DIAGNOSIS AND TREATMENT OF OCULAR DISEASES IN THE HORSE

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BACTERIAL KERATITIS
Simple, uninfected cases of corneal ulceration can be treated with prophylactic antibiotics, mydriatics and systemic antiinflammatory agents. However, aggressive medical therapy is indicated in all cases of confirmed or suspected bacterial keratitis. This includes topical and systemic antimicrobial drugs, mydriatics and antiproteases, and systemic non-steroidal anti-inflammatory drugs (NSAIDs).

Topical antibiotics
The choice of topical antimicrobial should ideally be made based on Gram stain and culture. For Gram-positive isolates, drugs such as moxifloxacin, chloramphenicol, neomycin and bacitracin can be used. For Gram-negative isolates, ciprofloxacin, ofloxacin, aminoglycosides, neomycin, polymyxin B and chloramphenicol can be used. Chloramphenicol should not have any expected efficacy against Pseudomonas sp.

Topical administration of moxifloxacin resulted in better penetration through healthy equine corneas and reached higher measurable AH concentrations than ciprofloxacin, suggesting moxifloxacin might be of greater value in the treatment of deep corneal or intraocular bacterial infections caused by susceptible organisms.

Systemic antibiotics
Following systemic administration of an antibiotic, drug concentrations in the aqueous humor are often much lower than plasma concentrations. The difference between aqueous humor and plasma drug concentrations can be explained by the blood-aqueous barrier (BAB). The BAB consists of both an epithelial and endothelial portion. This includes tight junctions present at the apico-lateral surface of the non-pigmented epithelium in the ciliary body as well as nonfenestrated capillaries within the iris vasculature. Evidence also exists supporting the presence of p-glycoprotein efflux pumps as a component of the BAB, just as is found in the blood-brain barrier, which may contribute to decreased drug penetration into the aqueous humor.

Several physicochemical characteristics of drugs have been correlated with the rate of drug penetration into the eye. These include lipophilicity, protein binding and molecular weight. The drugs that penetrate the BAB most readily are low molecular weight, lipophilic, protein unbound drugs. In the horse, based on a limited number of studies, lipophilicity appears to be the biggest determinant of drug penetration into the eye. The presence of corneal neovascularization may enhance penetration of drug at the site of infection.

Drugs that have been documented to penetrate into the aqueous humor in normal horse eyes include doxycycline, chloramphenicol and enrofloxacin. Doxycycline was also present in the pre-ocular tear film. Trimethoprim-sulfa combinations are also frequently used in horses due to their ease of use and cost.

Mydriatics
Mydriasis is essential for treatment of painful eyes and to decrease the incidence of posterior synechia and secondary glaucoma. These drugs also induce cycloplegia, which aids in the
control of pain. Tropicamide and atropine are both able to induce mydriasis in the horse, however, atropine (1%) lasts longer and this makes it the treatment of choice for ocular disease. An association with topical atropine use and the development of gastrointestinal ileus in horses has been demonstrated with frequent administration. Dosing should therefore not exceed every 6 hours, and should be tapered as quickly as possible as the corneal disease improves. If no response to topical atropine is seen, topical 10% phenylephrine HCl can be added. Phenylephrine is not a very effective mydriatic by itself in horses, however it can increase the efficacy of atropine when given in combination.

Topical antiproteases
Protease activity is upregulated in cases of infectious keratitis and may lead to corneal destruction and 'melting'. Drugs used as antiproteases include topical EDTA, N-acetylcysteine (N-AC), and ilomostat (synthetic), as well as topical and systemic tetracyclines. These drugs inhibit matrix metalloproteinases (MMPs) by chelating zinc and calcium. Autologous serum has also used as an antiprotease. It contains α₂-macroglobulins and α₁-antitrypsin which inhibit serine proteases as well as MMPs. Tetanus antitoxin has also been used as an anticollagenase. Of these drugs, autologous serum, EDTA, N-AC and tetracyclines have the most clinical application.

NSAIDs
Oral or parenteral NSAIDs can be used for additional analgesia and anti-inflammatory purposes. There are currently no studies evaluating the relative efficacy of NSAIDs for ocular analgesia. One study did demonstrate that firocoxib reached higher concentrations in the aqueous humor when compared to flunixin meglumine in non-inflamed horse eyes. Due to the long period of administration usually necessary for treatment, the horse's appetite and attitude, as well as fecal production and consistency should be closely monitored during treatment. If treatment is to be extended beyond 2 weeks, bloodwork, including creatinine and albumin, should be monitored. Steroids should be avoided in these cases, either topical or systemic, because they decrease wound healing and predispose to infection (ie fungal infection).

Fungal keratitis
The principles for treating fungal keratitis are similar to those for bacterial keratitis (antibiotics, mydriatics, antiproteases and NSAIDs), with the addition of topical and/or systemic antifungal drugs. Based on a recent study, the topical antifungals with the most activity against equine fungal keratitis isolates are voriconazole, natamycin and miconazole.

Voriconazole is the newest triazole antifungal. It has improved activity against Aspergillus and Fusarium spp. compared with other triazoles and an excellent safety profile in people. The drug penetrates well into the aqueous humor after topical administration of the IV formulation (1%), even in the presence of an intact corneal epithelium. Higher concentrations (up to 3%) did not result in higher concentrations of drug in the aqueous humor, and in fact caused noticeable conjunctival irritation. The IV formulation is stable for up to 30 days after reconstitution when kept in an airtight container and refrigerated.

Natamycin is a polyene antifungal with a mechanism of action similar to amphotericin B. It is approved for use in humans as a 5% ophthalmic suspension. Its systemic use is prohibited by expense, as well as toxicity. Natamycin has excellent activity against yeasts and filamentous fungi, and it is considered the treatment of choice for Fusarium keratomycosis in the horse. It is
unlikely to penetrate an intact corneal epithelium, therefore it is best used only in ulcerative diseases. Combination therapy with tobramycin, cefazolin, and equine serum results in lower MICs for natamycin than when natamycin is used alone.

Miconazole is an imidazole antifungal found to be effective against some fungi refractive to amphotericin B. Rapid clearance and poor oral absorption necessitate frequent IV infusions during hospitalization. In addition, the solubilizing agent in the parenteral form induces histamine-related toxic side effects, making its use hazardous. The intravenous formulation is no longer marketed in the United States. In veterinary medicine, miconazole is used as a 1% solution for topical treatment of keratomycosis.

Systemic antifungals can be used, however cost becomes an issue during treatment. Theazole antifungals have been studied for penetration into the eye, including fluconazole, itraconazole and voriconazole. Fluconazole has excellent penetration into the aqueous humor, a good safety profile, and it is affordable. Dosing recommendations are a loading dose of 14 mg/kg, followed by 5 mg/kg PO q24h. Unfortunately, activity of fluconazole against Aspergillus and Fusarium sp. is limited, therefore it may not be effective in equine keratomycosis. Itraconazole solution has good bioavailability and good activity against Aspergillus sp, however it is often cost prohibitive. Oral administration does not result in measurable concentrations in the aqueous humor, however it should result in adequate corneal tissue concentrations. Pharmacokinetic data on voriconazole in the horse shows excellent bioavailability and a long elimination half-life. It also has the greatest activity against Aspergillus and Fusarium sp, and excellent penetration into the aqueous humor in normal horses. Doses of 4 mg/kg PO q24h are recommended, however the drug is currently cost prohibitive in most cases.

In cases that do not respond to typical therapy, amphotericin B (0.2 mL of a 5 mg/mL solution) injected subconjuntivally q48h for up to 3 treatments can be used. This should provide a higher level of drug to the eye, however it may produce localized toxic effects, including conjunctivitis and conjunctival necrosis.

Viral keratitis
Herpesvirus keratitis is associated with corneal infection with EHV-2 infection and causes ocular pain with multifocal punctate corneal ulceration or erosion. It can sometimes be confused with early fungal keratitis, therefore prompt recognition and treatment is important. Specific efficacy of antiviral drugs against EHV-2 strains has not been demonstrated. However, trifluridine (1%) and idoxuridine (0.5%) have been used with some clinical success. In other species, these drugs are virostatic and not expected to have an effect on latent viral particles. Oral L-lysine has some anecdotal efficacy in decreasing clinical signs at doses of 10-30gm PO q24h. At this time, there are no reports of the use of other systemic antivirals for this disease. Adjunct therapy includes topical antibiotics if ulceration is present, as well as systemic NSAIDs and mydriatics. Corticosteroids should be avoided.

ANTERIOR UVEITIS
The two main goals of therapy for treating anterior uveitis are to relieve ocular pain and to control inflammation. Ocular pain is controlled with the application of topical mydriatics as previously described. Control of inflammation can be achieved with topical or systemic steroids, NSAIDs and Cyclosporine A. The use of antibiotics is often performed, but remains controversial.
**Topical Antiinflammatory Agents**

Topical prednisolone acetate (1%) or dexamethasone HCl (0.1%) can be used. Both drugs have good ocular penetration. Dexamethasone is available in an inexpensive ointment formulation. Topical corticosteroids may potentiate infection, collagenase enzymes, and calcific band keratopathy as well as delay healing of corneal ulcers.

Topical NSAIDs are also available and can be used without the concern for potentiating infections, however they can results in decreased corneal epithelialization. Formulations available include flurbiprofen (0.03%), diclofenac sodium (0.1%) and bromfenac sodium (0.09%). Bromfenac is considered the most potent of these topical NSAIDs, however NSAIDs on the whole are much less effective than topical corticosteroids.

**Systemic antiinflammatory agents**

Systemic NSAIDs are usually adequate for controlling inflammation in the eye. Flunixin meglumine appears to be much more effective than either phenylbutazone or aspirin for ocular inflammation. Experience with firocoxib is limited at this time. Systemic steroids are not indicated unless horses do not respond to NSAIDs. Choices for systemic steroids include dexamethasone and prednisolone. In severe cases, subconjunctival injection of triamcinolone (0.2 mL of a 10 mg/mL solution) can be given. This will deliver drug to the eye for 7-10 days, however caution should be used, since the chronic presence of steroids in the eye may increase the risk of infection or delayed corneal healing.

**Cyclosporine A**

Cyclosporine A (CsA) blocks the transcription of IL-2 and the responsiveness of the T cell, therefore it may be the ideal drug to prevent the activation of T lymphocytes and recurrence of uveitis. Unfortunately, CsA does not penetrate an intact cornea, and systemic administration is costly and carries a risk of renal, hepatic and neurologic toxicity. Therefore, alternative forms of the drug must be used. The most successful of these is the suprachoroidal CsA implant that can deliver drug for months to years. It is very important that the implant be placed during a time when the eye is quiescent. Additionally, it takes weeks-months for therapeutic concentrations to be achieved in the eye. If an episode of uveitis occurs prior to this, traditional treatments should be implemented.

**Antibiotics**

The use of antibiotics in cases of recurrent uveitis is based on the association of the development of the disease and ocular infection with *Leptospira* sp. Anecdotal reports are available of beneficial effects using doxycycline (10 mg/kg PO q12h for 4 weeks) or enrofloxacin (7.5 mg/kg PO q24h for 4 weeks).

**GLAUCOMA**

Primary glaucoma is rare in the horse compared to other species, therefore most cases are secondary to ocular inflammation or trauma. The principles of therapy remain the same between species, however: reduction of IOP and suppression of iridocyclitis. Suppression of iridocyclitis can be achieved with topical steroids and systemic NSAIDs, as described previously.
β-adrenergic blockers
β-blockers can be administered to reduce the production of aqueous humor via the inhibition of cAMP. Timolol maleate (0.5%) has been shown to decrease intraocular pressure (IOP) in normal horse eyes and decrease pupil size, with no other adverse effects.

Carbonic anhydrase inhibitors
These drugs work on the carbonic anhydrase enzyme found in the ciliary body and inhibition can result in a decrease of aqueous humor production up to 99%. Dorzolamide (2%) and brinzolamide (1%) have both been used in horses, with or without topical timolol maleate. Systemic carbonic anhydrase inhibitors can also be used. The only one commonly used in horses is acetazolamide. Its efficacy in horses with glaucoma has not been demonstrated, however.

Parasympathomimetic drugs
Drugs such as pilocarpine and demecarium bromide act as parasympathomimetic drugs, resulting in a constriction of the ciliary muscles which opens the trabecular meshworks. These drugs also inhibit unconventional outflow. Their use in dogs is effective at decreasing IOP and preventing the development of glaucoma in the non-affected eye. In normal horse eyes, however, they resulted in an increase in IOP, and therefore their use in horses with glaucoma is not currently recommended.