Efficacy of oral supplementation with L-lysine in cats latently infected with feline herpesvirus

David J. Maggs, BVSc; Mark P. Nasisse, DVM; Philip H. Kass, DVM, PhD

Objective—To examine the effects of orally administered L-lysine on clinical signs of feline herpesvirus type 1 (FHV-1) infection and ocular shedding of FHV-1 in latently infected cats.

Animals—14 young adult, FHV-1-naive cats.

Procedure—Five months after primary conjunctival inoculation with FHV-1, cats were rehoused and assigned to receive 400 mg of L-lysine in food once daily for 30 days or food only. On day 15, all cats received methylprednisolone to induce viral reactivation. Clinical signs of infection were graded, and viral shedding was assessed by a polymerase chain reaction assay throughout our study. Peak and trough plasma amino acid concentrations were assessed on day 30.

Results—Fewer cats and eyes were affected by conjunctivitis, and onset of clinical signs of infection was delayed on average by 7 days in cats receiving L-lysine, compared with cats in the control group; however, significant differences between groups were not demonstrated. Significantly fewer viral shedding episodes were identified in the treatment group cats, compared with the control group cats, after rehousing but not following corticosteroid-induced viral reactivation. Mean plasma L-lysine concentration was significantly increased at 3 hours but not at 24 hours after L-lysine administration. Plasma arginine concentration was not significantly altered.

Conclusions and Clinical Relevance—Once daily oral administration of 400 mg of L-lysine to cats latently infected with FHV-1 was associated with reduced viral shedding following changes in housing and husbandry but not following corticosteroid administration. This dose caused a significant but short-term increase in plasma L-lysine concentration without altering plasma arginine concentration or inducing adverse clinical effects. (*Am J Vet Res* 2003;64:37–42)

Despite routine vaccination of many cats, the advent of antiviral drugs with efficacy against **feline herpesvirus type 1 (FHV-1)**, and the environmental instability of this virus, FHV-1 remains a common pathogen of cats throughout the world.[1] The most likely reason for this is the virus' ability to establish lifelong neural latency interspersed with episodes of viral reactivation. It is estimated that 80% of cats become latently infected following primary exposure to FHV-1. Of the latently infected cats, approximately 50% shed virus at some stage during their lives, and 29% do so without a recognized stimulus.[2] Many latently infected cats shed virus without clinical evidence of disease. This subpopulation of cats represents an epidemiologically critical reservoir of virus that ensures perpetuation of infection and disease in the general feline population. This is of particular relevance in breeding and boarding catteries, research colonies, animal shelters, and multicat households. Currently, no treatment has been identified that reduces FHV-1 shedding by latently infected cats.

The amino acid L-lysine has received attention for treatment of human beings latently infected with **herpes simplex virus type 1 (HSV-1)**, another alphaherpesvirus with similar biological behavior to FHV-1. L-Lysine has been demonstrated to reduce the in vitro replication of HSV-1. The presumed mechanism is antagonism of the growth-promoting effect of arginine, which is an essential amino acid for HSV-1 replication.[3,4] Results of clinical trials in humans suffering recurrent HSV-1-related lesions indicate that patients taking L-lysine orally experienced a reduction in lesion recurrence rate, severity, and healing time. However, in some of these trials, patients were required to limit their arginine intake.[5-7]

Recently, we demonstrated that in vitro replication of FHV-1 is suppressed by approximately 80% when the L-lysine concentration in the culture medium is doubled.[8] This effect was negated at higher arginine concentrations suggesting a similar mechanism of arginine antagonism to that described for HSV-1. Because cats are exquisitely sensitive to arginine deficiency,[9] the practicality of oral lysine supplementation, with or without coincident arginine restriction for management of FHV-1 infections, requires careful investigation. Stiles et al[10] recently demonstrated the efficacy of oral administration of lysine to cats prior to primary exposure to FHV-1. Cats receiving 500 mg of L-lysine every 12 hours orally beginning 6 hours prior to experimental primary inoculation with FHV-1, had less severe conjunctivitis, compared with cats receiving placebo. However, viral shedding, as determined by **virus isolation (VI)**, did not differ between groups. No ill effects attributable to lysine administration were observed. The study reported here was designed to examine the effect of orally administered L-lysine on clinical signs of FHV-1 infection and spontaneous and reactivated shedding of FHV-1 in latently infected cats.

Received May 6, 2002.
Accepted August 19, 2002.
From the Department of Veterinary Medicine and Surgery, College of Veterinary Medicine, University of Missouri, Columbia, MO 65211 (Maggs, Nasisse) and the Department of Population Health and Reproduction, School of Veterinary Medicine, University of California, Davis, CA 95616 (Kass). Dr. Maggs' present address is the Department of Surgical and Radiological Sciences, 2112 Tupper Hall, School of Veterinary Medicine, University of California, Davis, CA 95616. Dr. Nasisse's present address is Carolina Veterinary Specialists, 501 Nicholas Rd, Greensboro, NC 27409.
Supported in part by a grant from the Winn Feline Foundation.
Presented in part at the 28th Annual Meeting of the American College of Veterinary Ophthalmologists, Santa Fe, New Mexico, November, 1997.
Address correspondence to Dr. Maggs.

Cats were also observed for overt clinical signs of arginine deficiency, and plasma amino acid concentrations were assessed.

Materials and Methods

Experimental design—Our study comprised 3 major parts. Primary inoculation with the virus and an initial dose analysis were followed by an efficacy study (**Fig 1**).

Animals—All cats involved in our study were maintained and handled in accordance with the Association for Research in Vision and Ophthalmology statement for the use of animals in ophthalmic and vision research, and all experimental procedures were approved by the University's Animal Care and Use Committee. Fourteen young adult, specific-pathogen-free cats were verified to be FHV-1 seronegative by use of a standard serum neutralization assay[11] and were housed as a single group in 1 large room. All cats were provided ad libitum access to a commercial feline ration[a] that contained 1.80% arginine and 1.64% lysine. Following an initial 1-month acclimation period, each cat was inoculated in both conjunctival sacs with 7×10^4 plaque-forming units of a plaque-purified field strain of FHV-1.[12] All cats had clinical disease consistent with primary FHV-1 infection, recovered without treatment, and seroconverted with respect to FHV-1.[11] Although cats did not receive daily veterinary examinations, no overt clinical signs of FHV-1-related disease were seen in the ensuing 5 months.

Initial dose analysis—Approximately 4 months after inoculation, a trial was conducted to determine the relationship between oral lysine dose and plasma lysine and arginine concentrations. These data were used to select the oral dose of lysine administered during the subsequent efficacy phase of our study. Six cats were selected at random from the main study group and administered a single oral dose of 100 mg (n = 2), 200 mg (2), or 400 mg (2) of L-lysine monohydrochloride[b] following a 14-hour period of withholding food. Blood was collected from an indwelling jugular catheter prior to (0 hours) and 1, 2, 3, and 5 hours following lysine administration. Because of obstruction of the jugular catheter, blood samples were available at 3 and 5 hours only from 1 cat administered 100 mg of L-lysine. Statistical analyses were therefore not conducted on data gathered from cats receiving 100 mg of L-lysine. Samples were collected into lithium heparin and placed immediately on ice until they were centrifuged at 15,000 × *g* for 5 minutes. Plasma was then separated, frozen, and shipped on dry ice to a commercial laboratory[c] for automated amino acid analysis. The following amino acids were assessed: alanine, arginine, asparagine, aspartate, glutamate, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, ornithine, phenylalanine, proline, serine, taurine, 3-methylhistidine, threonine, tryptophan, tyrosine, and valine.

Efficacy study—Approximately 5 months following primary infection (1 month following initial dose analysis), 14 cats were randomly assigned to 1 of 2 treatment groups and individually caged. All cats were provided, ad libitum, access to the same commercial feline ration[a] used previously. Cats in the treatment group received 400 mg of L-lysine monohydrochloride orally once daily for 30 days. This dose was derived from data obtained in the initial dose analysis phase of our study. The dosing interval was selected on the basis of clinical utility and previous studies in humans.[5,7] Lysine was administered as a powder mixed in a small amount of a canned commercial cat food.[d] Cats in the control group received a similar volume of the canned cat food once daily for 30 days. All cats in both groups were observed to eat the food. At the halfway point of our study (day 15), all cats were injected IM with 20 mg (approximately 5 mg/kg) of methylprednisolone acetate[e] in an attempt to induce viral reactivation.[13]

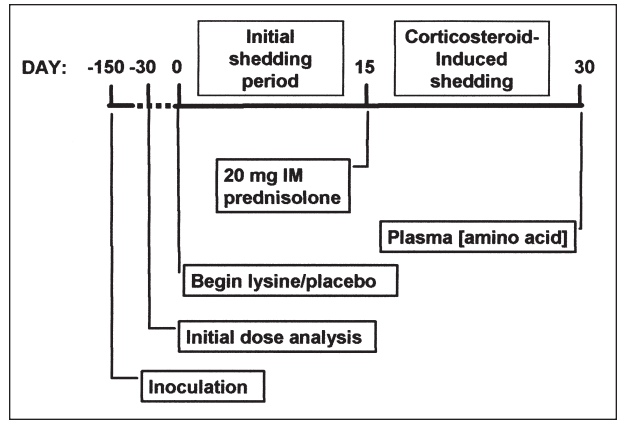

Figure 1—Timeline of experimental design for all phases of study.

All cats were assessed by 1 observer (DJM) once daily throughout the efficacy study period for clinical evidence of FHV-1-associated disease. Clinical signs of infection were graded according to a semi-quantitative scoring system[14] with some modifications (**Appendix**). Clinical scores were summed to give a total disease score for each cat. Median total disease scores were then calculated for each group. The highest disease scores, regardless of the day on which they were noted, were summed to give a peak disease score for each cat, and median peak disease scores were calculated for each group.[15] Both eyes of all cats were topically anesthetized and the right and left inferior conjunctival fornices individually swabbed on a total of 20 days during the efficacy study period by use of cotton-tipped sterile swabs premoistened in PBS solution. Swabs were then broken off into sterile vials of PBS solution and stored at –80°C until assessed for presence of viral DNA by use of a **polymerase chain reaction (PCR)** assay as described.[16] Briefly, vials containing swabs were thawed, vortexed, and cellular debris was pelleted by centrifugation at 14,000 × *g* for 5 minutes. The pellet was resuspended in 50 µL tris-hydrochloride-EDTA. A 25-µL aliquot was then subjected to 40 cycles of a PCR assay targeting a 322 base-pair fragment of the FHV-1 thymidine kinase gene. This protocol reliably detects ≤ 240 copies of FHV-1 DNA.[16]

At the conclusion of the efficacy study, blood was collected from all cats by jugular venepuncture 3 and 24 hours following lysine administration. The 3- and 24-hour samples were intended to represent peak and trough plasma lysine concentrations, respectively, and were selected on the basis of data generated in the initial dose analysis. Samples were handled and submitted for automated plasma amino acid analysis as described in the initial dose analysis.

Data analysis—In the initial dose analysis, median plasma amino acid concentrations at each time point following administration of 200 or 400 mg of L-lysine were compared with baseline amino acid concentrations by use of the Friedman 2-way ANOVA. In the efficacy study, the number of cats with clinical signs of infection, and the number of eyes in which clinical signs of infection were observed, were compared between the treatment and placebo groups by use of the Fisher exact test. Median total and peak disease scores were compared between the treatment and placebo groups by use of the Mann-Whitney rank sum test. The total number of occasions on which FHV-1 DNA was detected in any eye and in any cat was calculated for each group. Total shedding episodes were then compared between the treatment and

control groups by use of χ^2 analysis. Total shedding episodes within groups were compared before and after administration of methylprednisolone acetate by use of the Fisher exact test. Peak and trough plasma amino acid concentrations were compared between the treatment and placebo groups by use of the Student's 2-tailed *t*-test or, where indicated, the Mann-Whitney rank sum test. For all statistical analyses, a value of $P \leq 0.05$ was considered significant.

Results

Initial dose analysis—Oral administration of a single dose of 100, 200, or 400 mg of L-lysine resulted in a dose-related increase in plasma lysine concentration (**Fig 2**). Peak plasma lysine concentration was observed in each cat between 1 and 3 hours after L-lysine administration, regardless of dose. Following administration of 400 mg of lysine, median peak plasma lysine concentration (regardless of time of peak) approximately doubled (540 nmol/mL) and remained increased for approximately 3 hours, compared with baseline. By contrast, mean change in plasma arginine concentrations never exceeded 10% (14 nmol/mL), compared with baseline. Changes in plasma arginine concentrations were not significant (P = 0.11 to 0.31; data not shown).

Clinical signs of infection during efficacy study—No cat in either group had clinical evidence of FHV-1-associated disease during the first 15 days of the efficacy study period. However, cats from both groups had clinical evidence of conjunctivitis following corticosteroid administration. One cat in the treatment group had evidence of bilateral conjunctivitis from day 12 through 15 following corticosteroid administration. Two cats in the control group developed bilateral conjunctivitis; 1 cat on days 2 and 8, and 1 cat on day 8 following corticosteroid administration. Clinical signs of nasal disease were not observed in cats from either group. Fewer cats (n = 1) and eyes (2) were affected by conjunctivitis, and onset of clinical signs was delayed on average by 7 days in cats receiving L-lysine, compared with cats in the control group; however, significant differences in clinical signs of infection were not found between groups as a result of the low numbers of affected cats. Median total disease score and median peak disease score did not differ between the 2 groups. Other than the conjunctivitis described, all cats in the treatment group remained healthy throughout the 30-day period of L-lysine supplementation and had no adverse clinical signs that could be attributed to lysine administration or arginine deficiency.

Viral shedding during efficacy study—Feline herpesvirus DNA was detected in the conjunctival fornix of all but 2 cats (1 from each group) during the total study period. In cats with conjunctivitis, viral shedding was detected within 3 days of the day on which clinical signs of infection were observed. During the 15-day period prior to corticosteroid administration, viral DNA was detected in the conjunctival fornix of 5 cats (7 eyes) from the control group and 5 cats (6 eyes) from the treatment group. Significantly fewer (P = 0.024) FHV-1 DNA shedding episodes were detected in cats from the treatment group (n=6), compared with the control group (17; **Fig 3**). Following corticosteroid administration, viral DNA was detected in the conjunctival fornix of 4 cats (4 eyes) from the control group and 3 cats (4 eyes) from the treatment group. This did not represent a significant increase in shedding following corticosteroid administration in either group. Although the total number of animal shedding episodes (number of positive cat days) in the treatment group (n = 9) was less than the control group (15) following corticosteroid administration, a significant difference was not found (P = 0.32) at the power (0.16) of this test.

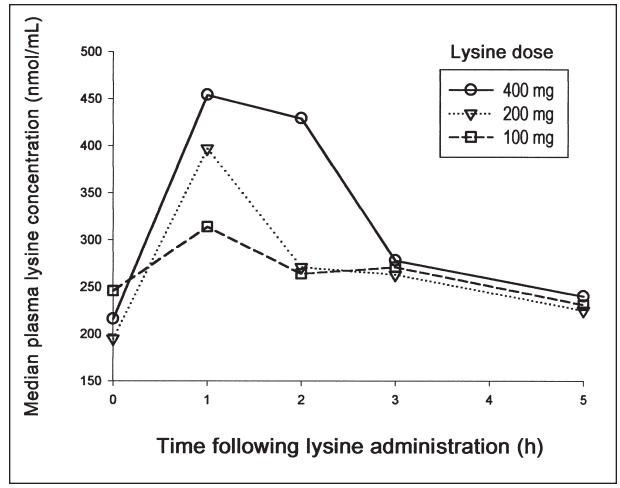

Figure 2—Median plasma lysine concentrations following oral administration of a single dose (100, 200, or 400 mg) of L-lysine monohydrochloride. All points represent median data from 2 cats except at 0, 1, and 2 hours when data were available from only 1 cat receiving 100 mg of L-lysine.

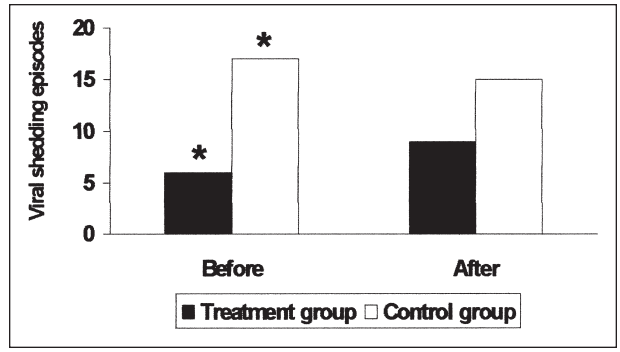

Figure 3—Viral shedding rates before and after corticosteroid administration in cats receiving L-lysine (treatment group) or placebo (control group). Shedding rates are expressed as number of shedding episodes of feline herpesvirus type 1 DNA detected per group. *Before corticosteriod administration, viral shedding was significantly (P = 0.024) decreased in cats receiving L-lysine, compared with cats receiving placebo.

Plasma amino acid concentrations during efficacy study—Approximately 3 hours following administration of L-lysine or placebo, mean plasma lysine concentration was significantly (P = 0.016) increased in the treatment group (309 nmol/mL), compared with the control group (143 nmol/mL; **Fig 4**). However at the same time point, mean plasma arginine concentration did not vary significantly between the 2 groups (P = 0.37). Mean plasma concentrations of other amino acids assessed also did not significantly differ between

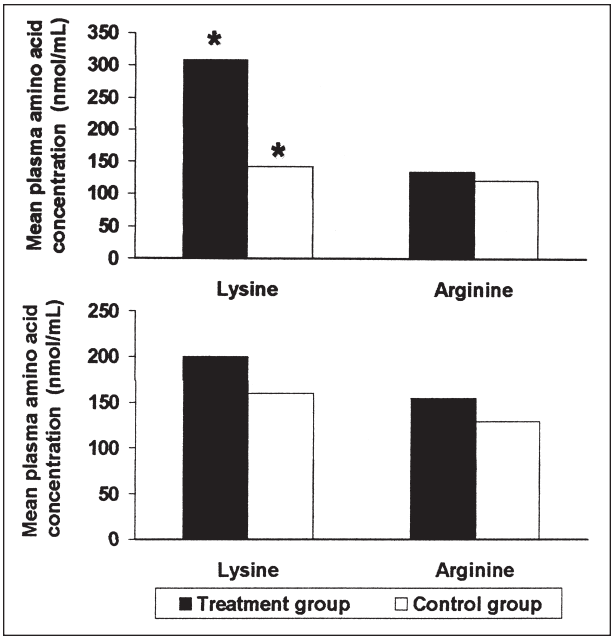

Figure 4—Mean plasma lysine and arginine concentrations in cats 3 hours (top panel) and 24 hours (bottom panel) after receiving 400 mg of L-lysine (treatment group) or placebo (control group) orally. Data are from blood samples drawn following 30 days of once-daily treatment. *Three hours following administration of L-lysine or placebo, plasma lysine concentration was significantly (P = 0.016) increased in cats given L-lysine, compared with cats given placebo.

cats in the treatment and control groups at this time point (data not shown). Twenty-four hours following administration of L-lysine or placebo, no significant difference in mean plasma arginine or lysine concentrations was detected between the treatment and control groups. Of all other amino acids tested at the 24-hour time point, only plasma serine concentration differed significantly between groups (data not shown). Mean plasma serine was significantly (P = 0.012) higher in cats receiving L-lysine (188 nmol/mL), compared with cats receiving placebo (145 nmol/mL).

Discussion

In our study, we used the ocular route of viral inoculation in FHV-1-naive cats, corticosteroid-induced reactivation, and monitoring by use of a PCR assay to investigate the effects of lysine on viral shedding from the conjunctival fornix. Following ocular inoculation with a field strain of FHV-1, all cats had clinical signs consistent with primary FHV-1 infection, recovered without treatment, and seroconverted. Subsequently, FHV-1 DNA was detected in the conjunctival fornix of 12 of 14 (86%) cats during a 30-day monitoring period. This suggests that these cats were latently infected. A previous study that used VI from the oropharynx over longer periods (3 to 22 months) provided a similar estimate of the prevalence with which latency is established (82%).[2] In our study, viral DNA was detected in the conjunctival fornix of all cats with conjunctivitis within 3 days of the time when clinical evidence of disease was first observed, confirming excellent correlation between this PCR assay and clinical evidence of FHV-1-related disease.

The initial 15-day period of our study was designed to provide data on spontaneous viral shedding. During that period, 83% of untreated cats shed virus. In previous studies,[2,13] spontaneous shedding was reported in 4 and 29% of cats. These studies both used VI to detect shedding. In part, the higher basal shedding rate detected in our study is likely the result of the greater sensitivity of the PCR assay, compared with VI.[16-18] Additionally, it is likely that, in retrospect, the initial 15 days in our study did not represent true spontaneous shedding because all cats underwent a change in housing from a single large group to individual cages immediately prior to this phase. Change in housing has previously been identified as a potent stimulus for viral shedding.[2,19] Daily restraint and conjunctival swabbing was also initiated at this time and may have been associated with stress and subsequent viral reactivation.

Following corticosteroid administration, FHV-1 DNA was detected in 7 of 14 (50%) cats in our study. This was not significantly different from the proportion of cats shedding prior to corticosteroid administration. In a previous report[13] in which VI was used, FHV-1 was detected in 4 and 21% of cats prior to and following corticosteroid administration, respectively. In a separate study,[19] FHV was detected in 0 and 81% of cats prior to and following corticosteroid administration, respectively. These authors noted that prior episodes of shedding appeared to cause cats to be temporarily refractory to corticosteroid-induced reactivation.[19] The high rate of shedding during the initial 15-day period of our study, along with the apparent failure of corticosteroid administration to induce further viral shedding, reinforces the likelihood that viral reactivation caused by rehousing and additional handling had likely occurred in most cats prior to corticosteroid administration. Therefore, we believe the initial 15-day period in the our study represented a period of physiological or natural stress, and the second 15-day period represented a period of pharmacological reactivation of virus, potentially reduced in potency as a result of prior viral shedding. Both periods are clinically relevant and provide a useful model to investigate the effect of lysine on viral shedding.

Because FHV-1 is relatively unstable in the environment, latently infected cats represent the most epidemiologically important reservoir of virus.[20] Control of spontaneous and induced shedding in latently infected cats is therefore an important control strategy. In the initial 15-day period of our study, we demonstrated that once daily oral administration of 400 mg of lysine was associated with a reduction in viral shedding from the conjunctival fornix. This suggests that L-lysine limits viral shedding in cats placed under physiologic stress such as rehousing. Lysine administration, therefore, may be a useful clinical and epidemiologic strategy for control of viral shedding in situations such as shelters, catteries, research colonies, or multicat households where cats are exposed to similar stresses.

Orally administered L-lysine did not significantly reduce clinical signs of FHV-1-associated disease in latently infected cats before or following corticosteroid administration in our study. However, these data must

be interpreted cautiously because so few cats had clinical evidence of disease at either stage of the experiment. Therefore, the power of statistical analyses was frequently lower than desired. In a similar study, 500 mg of lysine was orally administered twice daily to cats beginning 6 hours prior to experimental inoculation with FHV-1.[10] In that study, clinical signs of primary FHV-1-related conjunctivitis were significantly reduced in cats in the treatment group, compared with cats receiving placebo. There were many differences between experimental design of that study and our study. It is likely that the dose rate and interval, along with the timing of medication relative to infection and the fact that primary rather than recrudescent infection was examined in that study, produced different results to those of our study. It appears that peak plasma concentration occurs within 3 hours of oral administration of a single dose, and that even after once a day oral administration for 30 days, there is not an increase in plasma lysine concentration at 24 hours after administration. On the basis of data from that study and our study, administration of L-lysine more than once daily may be necessary.

The mechanism by which lysine restricts viral replication remains unclear. In vitro data generated with HSV-1[3,4] and FHV-1[8] suggest that lysine antagonizes a growth promoting effect exerted by arginine. Lysine-arginine antagonism has been demonstrated in many mammalian and avian species and at a number of points including sites of absorption, utilization, metabolism, and excretion. Specific sites and mechanisms include altered amino acid availability within the gastrointestinal tract,[21] competitive inhibition of amino acid transport across the wall of the small intestine[22,23] or cell membranes at sites of utilization,[23,24] altered metabolism of 1 or both amino acids,[25,26] and altered reabsorption at the renal tubules.[23,27] Oral administration of lysine might therefore be expected to cause a reduction in plasma arginine concentration, which in cats could be clinically important. Although we did not measure renal or fecal excretion of arginine, plasma arginine concentrations were not affected, and clinical signs of arginine deficiency were not observed during once daily oral administration of 400 mg of L-lysine for 30 consecutive days. In a related study[10] in which cats received 500 mg of L-lysine orally for 21 days, plasma arginine concentration was similarly unaffected, and no clinical signs of arginine deficiency were observed. Clinical evidence in humans[7,28] and experimental data in chickens[29] suggest that genetic variations in lysine-arginine metabolism exist. This may contribute to the observation that some individuals are more vulnerable to viral infections than others and could be examined by studies of the effect of lysine supplementation in larger at-risk feline populations.

Results of our study suggest that once daily oral administration of 400 mg of L-lysine to cats latently infected with FHV-1 reduced viral shedding in the face of stresses, such as changes in housing or husbandry, that are known to induce viral reactivation. This dose caused a short-term, but significant, increase in plasma lysine concentration without altering other essential amino acid concentrations. Importantly, no significant alterations in plasma arginine concentration or clinical signs attributable to L-lysine administration or arginine deficiency were associated with oral lysine administration using this regimen.

[a]Laboratory feline diet #5003. Purina Mills Inc, St Louis, Mo.
[b]Spectrum Chemical Manufacturing Corp, New Brunswick, NJ.
[c]Amino Acid Analysis Laboratory, School of Veterinary Medicine, University of California Davis, Davis, Calif 95616.
[d]Whiska's Kal Kan Foods Inc, Vernon, Calif.
[e]Depo-Medrol 40 mg/mL suspension, the Upjohn Co, Kalamazoo, Mich.

Appendix

Scoring system used to monitor cats for clinical evidence of feline herpesvirus type 1-associated disease

Clinical signs of infection	
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 to 50% closed 3 = Eye 50 to 75% closed 4 = Eye completely 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. Maggs DJ, Lappin MR, Reif JS, et al. Evaluation of serologic and viral detection methods for diagnosing feline herpesvirus-1 infection in cats with acute respiratory tract or chronic ocular disease. *J Am Vet Med Assoc* 1999;214:502–507.

2. Gaskell RM, Povey RC. Experimental induction of feline viral rhinotracheitis virus re-excretion in FVR-recovered cats. *Vet Rec* 1977;100:128–133.

3. Griffith RS, DeLong DC, Nelson JD. Relation of arginine-lysine antagonism to herpes simplex growth in tissue culture. *Chemotherapy* 1981;27:209–213.

4. Tankersley RW. Amino acid requirements of herpes simplex virus in human cells. *J Bacteriol* 1964;87:609–613.

5. Griffith RS, Norins AL, Kagan C. A multicentered study of lysine therapy in herpes simplex infection. *Dermatologica* 1978;156:257–267.

6. Griffith RS, Walsh DE, Myrmel KH, et al. Success of L-lysine therapy in frequently recurrent herpes simplex infection. Treatment and prophylaxis. *Dermatologica* 1987;175:183–190.

7. Thein DJ, Hurt WC. Lysine as a prophylactic agent in the treatment of recurrent herpes simplex labialis. *Oral Surg Oral Med Oral Pathol* 1984;58:659–666.

8. Maggs DJ, Collins BK, Thorne JG, et al. Effects of L-lysine and L-arginine on in vitro replication of feline herpesvirus type-1. *Am J Vet Res* 2000;61:1474–1478.

9. Morris JG, Rogers QR. Ammonia intoxication in the near-adult cat as a result of a dietary deficiency of arginine. *Science* 1978;199:431–432.

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. Povey RC, Johnson RH. A standardized serum neutralization test for feline viral rhinotracheitis. II. The virus-serum system. *J Comp Pathol* 1969;79:387–392.

12. Nasisse MP, Guy JS, Davidson MG, et al. Experimental ocu-

lar herpesvirus infection in the cat. Sites of virus replication, clinical features and effects of corticosteroid administration. *Invest Ophthalmol Vis Sci* 1989;30:1758–1768.

13. Hickman MA, Reubel GH, Hoffman DE, et al. An epizootic of feline herpesvirus, type 1 in a large specific pathogen-free cat colony and attempts to eradicate the infection by identification and culling of carriers. *Lab Anim* 1994;28:320–329.

14. Maggs DJ, Chang E, Nasisse 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.

15. Grau DR, Visalli RJ, Brandt CR. Herpes simplex virus stromal keratitis is not titer-dependent and does not correlate with neurovirulence. *Invest Ophthalmol Vis Sci* 1989;30:2474–2480.

16. Weigler BJ, Babineau CA, Sherry B, et al. High sensitivity polymerase chain reaction assay for active and latent feline herpesvirus-1 infections in domestic cats. *Vet Rec* 1997;140:335–338.

17. 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.

18. Sykes JE, Browning GF, Anderson G, et al. Differential sensitivity of culture and the polymerase chain reaction for detection of feline herpesvirus 1 in vaccinated and unvaccinated cats. *Arch Virol* 1997;142:65–74.

19. Gaskell RM, Povey RC. Re-excretion of feline viral rhinotracheitis virus following corticosteroid treatment. *Vet Rec* 1973;93:204–205.

20. Povey RC, Johnson RH. Observations on the epidemiology and control of viral respiratory disease in cats. *J Small Anim Pract* 1970;11:485–494.

21. Jones JD. Lysine-arginine antagonism in the chick. *J Nutr* 1964;84:313–321.

22. Kadirvel R, Kratzer FH. Uptake of L-arginine and L-lysine by the small intestine and its influence on arginine-lysine antagonism in chicks. *J Nutr* 1974;104:339–343.

23. Milne MD. Disorders of amino-acid transport. *BMJ* 1964; 1:327–336.

24. Banos G, Daniel PM, Pratt OE. Saturation of a shared mechanism which transports L-arginine and L-lysine into the brain of the living rat. *J Physiol (Lond)* 1974;236:29–41.

25. Jones JD, Petersburg SJ, Burnettt PC. The mechanism of the lysine-arginine antagonism in the chick: effect of lysine on digestion, kidney arginase, and liver transamidinase. *J Nutr* 1967;93:103–116.

26. Hunter A, Downs CE. The inhibition of arginase by amino acids. *J Biol Chem* 1945;157:427–446.

27. Boorman KN. The renal reabsorption of arginine, lysine and ornithine in the young cockerel (Gallus domesticus). *Comp Biochem Physiol A* 1971;39:29–38.

28. Omura K, Yamanaka N, Higami S, et al. Lysine malabsorption syndrome: a new type of transport defect. *Pediatrics* 1976;57:102–105.

29. Nesheim MC. Genetic variation in arginine and lysine utilization. *Fed Proc* 1968;27:1210–1214.