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Effect of ciclosporin and methylprednisolone acetate on cats previously infected with feline herpesvirus 1

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Abstract

Feline herpesvirus 1 (FHV-1) is a common ocular and respiratory pathogen of cats that can be associated with recurrent clinical signs of disease. Ciclosporin (cyclosporine) is commonly administered per os (PO) for the treatment of a number of inflammatory diseases in cats. A number of client-owned cats administered ciclosporin (cyclosporine) A (CsA) PO to block renal transplant rejection have developed clinical signs of upper respiratory tract disease that may have been from activated FHV-1. In this study, cats experimentally inoculated with FHV-1 several months previously were administered methylprednisolone acetate intramuscularly, CsA PO or a placebo PO. While clinical signs of activated FHV-1 occurred in some cats, disease was mild and self-limited in most cats. There was no vomiting, diarrhea, inappetence, weight loss, polydipsia, polyuria or polyphagia recognized.

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Introduction

Feline herpesvirus 1 (FHV-1) infection is common in cats, is extremely contagious among cats and frequently results in severe clinical disease that most commonly manifests as ocular disease (most commonly conjunctivitis or keratitis), respiratory disease (sneezing, nasal discharges and nasal congestion) or dermatitis.[1–10] Currently available vaccines do not prevent infection but only lessen severity of disease when the cat is exposed to a virulent FHV-1 challenge.[11,12] In addition, most FHV-1 containing vaccines in the USA use modified-live strains that infect the host and occasionally are associated with disease. Thus, FHV-1 infection of cats is extremely common. For example, a prevalence study at a humane society in north central Colorado showed that FHV-1 DNA could be amplified by polymerase chain reaction assay from pharyngeal swabs (42/45 samples; 93.3%) or nasal discharges (41/45 samples; 91.1%) from most cats tested.[1] FHV-1 persists in the body of most cats, with repeated active replication occurring spontaneously or following periods of stress, resulting in multiple recurrences of clinical disease. For example, one parenterally administered dose of methylprednisolone acetate effectively activates latent FHV-1 infection in most cats.[13]

Ciclosporin (cyclosporine) A (CsA) was historically administered PO in cats at high doses to aid in the prevention of renal transplant rejection.[14] More recently, CsA has been administered PO at lower doses for treatment of allergic dermatitis, inflammatory bowel disease and stomatitis in cats that are refractory to other drugs.[15–21] When administered PO at high doses, CsA has occasionally been associated with activation of a variety of chronic infectious diseases or worsening of disease when primary exposure to an infectious agent occurs. The role of CsA in disease reactivation is unclear. In one study of 60 cats undergoing renal transplantation, 22 cats (37%) developed an infectious complication.[14] However, the doses of CsA administered PO to lessen risk of organ rejection are higher than those used clinically for

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inflammatory diseases, CsA is often administered PO concurrently with glucocorticoids and cats requiring organ transplant are usually under a great degree of stress. CsA administered PO has been shown to inhibit transcription of cytokine genes and decrease the frequency of interleukin 2 (IL-2) producing cells in cats, which may explain both its efficacy and its potential to activate some infectious diseases.[22] Cell-mediated immunity is important in maintaining FHV-1 latency and so administration of CsA PO could potentially cause reactivation of infection.[23] In renal transplantation cats, 7/60 cats developed clinical signs of upper respiratory disease during CsA therapy, which may have been related to FHV-1 infection.[14] In addition, bullous keratopathy has been reported in a cat administered CsA PO.[24] In contrast, CsA has been administered PO to cats at lower doses for the treatment of dermatologic diseases in several recent studies and none of the cats were reported to develop clinical signs of FHV-1 infection.[18–21]

The objectives of the study described here were to determine whether administration of CsA PO to cats previously infected with FHV-1 experimentally would activate clinical signs of disease and whether clinical signs would be greater than those induced by administration of one dose of methylprednisolone acetate.

Materials and methods

Research cats

The 23, young adult, mixed sex, neutered cats used in this study were purchased from a commercial breeder and had been administered the USDA vaccine challenge strain of FHV-1 by aerolization, as previously described.[25] After FHV-1 inoculation, all cats developed conjunctivitis, sneezing and nasal discharge. None of the cats had been administered a drug with anti-FHV-1 activity before use in the current study, which began 14 weeks after the primary FHV-1 inoculation. The protocols of the previous and current studies were approved by the Institutional Animal Care and Use Committee and the Biosafety Committee at Colorado State University. The current study was considered a pilot study and so approved for a minimal number of cats to perform the statistical methods described. The cats were group housed in three separate rooms for the duration of the study. They were given dry food and water ad libitum between 6 am and 5 pm each day during the study, as well as multiple enrichment devices.

Treatment groups

The cats were randomized to one of three treatment groups (methylprednisone acetate, CsA or a placebo control) and to one of the three rooms 7 days prior to being administered the primary treatments. The food was removed from each room every evening and then placed back into the group housing areas approximately 30 mins prior to dosing CsA or placebo, as described, every morning. Group 1 cats (n = 8) were administered CsA (Neoral; Novartis Pharmaceuticals Corporation) at 7.0 mg/kg, PO, daily for 42 days; group 2 cats (n = 7) were administered a similar volume of a placebo (corn syrup; 0.075 ml/kg) for 42 days; group 3 cats (n = 8) were administered 5 mg/kg methylprednisolone acetate (Depo-Medrol; Zoetis) intramuscularly on day 0 and day 21. Corn Syrup was used as the placebo due to its visual similarity to the CsA used in the study.

Clinical and laboratory evaluations

Each cat was assigned a daily individual clinical score by a trained, masked observer using a standardized score sheet during the initial pretreatment time period (the 7 days prior to treatment) and throughout the 42 day treatment period (Table 1).[26] Prior to entering the study and on days 0 and 42, blood was collected for performance of a complete blood cell count, serum biochemical panel and FHV-1 antibody titer determination. Serum CsA concentrations were measured in group 1 cats on day 0 and in all cats on the morning of day 42, approximately 24 h after the last dose was administered to group 1. Body weights were recorded 14 days prior to treatment and then on days 0, 21, 42 and 56.

Statistical evaluation

All analyses were performed using SAS/STAT software (Version 9.1.3, SAS Institute Inc). Hematology and clinical chemistry variables were statistically evaluated using an analysis of covariance (ANCOVA; PROC MIXED) with the day 0 pretreatment value used as the covariate. Prior to performing the ANCOVA, Levene's test for homogeneity of variance was performed and, if significant ($P \leq 0.01$), the data was transformed (logarithmic, square root, reciprocal or rank) prior to analysis. The transformation that resulted in the highest overall non-significant P value from Levene's test was used to transform the variable; if the results from the Levene's test were all significant, the data was rank ordered.

The FHV-1 titer data were analyzed using ANCOVA with the day 0 value as the covariate. All data were transformed using log base 2 prior to analysis. Animal titer values were also classified by their behavior from pre- to post-measurement (increased, decreased or unchanged). The number and percentage of animals having increased, decreased or unchanged titer values by treatment group were categorized.

Each individual clinical score (conjunctivitis, blepharospasm, ocular discharge, sneezing, nasal discharge, nasal congestion and body temperature), the total clinical score (sum of all parameters), the total ocular score (sum of conjunctivitis, blepharospasm and ocular discharge) and total respiratory score (sum of sneezing, nasal

Table 1 Clinical scoring system used to monitor for clinical evidence of disease induced by feline herpesvirus 1

Clinical sign	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 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
Nasal congestion	0 = None
	1 = Minor congestion (barely audible)
	2 = Moderate congestion (easily audible)
	3 = Marked congestion with open-mouth breathing
Body temperature	0 = <102.5°F
	1 = >102.5°F

discharge and nasal congestion) were analyzed using PROC GLIMMIX with 'Treatment', 'Time' and the two-way interaction 'Treatment by Time' all as fixed effects. The day 0 pretreatment value was used as the covariate. If the 'Treatment by Time' interaction was significant ($P \leq 0.05$), then all groups were compared at each time point; if the 'Treatment by Time' interaction was not significant ($P > 0.05$), the 'Treatment' main effect was evaluated. If the 'Treatment' effect was significant ($P \leq 0.05$), all groups were compared using appropriate contrasts.

A total score, total respiratory score or total ocular score of 1 reflects very mild clinical signs of disease. Thus, to further evaluate the severity of disease in individual cats and groups of cats, a value ≥2 was defined as clinically significant. The frequencies of values ≥2 in total score, total ocular score and total respiratory score were then determined by group for the 7 days prior to treatment and then for days 1 to 7, days 8 to 14, days 15 to 21, days 22 to 28, days 29 to 35 and days 36 to 42. The number and percentage of scores ≥2 within each period were compared using Fisher's exact test.

Body weight was analyzed using a repeated measures analysis of covariance (RMANCOVA; PROC MIXED) with 'Treatment', 'Time' and the two-way interaction 'Treatment by Time' all as fixed effects. The day 0 measurement was utilized as the covariate. Four covariance structures were explored (CS, CSH, AR[1] and ARH[1]) and the results from the model with the smallest Akaike's Information Criterion were used. If the 'Treatment by Time' interaction was significant ($P \leq 0.05$), then all groups were compared at each time point; if the 'Treatment by Time' interaction was not significant ($P > 0.05$), the 'Treatment' main effect was evaluated. If the 'Treatment' effect was significant ($P \leq 0.05$), all groups were compared using appropriate contrasts.

Results

Complete blood cell counts and serum biochemical panels

In the methylprednisolone and CsA groups, lymphopenia was present in the post-treatment samples and the lymphocyte counts were significantly lower compared with the control group ($P < 0.0001$). Significant differences among groups were detected for a number of other hematology parameters and some serum biochemical test results, but the findings were within normal ranges and so were not considered to be clinically relevant.

CsA concentrations

Prior to the first CsA dose, all cats in the CsA group were negative in serum. On day 42, all of the CsA treated cats had detectable concentrations that ranged from 110 ng/ml to 1001 ng/ml (mean = 406.1; SD = 291.8; median = 388.5). CsA was not detected in the serum of the control group cats or the methylprednisolone group cats analyzed in the study.

FHV-1 titers

The CsA group mean FHV-1 titer value decreased slightly over time while the methylprednisolone group and the control group mean FHV-1 titers increased. Significant differences in titer values existed between the methylprednisolone group and the control group ($P = 0.0496$), and between the CsA and methylprednisolone groups ($P = 0.0095$), with the methylprednisolone group having the higher mean post titer value. There were no differences in titer values between the CsA group and the control group ($P = 0.5059$). Cats with increased, decreased or unchanged pre- to post-titers are summarized by group in Table 2.

Clinical parameters

All groups increased in mean body weight over time. Significant differences in body weight over time existed between the CsA group and the control group ($P = 0.0105$) and between the methylprednisolone group and the control group ($P = 0.0003$), with the

Table 2 Frequency of feline herpesvirus 1 titer change by treatment group

Treatment group	Titer change from pre- to post-measurement			Total
	Increase	No change	Decrease	
Ciclosporin (cyclosporine)	3 (37.50%)	1 (12.50%)	4 (50.00%)	8
Methylprednisolone	5 (62.50%)	3 (37.50%)	0 (0.00%)	8
Control	2 (28.57%)	2 (28.57%)	3 (42.86%)	7
Total	10	6	7	23

Feline herpesvirus 1 titers were measured on days 0 (pre) and 42 (post)

control group having a higher mean body weight at every time point. Signs of potential drug toxicity like inappetence, vomiting, diarrhea, polyphagia, polyuria or polydipsia were not observed in any of the groups.

When group mean values for clinical signs were compared over time, as described, significant differences in individual clinical score measurements in total score, total ocular score and total respiratory score were not detected over time among any of the treatment groups. Clinical signs of respiratory disease were uncommon in all three groups. Only one cat had a respiratory score >2 over the course of the study; the cat was in the CsA group and the elevated scores were detected on days 18–21, 23, 25–29, 31 and 32 (range = 3–5). This cat also had a CsA concentration of 1001 ng/ml on day 42 of the study.

Table 3 Frequency rates of total scores ⩾2, with number of cats experiencing at least one total score ⩾2, by group and by week

Days	Treatment groups			*P* values		
	CsA % of events (number of cats)	Control % of events (number of cats)	MP % of events (number of cats)	CsA vs control	CsA vs MP	Control vs MP
7 days before treatment	11.1 (2)	4.1 (2)	3.6 (2)	0.2944	0.1698	1
1–7	10.7 (3)	8.2 (2)	8.9 (3)	0.7475	1	1
8–14	5.4 (2)	10.2 (3)	25.0 (4)	0.4685	**0.0070**	0.0741
15–21	10.7 (2)	0 (0)	16.1 (3)	**0.0289**	0.5803	**0.0032**
22–28	16.1 (3)	0 (0)	17.9 (2)	**0.0032**	1	**0.0015**
29–35	10.7 (1)	0 (0)	14.3 (2)	**0.0289**	0.7761	**0.0067**
36–42	8.9 (1)	0 (0)	8.9 (2)	0.0593	1	0.0593
Overall*	10.4 (5)	3.1 (5)	15.2 (5)	**0.0003**	0.0828	<**0.0001**

Statistical comparisons made by Fisher's exact test with significance defined as $P<0.05$. Statistically significant differences are shown in bold
*Overall test run on data from days 1–42 (pretreatment data [days –6 to 0] were excluded from overall analysis)
CsA = ciclosporin (cyclosporine) A given at 7.0 mg/kg, PO, daily on days 0–42; MP = methylprednisolone at 5 mg/kg, IM, days 0 and 21; control cats were administered corn syrup, PO, daily on days 0–42

A total clinical score of >2 was detected in some cats in each group prior to treatment administration (Table 3). The frequency rates for total score events of ⩾2 (Table 3) and ocular score events of ⩾2 (Table 4) were calculated and stratified by week of the study and treatment group. A total score of ⩾2 was detected at least one time after treatment was started in the CsA group (five cats), the control group (five cats) and the methylprednisolone group (five cats). A total ocular score of ⩾2 was detected at least one time after treatment was started in the CsA group (three cats), the control group (two cats) and the methylprednisolone group (three cats). Cats in the CsA group and the methylprednisolone group had significantly more total score events ⩾2 in the treatment period than control cats (Table 3). Cats in the methylprednisolone group had significantly more ocular score events ⩾2 in the treatment period than control cats or cats in the CsA group (Table 4).

Discussion

The results of this study suggest that the stress associated with placebo administration, CsA administered PO and methylprednisolone administered intramuscularly can exacerbate FHV-1 infection in previously infected cats. Associated clinical signs of disease were mild in all three groups of cats. However, the sample sizes used per group in this study were small and only one strain of FHV-1 was used and so the data should be interpreted carefully.

While the same dose of CsA was administered to all cats and there was no evidence that the cats vomited the

Table 4 Frequency rates of ocular scores ⩾2, with number of cats experiencing at least one total ocular score ⩾2, by group and by week

Days	Treatment groups			*P* values		
	CsA % of events (number of cats)	Control % of events (number of cats)	MP % of events (number of cats)	CsA vs control	CsA vs MP	Control vs MP
7 days before treatment	0 (0)	0 (0)	0 (0)	1	1	1
1–7	1.8 (1)	0 (0)	5.4 (3)	1	0.6182	0.2462
8–14	3.6 (2)	6.1 (2)	19.6 (2)	0.6624	**0.0155**	**0.0486**
15–21	5.4 (1)	0 (0)	16.1 (3)	0.2462	0.1239	**0.0032**
22–28	8.9 (3)	0 (0)	17.9 (2)	0.0593	0.2668	**0.0015**
29–35	0 (0)	0 (0)	12.5 (2)	1	**0.0128**	**0.0140**
36–42	0 (0)	0 (0)	5.4 (2)	1	0.2432	0.2462
Overall*	3.3 (3)	1.02 (2)	12.8 (3)	0.0622	<**0.0001**	<**0.0001**

Statistical comparisons made by Fisher's exact test with significance defined as P <0.05. Statistically significant differences are shown in bold
*Overall test run on data from days 1–42 (pretreatment data [days –6 to 0] were excluded from overall analysis)
CsA = ciclosporin (cyclosporine) A given at 7.0 mg/kg, PO, daily on days 0–42; MP = methylprednisolone at 5 mg/kg, IM, days 0 and 21; control cats were administered corn syrup, PO, daily on days 0–42

CsA, concentrations varied among treated cats (mean = 406.1 ng/ml; SD = 291.8 ng/ml). This finding suggests variable bioavailability among the cats even though a consistent diet and feeding protocol was used throughout the study. The cat with a CsA concentration of 1001 ng/ml was also the cat with the most severe clinical manifestations of FHV-1 infection (highest and longest duration of ocular and respiratory scores ⩾2). The pre- and post-treatment FHV-1 titers in this cat were 1:256 and 1:512, respectively. It suggests that a greater degree of immune suppression associated with the higher CsA concentration may occur in some cats. The titer change (two-fold) is within normal variation of the assay. However, these results also could suggest activity of FHV-1 inducing an anamnestic humoral immune response.

While all of the cats in the study were administered the same strain of FHV-1 at the same time, clinical signs potentially attributable to FHV-1 infection were not distributed uniformly among the cats during the treatment period. While the methylprednisolone dose used here has been used as a positive control to activate FHV-1 in other studies,[13] clinical signs of disease in this treatment group were generally mild and four of the eight cats never reached a clinical score ⩾2 in any category post-treatment. In addition, during the first 14 days of the treatment study, some of the control cats developed clinical signs of FHV-1 associated illness which may have been related to the stress of administering the placebo. These factors may have influenced the failure to document statistical differences in mean results over time in any clinical disease category.

However, when total scores and ocular scores were grouped by frequency of events ⩾2 (Tables 3 and 4), several findings may have clinical significance. The finding of an overall increased number of total score events ⩾2 in both the CsA group and methylprednisolone group when compared with the control group suggests that both drugs were more likely to activate FHV-1 than would administration of a placebo, suggesting immune suppression, but not all cats will be affected. However, for ocular score events ⩾2, methylprednisolone but not CSA induced a significant overall effect, suggesting that immune suppression associated with methylprednisolone was more likely to induce these manifestations. The finding that none of the control cats had a total score or ocular score events ⩾2 after day 11 suggests that the cats became tolerant of the placebo administration and that the differences between groups were related to the drugs. Cats administered methylprednisolone had higher FHV-1 antibody titers than cats administered CsA or control cats. These results also suggest that methylprednisolone activated FHV-1 infection to a greater degree than was experienced in the other groups. If serious systemic illness associated with FHV-1 develops after administration of CsA or methylprednisolone, the drugs should be discontinued and appropriate therapy initiated.

The classic glucocorticoid associated side effects of polyuria, polydipsia and polyphagia, were not recognized in the methylprednisolone group. However, this may have been related to the cats being housed in groups where it is more difficult to detect changes in individual cats. While methylprednisolone is a known appetite stimulant and can induce diabetes mellitus, the control group cats gained more weight and there was no evidence of diabetes mellitus on serum biochemical tests in the methylprednisolone group. In some previous studies,

CsA has been associated with inappetence, vomiting and diarrhea in some treated cats.[14,19,20,22] However, none of these abnormalities were noted in the cats described here, which may merely reflect the small number of cats in the treatment groups. It is also possible that in other reports different CsA preparations, CsA doses or clinical factors may have had an effect on tolerability. All of the CsA group cats gained weight and had no significant changes outside normal ranges in complete blood cell findings (other than lymphopenia) or in serum biochemical tests. These results taken together show that this CsA formulation was well tolerated at this dose administered PO.

Conclusions

Clinical signs of reactivation of FHV-1 infection in these cats were mild and did not require specific therapy. These findings suggest that use of these drugs in the protocols described are unlikely to induce significant FHV-1 associated disease in previously infected cats.

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