Cats with Runny Eyes. Treatment of Feline Herpes Virus Infections

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INTRODUCTION

Feline Herpes Virus (FeHV-1) is widespread in the domestic feline population, especially in colonies and catteries. More than 95% of the world's cat population has been exposed to the virus, and more than 80% are carriers (1, 2). Cats are infected after direct or indirect contact with sick or carrier animals; the infection occurs through the oronasal and conjunctival routes. Clinical signs of active disease include conjunctivitis and keratitis with ulceration (early, superficial dendritic ulcers may stain with rose Bengal but not with fluorescein) and possible upper respiratory signs. Stromal vascularization and cellular infiltration characterize the immune response to viral particles in the cornea, either with or without active viral replication. Secondary bacterial infections, especially with *Chlamydia felis* and possibly with *Mycoplasma* spp., are frequent, and symblepharon is a common sequel. FeHV-1 may also play a role in the pathogenesis of corneal sequestration and eosinophilic keratitis (1-3).

Cats that recover from the disease probably remain persistent carriers due to latent infection in the trigeminal ganglia. The latent disease is characterized by the absence of clinical signs, but viral shedding and reactivation can occur (1, 2). Stressful events, such as an unrelated illness, the introduction of a new pet or baby into the house, travel or fighting with other animals, can serve as triggers of shedding and reactivation of latent infection. Treatment with corticosteroids can have similar consequences. The presence of a latent disease, as well as the confounding impact of an overly-aggressive immune response, presents great therapeutic challenges to the practitioner. Drug availability, irritancy and dosing frequency further complicate treatment of the disease.

PRINCIPLES OF TREATMENT

Antiviral medications are indicated in cats with active disease. The drugs are pyrimidine and purine nucleoside analogues which interfere with the viral replication cycle, by inhibiting target enzymes that incorporate nucleosides into nucleic acids. Compiling results of multiple studies (4-8), *in vitro* efficacy against FHV-1 is:

trifluridine> ganciclovir >idoxuridine>cidofovir>penciclovir>vidarabine>valacyclovir> acyclovir

Importantly, antivirals are virostatic and are only effective in treating actively replicating virus, achieving their effect by interfering with viral DNA replication. The drugs are not virucidal and therefore are unable to eradicate latent infection. Significant toxicity can occur with antiviral administration, due to the intracellular location of the virus and the inability of available medications to selectively target viral, rather than host cell, replication.

Virostatic drugs usually have to be administered frequently, and treatment is often continued for 10-14 days after remission of clinical signs. Furthermore, as the drugs are not virucidal, owners should be warned of the possibility of shedding, reactivation and recrudescent infection (9).

There are two iatrogenic factors that may induce recrudescent FeHV-1 infection. One is corticosteroid treatment. Corticosteroids are contraindicated in all cases of primary ocular FeHV-1infection, because they will exacerbate active viral infection; thus, due to corticosteroid treatment a self-limiting conjunctivitis may become a chronic corneal infection. Therefore, any corticosteroid treatment in cats must be carefully considered, as most cats should be suspected of being potential FeHV-1 carriers. When such treatment is

unavoidable (e.g. in cases of eosinophilic keratitis) it should probably be combined with concurrent anti-viral therapy. In this context it is important to note that because the FeHV-1 may be reactivated due to immunosuppression, the prognosis for the diseases is poor in immunosuppressed patients (i.e. FeLV- or FIV-infected) because the recurrence rate can be high (1-3).

Another factor which may induce viral shedding and reactivation is stress, and events such as the introduction of a new animal to the household or traveling to cat shows may exacerbate the symptoms. Similarly, frequent treatment with multiple drugs may sometimes aggravate the clinical signs of the disease. If worsening of signs is noted, the clinician is advised to carefully consider reducing (or even ceasing) treatment rather than increasing it.

Topical antiviral medications

Trifluridine 1% (Viroptic®), idoxuridine 0.1% (Stoxil®) and vidarabine 3% (Vira-A®) are variably effective against FeHV-1, with trifluridine having the highest efficacy as well as transcorneal penetration (4-6). However, trifluridine also tends to be more irritating to cats, and in fact sometimes induces hyperemia of the eyelids and conjunctiva that may mimic worsening of the disease. In such cases, other drugs should be considered. Furthermore, the drug requires frequent administration (5-6 times/day), which can increase stress and decrease compliance (6, 10). Idoxuridine and vidarabine are less irritating and are administered less frequently, but are difficult to obtain because they are not widely available commercially, although they may be ordered from compounding pharmacies (9).

Newer recommendations for topical antiviral administration in cats include cidofovir 0.5% (7, 11, 12). Cidofovir, which is not commercially available as an ophthalmic preparation, has strong *in vitro* and *in vivo* efficacy against FeHV-1 infection, with treatment reducing severity of clinical signs and viral shedding. Importantly, cidofovir's beneficial effect has been demonstrated with twice daily administration, a significant advantage compared to other topical antiviral medications. Cidofovir is less toxic than other antivirals due to its relatively high specificity for viral, rather than host, replication proteins. However long-term safety studies have yet to be published; indeed, cidofovir has been associated with a dose-dependent nephrotoxicity in humans and cat owners should be warned to protect themselves from exposure to cidofovir solutions. Ganciclovir (Zirgan®) is commercially available as a 0.15% ophthalmic gel and has *in vitro* efficacy against FeHV-1, but has not been studied in clinical feline patients and may be toxic (5, 8). Even if found effective and non-toxic, it is not likely to be of any value in treating FeHV-1 in cats due to its high cost.

Antiviral therapy with acyclovir (Zovirax®) or valacyclovir, a prodrug of acyclovir, is the drug of choice for treating ophthalmic herpes disease in humans, but neither drug appears to suppress FeHV-1 replication. In fact, both drugs are contraindicated in cats as acyclovir is myelosuppressive in this species, and valacyclovir is extremely toxic and often fatal to cats (13-15).

Oral antiviral medications

Famciclovir, a prodrug of penciclovir, is a very safe and effective oral drug for the treatment of FeHV-1 (16-22). Due to complex pharmacokinetics of famciclovir and penciclovir in cats, and the variable target penciclovir concentrations needed to produce a clinical effect, the accurate oral dose is currently not definitively known. In clinical studies, oral administration of 90 mg/kg famciclovir three times daily for 3 weeks to cats with experimentally-induced FeHV-1 disease improved outcomes for systemic, ophthalmic, clinicopathologic, virologic, and histologic variables and reduced viral shedding. In naturally-infected cats, 62.5 mg orally once daily for 7 days then twice daily was reported to result in clinical improvement. However, a single dose of 125 mg or 500 mg famciclovir, administered at the time of admission to a shelter, did not lessen clinical signs or viral shedding in cats, even in the presence of appropriate plasma penciclovir levels (16-22).

Additional therapies

It has been suggested that recurrent infection may be minimized by oral lysine supplementation (23-25). It is hypothesized that lysine can be helpful in the treatment of FeHV-1 infection because viral growth appears to be inhibited by high intracellular concentrations of lysine and low levels of arginine. Thus, long-term treatment (250-500 mg PO twice daily) may decrease shedding, viral replication, and severity of conjunctivitis, and may be used for long-term maintenance therapy. However, results of clinical investigations are equivocal, perhaps due to the high levels of dietary arginine in cats. The efficacy of lysine to prevent herpes simplex in humans

is associated with severely arginine-restricted diets. This is not possible with obligate carnivore patients, and the higher arginine content of feline diets may continue to hinder the success of lysine prophylaxis of FeHV-1 (23-26).

Interferons are components of the innate immune system that induce expression of antiviral proteins within host cells, thus creating an antiviral environment, and also exert immunomodulatory effects that further limit the impact of viral infections (26-30). Recombinant human IFN-α and feline IFN-ω have been evaluated relative to anti-FeHV-1 effect, with the feline version demonstrating greater *in vitro* efficacy. The drug can be given as low oral doses (25 units/day) or eye drops (10^3 to 10^6 units/ml) applied 2 to 3 times daily, and has decreased the severity of clinical signs in experimentally-infected cats. However, results of clinical field studies have been disappointing, possibly due to the timing of administration relative to infection and shedding, as well as uncertainty surrounding appropriate dosing protocols and handling of IFN preparations (27-31).

Supportive therapy may include tear replacements, topical antibiotics and debridement of necrotic corneal epithelium with a cotton-tipped swab to remove viral particles.Topical tetracycline is frequently added because coinfections with *Mycoplasma* spp. or *Chlamydia felis* are common. Eyes that are irritated by topical tetracycline may be treated with ciprofloxacin. In cases of respiratory diseases, oral azithromycine or doxycycline should be considered (2, 9).

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