varnell ED, Thompson HW. Trifluridine, cidofovir, and penciclovir in the treatment of experimental herpetic keratitis. *Arch Ophthalmol* 1998;116:777–780.
12. Kaufman HE, Varnell ED, Thompson HW. Cidofovir and experimental herpetic stromal disease. *Arch Ophthalmol* 1999;117:925–928.
13. Hillenkamp J, Reinhard T, Ross RS, et al. The effects of cidofovir 1% with and without cyclosporin 1% as a topical treatment of acute adenoviral keratoconjunctivitis: a controlled clinical pilot study. *Ophthalmology* 2002;109:845–850.
14. Hillenkamp J, Reinhard T, Ross RS, et al. Topical treatment of acute adenoviral keratoconjunctivitis with 0.2% cidofovir and 1% cyclosporine: a controlled clinical pilot study. *Arch Ophthalmol* 2001;119:1487–1491.
15. Maggs DJ, Chang E, Nasissé MP, et al. Persistence of herpes simplex virus type 1 DNA in chronic conjunctival and eyelid lesions of mice. *J Virol* 1998;72:9166–9172.
16. Vöglin A, Fraefel C, Albini S, et al. Quantification of feline herpesvirus 1 DNA in ocular fluid samples of clinically diseased cats by real-time PCR. *J Clin Microbiol* 2002;40:519–523.
17. Leutenegger CM, Klein D, Hofmann-Lehmann R, et al. Rapid feline immunodeficiency virus provirus quantitation by polymerase chain reaction using the TaqMan fluorogenic real-time detection system. *J Virol Methods* 1999;78:105–116.
18. De Clercq E. Therapeutic potential of cidofovir (HPMPC, Vistide) for the treatment of DNA virus (ie herpes-, papova-, pox-, and adenovirus) infections. *Verh K Acad Geneesk Belg* 1996;58:19–47.
19. Maggs DJ, Clarke HE. In vitro efficacy of ganciclovir, cidofovir, penciclovir, foscarnet, idoxuridine, and acyclovir against feline herpesvirus type-1. *Am J Vet Res* 2004;65:399–403.
20. De Clercq E. Acyclic nucleoside phosphonates in chemotherapy of DNA virus and retrovirus infections. *Intervirology* 1997;40:295–303.
21. Romanowski EG, Bartels SP, Gordon YJ. Comparative antiviral efficacies of cidofovir, trifluridine, and acyclovir in the HSV-1 rabbit keratitis model. *Invest Ophthalmol Vis Sci* 1999;40:378–384.
22. Owens JG, Nasissé MP, Tadepalli SM, et al. Pharmacokinetics of acyclovir in the cat. *J Vet Pharmacol Ther* 1996;19:488–490.
23. Nasissé MP, Dorman DC, Jamison KC, et al. Effects of valacyclovir in cats infected with feline herpesvirus 1. *Am J Vet Res* 1997;58:1141–1144.
24. Gordon YJ, Romanowski EG, Aroullo-Cruz T. Topical HPMPC inhibits adenovirus type 5 in the New Zealand rabbit ocular replication model. *Invest Ophthalmol Vis Sci* 1994;35:4135–4143.
25. Taskintuna I, Banker AS, Rao NA, et al. An animal model for cidofovir (HPMPC) toxicity: intraocular pressure and histopathologic effects. *Exp Eye Res* 1997;64:795–806.
26. Pavan-Langston DL, Dunkel EC. Antiviral drugs. In: *Handbook of ocular drug therapy and ocular side effects of systemic drugs*. Boston: Little Brown, 1991;159–163.
27. Sherman MD, Feldman KA, Farahmand SM, et al. Treatment of conjunctival squamous cell carcinoma with topical cidofovir. *Am J Ophthalmol* 2002;134:432–433.