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A NOTE ON OPHTHALMIC ANTIMICROBIAL AGENTS OF VETERINARY IMPORTANCE

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ABSTRACT

Most of the drugs that are used for other organs or systems, are routinely used orally or parenterally for ocular disease conditions. Response to the treatment of ophthalmological infections varies depending on the medicine usage. The present note briefs about proper selection of antimicrobial agent and usage for the treatment of ophthalmic disorders in pets.

KEYWORDS: ophthalmic, antimicrobial agent.

INTRODUCTION[1,2]

Before the start of therapy, due consideration should be given for the presence of the blood–ocular barrier and vascular supply of the eye.

1. The presence of blood–ocular barrier makes drug penetration complex process, protective mechanisms that complicate drug delivery to the interior of the uninflamed eye. In corneal and conjunctival diseases, where the epithelium is compromised or removed, resistance to drug absorption/corneal penetration is reduced or eliminated.

2. Vascular supply of the eye: The eye is a complex organ with an intricate vascular supply to nourish highly specialized neuroreceptors and unique tissues that must remain transparent to focus light on the photo receptors deep within the organ, and a system for secretion, circulation and absorption of a fluid to nourish and maintain intraocular pressure compatible with the primary function of vision.[1]

Topical drug therapy

Topical application of medication can have the advantage of establishing high local drug levels, with reduced systemic side effects / toxicity. In general, ointments or suspensions can increase bioavailability by increasing corneal contact time.

A. Eye drops

1. Delivery volume should not exceed 50 µL. 20 µL is ideal for small animals.
2. Repeat or continuous dosing increases the pharmacologic effect. Frequent dosing can be facilitated with subpalpebral lavage or reverse nasolacrimal lavage, especially in horses.
3. A 5-minute interval between drops reduces irritation and is consistent with the average washout period of 3–6 minutes.
4. Punctual occlusion prolongs clearance time from tears and reduces systemic side effects.

B. Ointments

Ointments achieve prolonged contact time due to delayed melting, dilution, breakdown and punctual occlusion.

C. Suspensions

Have no advantages; only result from poorly soluble drugs.

D. Inactive ingredients

1. They are added to adjust pH, prevent oxidation and increase the absorption. Increased lipid solubility results from pH buffering with acetic acid, boric acid, hydrochloric acid or bicarbonate, phosphates, citrates, or borates.
2. Controlling the pH (7.2–7.4) and tonicity (0.9%) of the preparation to match the tears increases the comfort of the patient.
3. Methyl, hydroxyl and hydoxypropyl methylcellulose, polyvinyl alcohol, polyvinylpyrrolidone, dextran 70, polysorbate 80 and PEG 400 are viscous substances used as tear substitutes as well as drug delivery vehicles to increase corneal contact time.

The uniqueness of ocular pharmacology is in the vehicle or formulation appropriate for delivery of these drugs for absorption and distribution to the targeted tissues or compartments of the eye at a sufficiently high concentration without creating toxic or physical damage to other ocular tissues. In many analyses, the effects of the drug (change in pupil size, lowered intraocular pressure, change in corneal thickness, changes in optical transparency, or

electrophysiologic or imaging recordings) are the basis for determining absorption, distribution and metabolism. Drug concentrations in tissues or compartments of the eye cannot be done without disturbing and impairing the "system." Intraocular inflammation accompanying infections reduces or eliminates blood–ocular barriers to drug penetration, so choices of antibiotics are similar to selection of antimicrobials for treatment of soft tissue infections. Ophthalmic antibiotics are used to treat ocular infections including blepharitis, conjunctivitis, keratitis and several others. Many are available as combination products with other antibiotics or corticosteroids.

General considerations

a. Topical preparations are intended for ocular surface infections or prophylaxis, but there are a limited number of commercially available preparations. Alternative to topical formulations may be prepared with injectable antibiotic solutions if indicated.

b. Systemically administered antibiotics are generally ineffective in treating corneal and conjunctival infections.

c. Culture and sensitivity testing are advised but, selection of an antibiotic for initial treatment is often an empirical decision or based on cytology.

d. Concern for penetration of the corneal epithelium (to the stroma or intraocularly) is not relevant in ulcerative keratitis as the epithelial barrier has been lost. For a stromal abscess in the deep cornea, where the surface epithelium is intact, penetration is a concern. Intraocular inflammation breaks down blood–ocular barriers so transport of systemically administered antibiotics to intraocular structures is usually not an issue.

e. Topical antibiotics should be administered frequently as the preparation will not remain on the ocular surface more than a few minutes. Dilution and washout in the tears may be overcome with fortified solutions created with injectable solutions added to proprietary preparations or to methylcellulose (artificial tears) especially for horses. Increased frequency of medication may be preferable as high concentrations may be toxic to regenerating epithelium.

f. Topical antibiotics are combined, that is neomycin, polymyxin and gramicidin, to increase the spectrum of activity of the preparation. Synergy is sometimes achieved such as with an aminoglycoside and a cephalosporin.

g. Bactericidal and bacteriostatic antibiotics should not be used concurrently.

h. Adverse effects vary among the different topical antibiotic preparations, but all have the potential to cause irritation, leading to tearing, blepharospasm, conjunctival hyperemia, or chemosis. Tonicity, pH and preservatives, or the drug itself may be the cause.[1, 2]

Antibiotics[3,4]

a. Penicillins: These antibiotics are rarely used topically in veterinary medicine. Preparations for intramammary infusion in bovine mastitis are often used topically for infectious keratitis (pink eye) and subconjunctival injections of systemic injectables may be efficacious for bovine or equine infectious keratitis agents. Any of the natural or synthetic injectable penicillin preparations may be compounded for topical use or administered subconjunctivally. They include natural penicillins G, V and K; penicillinase-resistant oxacillin, cloxacillin, dicloxacillin, nafcillin; and the aminopenicillins and carboxycillins including ampicillin, amoxicillin, carbenicillin, piperacillin and ticarcillin.

b. Cephalosporins: There are no topical ophthalmic preparations available. Agents for systemic use are compounded for topical treatment of infected corneal ulcers. First-generation drugs: cefazolin, cefadroxyl, cephalexin and cephalothin are active against most Gram-positive organisms. Second-generation and third generation drugs in this category are rarely used in ophthalmic preparations except when sensitivity testing dictates. Compounded fortified cephazolin solution for infected corneal ulcers in horses is commonly used in combination with fortified amikacin.

c. Aminoglycosides: Aminoglycosides are commonly used drugs in the veterinary ophthalmology. These are generally bactericidal against a wide range of Gram (+) and Gram (-) bacteria.

Neomycin, gentamicin and tobramycin are widely available as topical solutions and ointments. Neomycin is commonly combined with bacitracin or gramicidin and polymyxin B (referred as “triple antibiotic”) to increase the spectrum of activity. Topically these drugs do not penetrate the intact cornea. Amikacin is compounded and used to complement cephazolin for treatment of infected equine corneal ulcers.

(1) Subconjunctival injections of gentamicin and tobramycin readily enter the corneal stroma and aqueous humor, and pass through the sclera into vitreous of inflamed eyes.

(2) The low pH of gentamicin parenteral solution is locally irritating and may be painful. Neomycin and kanamycin do not penetrate eye from the subconjunctival injection site.
(3) Parenteral (or oral) administration results in low concentrations in the anterior segment.
(4) Except for neomycin, aminoglycosides should be reserved for use in established infections. Allergic and hypersensitivity reactions are more common in this group, especially to neomycin.
(5) All aminoglycosides are toxic to intraocular structures. Amikacin is safer for intravitreal injections than gentamicin.

d. Tetracyclines: Tetracyclines are bacteriostatic, but have a wide range of activity, including both Gram (+) and (-) including Moraxella, Chlamydophila and Mycoplasma.

(1) Topical proprietary preparations are either ointments or suspensions of topical tetracycline or oxytetracycline combined with polymyxin B. Topical tetracycline can be a drug of choice for feline conjunctivitis. Oxytetracycline can be used subconj or IM for pink eye infections in cattle.

(2) Doxycycline and minocycline are lipophilic and penetrate the eye well when given systemically to dogs for rickettsia and cats for chlamydial infections, but do not penetrate aqueous or vitreous of horse to be sufficiently effective against Leptospira. Oral doxycycline may be superior to topical tetracycline for clearing chronic Chlamydial conjunctivitis in cats, as well as clearing internal foci of infection. It is also a drug of choice for treating tick-borne disease.

(3) Oral doxycycline is more beneficial for chlamydial infections in cats than topical preparations. Subconjunctival oxytetracycline gives therapeutic concentrations in tears for treatment of Moraxella, but not when administered IM.

(4) Adverse effects: Oxytetracycline is painful when given subconjunctivally and causes chemosis and hyperemia.

e. Polypeptides: Polymyxin B, bacitracin and ointments are used. Vancomycin is rarely indicated parenterally, but is the drug of choice for intravitreal injection for Gram-positive bacteria. There are no topical forms. Polypeptides do not penetrate the intact cornea or conjunctiva.

f. Fluoroquinolones: are increasingly popular in veterinary ophthalmology. They are bactericidal for a wide range of Gram (+) and (-) bacteria, including good activity against Pseudomonas, Mycoplasma and Chlamydophila. Fluoroquinolones inhibit bacterial DNA gyrase (topoisomerase II) and topoisomerase IV. DNA gyrase is an essential enzyme involved in the replication, transcription and repair of bacterial DNA. Topoisomerase IV is an enzyme known to play a key role in the partitioning of the chromosomal DNA during bacterial cell division A variety of topical preparations are available; ciprofloxacin, Norfloxacin, ofloxacin, Levofloxacin, gatifloxacin and moxifloxacin. They also have the advantage of excellent corneal penetration, even in intact corneas and having low tissue toxicity. Systemic use also reaches therapeutic intraocular levels. Because of the fear of inducing drug resistance, their use should be limited to treating established infections. Systemic use, especially with enrofloxacin, can cause retinal degeneration in cats. Systemic daily dose for cats should not exceed 5 mg/kg/day.[3]

Norfloxacin and ofloxacin solutions and ciprofloxacin solution and ointment are the common topical preparations. They are well tolerated and not toxic topically. Ofloxacin and norfloxacin penetrate the intact cornea readily; ciprofloxacin does poorly. Levofloxacin, pefloxacin, marbofloxacin and enrofloxacin parenterally penetrate to therapeutic levels in aqueous and vitreous humor in the dog and cat; however, they may cause retinal degeneration in cats even at recommended doses. Toxicity is dose-related and aged cats are more susceptible.

g. Chloramphenicol: Chloramphenicol has fallen from favor because of fear of creating aplastic anemia, but, although it is only bacteriostatic, may still be a good alternative in cases of feline conjunctivitis because of its activity against Mycoplasma and Chlamydophilia, as well as a range of Gram (+) and (-) bacteria. It may also be useful in corneal ulcers infected with Staph or Strep *spp.*

Readily diffuses through the cornea into anterior chamber, especially if ointment form is used. Through systemic administration, it crosses the blood–ocular barriers and enters the aqueous at the same rate that it enters the cerebrospinal fluid. Topical dosing in the cat leads to systemic absorption.

Chloramphenicol is antagonistic to erythromycin.

h. Lincosamides and macrolides: Erythromycin ointment is the only topical preparation in this class. Clindamycin orally is the drug of choice for toxoplasmosis endophthalmitis at a dose of 25 mg/kg for 2-6 weeks.

Many cases of feline anterior uveitis with increasing *Toxoplasma gondii* titers, as shown by serology and anterior chamber centesis, remain undiagnosed. Chorioretinitis is often the most common presentation. Treatment is clindamycin at 8–17 mg/kg, PO, tid, or 10–12.5 mg/kg, PO, bid for 3–4 wk, in association with topical corticosteroids (0.5%–1% prednisolone acetate or 0.01% dexamethasone alcohol tid-qid) and topical atropine for mydriasis.[1] Clindamycin finds it main use in ophthalmology for treatment of toxoplasmosis.

Azithromycin orally is used for Borrelia and Bartonella infections.

Erythromycin is used topically for use in Mycoplasma and Chlamydophila infections in cats, and can be a good choice for corneal ulcers associated with Gram (+) infections. Azithromycin binds to the 50S ribosomal subunit of susceptible microorganisms and interferes with microbial protein synthesis.

i. Sulfonamides. inhibits bacterial dihydrofolate synthetase, an enzyme responsible for the conversion of p-aminobenzoic acid (PABA) into folic acid. Folic acid is essential for bacteria for the transport of one-carbon fragments from one molecule to another and is crucial during the synthesis of thymidine, purines and certain amino acids. Sulfacetamide and sulfisoxazole topicals are rarely used in veterinary medicine. Trimethoprim-sulfadiazine orally penetrates the aqueous and vitreous humor readily. Systemic sulfonamides may be toxic to the lacrimal gland leading to keratoconjunctivitis sicca.

ANTIVIRALS

These are predominantly used for feline herpes virus (FHV) infections (and equine to some degree). Medications are virustatic, requiring frequent application and do not resolve latent infections. Idoxuridine and trifluridine are pyrimidine nucleoside analogues with good FHV activity. Trifluridine is the only topical antiviral commercially available, but may be less well tolerated than Idoxuridine. Purine analogues include vidarabine, which may be less effective clinically. Acyclovir and its prodrug, valacyclovir, are systemic preparations that also may be less effective for FHV and are not well tolerated by cats. Valacyclovir can be particularly toxic. Ganciclovir, cidovir and famciclovir are becoming more popular because they have

better activity with less toxicity. Famciclovir is used at doses starting at 31 mg/kg b.i.d. for 10-21 days, although higher doses also seem to be well tolerated.[5]

1. Pyrimidine nucleoside analogs

a. Idoxuridine (2.5% ointment, 0.1% solution compounded) and triflurothymidine (1% solution) for topical use.

They are used for the treatment of feline herpesvirus-1 conjunctivitis and keratitis and punctate keratitis in horses due to equine herpesvirus-2. Trifluorothymidine is the drug of choice. However, latent infections are resistant. Adverse effects: Local irritation and hypersensitivity are occasional problems especially in cats. Trifluorothymidine is the least toxic of nucleic acid analogs.

2. Purine nucleoside analogs

Adenine arabinoside (or vidarabine 3% ointment, 1% suspension compounded) for topical use. This is used to treat feline herpesvirus-1 conjunctivitis and keratitis and punctate keratitis in horses due to equine herpesvirus-2. Adverse effects: Local irritation and hypersensitivity are occasional problems for cats.

3. Acyclovir: is a guanidine derivative. It is not available commercially as a topical preparation.

Therapeutically used as antiherpetic treatment for cats with chronic conjunctivokeratitis.
Used topically, as oral administration does not achieve plasma concentrations sufficient to inhibit FHV-1.

Adverse effects: renal, liver and bone marrow toxicity potential at therapeutic levels. It is reserved for severe, unresponsive cases. Gangciclovir, cidofovir and penciclovir are new compounds. Gangciclovir is related to acyclovir, cidofovir is cytotoxic and less potent.[7]

4. Povidone iodine: 1:20 dilution of disinfectant in artificial tear solution is administered one drop twice daily on the eye.

5. Interferons (IFNs)

Available as human recombinant IFN-α and feline recombinant IFN-ω´. These are cytokines component of natural defense mechanism. They stimulate cell-mediated lysis of virus-infected cells. Interferons are synergistic with acyclovir.

These are used for the treatment of FHV-1 conjunctivitis and keratitis. Topical administration is effective only for active infection that is in the conjunctival and corneal epithelium. Combinations of IFN and topical antiviral drugs are synergistic. Parenteral administration prior to exposure does not prevent infection but the symptoms are less severe. Oral dosing within 48 hours postexposure diminishes the severity of the clinical disease. It is less effective for established infections and has no effect on latent infection or the carrier state. It is used topically, one drop, 30 IU/mL (diluted in artificial tear solution) and orally, 30 IU/day.

6. L-lysine

Available as tablet or powder form, over the counter preparation; commercially in flavored vehicle. L-lysine interferes with viral replication. It prevents or suppresses feline herpesvirus-1 conjunctivitis and keratitis. It is given orally, 500 mg in food twice daily. Adverse effects: None reported at recommended doses.

ANTIFUNGALS[5-7]

Fungal keratitis is common in horses, but rare in small animal practice, where antifungals may be more important when dealing with dermatophyte infection or systemic mycoses. Polyenes include amphotericin B and natamycin (Natacin). Amphotericin is limited by poor corneal penetration, irritation with topical use and poor spectrum against filamentous fungi.[4]

Natamycin is the only commercial antifungal preparation available and has a much better spectrum especially for Fusarium spp. Imidazoles (miconazole 1%, ketoconazole 1% and econazole 2%) and triazoles (fluconazole 0.2% and itraconazole) tend to be well tolerated topically and have good spectrum against common fungi, although they tend not to penetrate intact cornea well. Itraconazole may be most useful in treating systemic mycosis but has gained popularity with general practitioners as a 1% ointment with 30% DMSO to treat keratomycosis in horses.

Keratomycoses are most common in horses, especially in warmer climates and dogs and cats less frequently. Deep puncture wounds in the cornea may lead to stromal abscesses beneath an intact surface epithelium. Intraocular infection with systemic mycotic organisms occurs mostly in dogs.

Polyenes, azoles, 5-fluorocytosine, and iodides used for therapy.

a. Povidone iodine and tincture of iodine

Povidone iodine is an iodine antiseptic and is effective at 1:10– 1:20 dilution in saline or ocular irrigation solution. It is more effective in an electrolyte solution. Betadine is effective for mycotic and bacterial infection in stromal ulcers, but not for deep stromal abscesses as it does not penetrate intact epithelium. Tincture of iodine is absorbed into the corneal stroma better than betadine. Each is antibacterial and antifungal at the same dilutions. As a presurgical disinfectant for the conjunctiva and cornea, betadine is used at 1:50 dilution to minimize chemosis. Repeat topical betadine application every 2–3 hours for 24–48 hours. Tincture (2 or 7%) is used only once at the time of initial debridement.

Adverse effects: Betadine causes a local irritation, and chemosis in some individuals. Tincture of iodine is very irritating and should be preceded with a topical anesthetic.

b. Silver sulfadiazine: This is a broad spectrum antibacterial and antifungal dermatologic cream that is compatible with the cornea and conjunctiva. It is used for topical application for equine keratomycosis.

c. Azoles (Imidazoles)

Available as Itraconazole, miconazole, clotrimazole, ketoconazole, and fluconazole.

These drugs inhibit mitochondrial oxidative enzymes resulting in cell death. Damage to the cell wall by interaction with phospholipids leads to increased permeability. Imidazoles have a broad spectrum of activity against filamentous and dimorphic fungi and yeasts. Intraocular infections by systemic fungi are treated with oral or IV preparations; itraconazole is preferred. Keratomycoses are treated using IV preparations topically. Oral forms of miconazole and itraconazole are compounded as ointments for topical use. Itraconazole and fluconazole systemically are effective against filamentous organisms infecting the deep cornea.[6]

Clotrimazole and miconazole vaginal and dermatologic creams have been used topically on the eye, but the alcohols in these preparations are harmful to the corneal epithelium and should not be used on the eye. These can be mixed to a 1% ointment in 30% dimethyl sulfoxide (DMSO) for topical use for superior penetration deep into the cornea. Fluconazole solution can be given subconjunctivally. Topical treatment of keratomycosis requires hourly or every other hour application for 2–3 days then tapering to four times a day for at least 4–6 weeks.

Adverse effects: Except for vaginal and dermatologic creams, oral and injectable preparations are well tolerated topically. DMSO preparations should be handled with gloves to minimize skin absorption that is enhanced by the DMSO solvent.

Ketoconazole has also been used to treat blastomycosis, histoplasmosis, cryptococcosis, coccidioidomycosis, and aspergillosis.[2]

d. Polyene macrolide antibiotics

(1) Natamycin (5% suspension) is the only topical antifungal commercially available.
(2) Amphotericin B is compounded in 0.3–0.5% colloidal suspension for topical use.
(3) Nystatin is compounded in isohydric phosphate buffer solution for topical use.

griseofulvin is the only antifungal approved for systemic administration by the Food and Drug Administration (FDA) for veterinary use.

Amphotericin B has a broad spectrum of activity against systemic fungal infections. It may be formulated for topical use on fungal keratitis. Natamycin has a broad spectrum of activity against filamentous fungi and yeasts. Nystatin is effective on some filamentous fungi and yeast.[4]

CONCLUSION

Eye is a complex organ with an intricate vascular supply. The treatment for ophthalmological infections varies depending on the medicine usage. Considerations should be given for the presence of the blood–ocular barrier and vascular supply of the eye, the presence of blood–ocular barrier etc. Proper diagnosis with the usage of suitable antimicrobial agent should be opted for ideal therapy.

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