CONTI Symposium
Ophthalmology 2021

Animal Ophthalmology Clinic
Dallas and Grapevine, TX
Robert J. Munger, DVM, DACVO

Ophthalmology Truth or Dare
Common Misconceptions on Treatment and Prevention of Ocular Diseases
All eye drops should be discarded after 1 month because of the potential for bacterial contamination.

It’s a good idea to discard eyewashes and eye drops used in the clinic (tropicamide, topical local anesthetics, etc.) after 2 weeks.

Microbial Contamination of Eye Drops

Alain Regnier

Gelatt’s Veterinary Ophthalmology,

Really????

Quotes article in BJO


Control of Microbial Contamination in Unpreserved Eyedrops


UDVs (Unit Dose Vials) – cumbersome, expensive (up 1169% more expensive than preserved eyedrops)

BNF (British National Formulary) – “Eyedrops in multiple application containers...should not be used for more than 4 weeks after opening...”
Does this make sense?

- Have you ever caused an infection in a patient’s eye with preserved topical drops?
- Let’s take a look!

Sankey, et. al. – ACVO 2016

- Dorzolamide/Timolol, Tropicamide 1%, Proparacaine 0.5%, OCuSOFT™ Eyewash
- 3 Bottles of each – Aerobic cultures: solution – Prestudy; drops and tips & inside cap at 2, 4, & 6 weeks plus solution at 6 weeks (added samples found in office at 6 months)
- NO GROWTH!
- Conclusion – Discard recommendation at 1 month is fallacious!

Control of Microbial Contamination in Unpreserved Eyedrops

- “This has always been an arbitrary figure as studies have never been conducted to confirm the validity of this open storage life.”
- “The Health Service Circular…but again the recommendations made in this document were never based on scientific data…”
- “The arbitrary nature of all these recommendations probably explains why
Uveitis
Insight Into Problem Cases

Uveitis By Any Other Name
- Iritis
- Cyclitis
- Iridocyclitis
- Choroiditis
- Panuveitis
Uveitis Types

- **Acute** – exudates: serous, fibrinous, serosanguinous, and purulent
- **Subacute** – immunologic reactions initiated ➔ healing, necrosis, recurrence, or chronicity
- **Chronic** – inflammation persist due to uncontrolled inflammatory event +/- inability to eliminate causative agent

Acute vs. Chronic Uveitis

<table>
<thead>
<tr>
<th>Acute</th>
<th>Chronic</th>
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<tr>
<td>&lt; 4 weeks</td>
<td>&gt; 4 weeks</td>
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<tr>
<td>Higher aqueous protein</td>
<td>Lower aqueous protein</td>
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<tr>
<td>PMNs predominate</td>
<td>Small and large mononuclear cells predominate</td>
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Immune Response in Uveitis

- Potential for cell mediated and humoral immunity
- Active T-cells in the uveal tissues mediating inflammation and recruiting replacements
- Present even when signs are subclinical
- Consider what the immune system is supposed to do!
Lens-induced Uveitis (LIU)

- Lens cells sequestered inside lens capsule
  - When is the antigen gone?
- Virtually all cataracts (especially those that progress rapidly)
- Phacolytic nongranulomatous (lymphocytic/plasmacytic) and granulomatous (especially older dogs)
- Secondary glaucoma may occur !!!

Virtually all eyes with significant cataract

- Especially a problem with rapid progression (diabetes mellitus, lens capsule rupture, hypermature etc.)
- A complicating factor in cataract surgery

Familial Uveitis of Golden Retrievers

- Pigmentary Uveitis and Cystic Glaucoma
- Early low IOP, conjunctival hyperemia, pigment on anterior lens capsule, aqueous flare, uveal cysts, fibrin, posterior synechiae, secondary cataract, secondary glaucoma
- Very stubborn! Treat early, continuously, and long term
- Enucleation, intraocular prosthesis, or intravitreal injection of gentamicin may be needed.
Familial Uveitis of Golden Retrievers

- Histopathology can be confusing - so chronic that pathologists are not always agreed uveitis is present
- Familial > Inheritance has not been defined completely BUT …. See next slide
- Fibrin that is beyond belief!
- Iris cysts may be blood filled
- Cataract can become severe

Research Findings

- Golden retriever cystic uveal disease: a longitudinal study of iridociliary cysts, pigmentary uveitis (PU), and pigmentary/cystic glaucoma (PCG) over a decade in western Canada
- 830 golden retrievers from Alberta, Saskatchewan, and Manitoba – 2004-2014

Holly et. al. (Cont.)

- CERF/OFA (630 dogs) and WCVM clinical consults (200 dogs) data
- Dogs with attached iridociliary cysts had high risk of being diagnosed with PU or PCG upon re-examination.
- No dogs diagnosed with thick-walled anterior chamber cysts (n = 7) developed PU or PCG during the study.
- Pedigree analysis suggests autosomal dominant mode of inheritance with partial penetrance.
Dr. Wendy Townsend

- Multifactorial disease
- Working on identifying related genetic links/mutations and are interested in receiving blood samples (1-2 purple top tubes, 6 ml) that can be sent by regular mail. The address is:
- Dr. Wendy M. Townsend at Purdue University Veterinary Teaching Hospital, 625 Harrison Street, W. Lafayette, IN 47907-2026

G. Retriever Cysts

Thick Walled Cyst  Thin Walled Cysts

Photos courtesy or Dr. Bruce Grahn

Golden Retriever Cystic Uveal Disease

Photo courtesy of Dr. Bruce Grahn
Golden Retriever Cystic Uveal Disease

Photos courtesy of Dr. Bruce Grahn

Conclusions

- Thin-walled iridociliary cysts are associated with PU and PCG
- All breeding golden retrievers should be examined annually by an ophthalmologist
- The incidence of this disorder is higher in western Canada than previous reports in North America.
- Regional differences?

Management of PU/PCG

- Early detection – exam with dilation, low IOP, ID of related dogs
- Aggressive suppression of uveitis – Start early and don’t stop!
- Early detection and treatment of secondary glaucoma.
- Discourage cataract surgery
**Rx of LIU vs. PU**

- LIU easier than GRU
- LIU - Topical (NSAIDs or Steroids) often effective
- LIU - Systemic therapy rarely needed
  - Exceptions: severe uveitis with rapidly progressing cataracts +/- lens capsule rupture
- GRU/PU - Topical NSAIDs not very effective; systemic steroids and immune modulators may be needed.

**General Uveitis Treatment**

- Topical and systemic anti-inflammatory therapy (steroids and non-steroidal)
- Mydriatics when needed to prevent posterior synechiae
- Long term immune suppression may be needed: azathioprine, oral cyclosporine, others? (especially with PU/PCG)
- Systemic antibiotics as appropriate

**Topical Therapy**

- Mydriatics - short acting vs. long acting; may predispose to or prevent glaucoma
- Steroids – 0.1% dexamethasone and 1% prednisolone acetate
- Topical NSAIDs - ketorolac, flurbiprofen, etc.
  - * Not as effective as steroids
  - * Still problematic with corneal ulcers
**Systemic Therapy for Uveitis**

- Prednisone - anti-inflammatory to immune suppressive doses (1.0 mg/kg b.i.d. and tapered (when possible)
- NSAIDs - Systemic not concurrent with systemic steroids (Duh!)
- Long term immune suppressive therapy
  - Ex: Azathioprine - 1.0 mg/kg (0.5 mg/lb) q.d. for 7 days; then q.o.d. thereafter.
  - Monitor CBC (RBC count) and liver enzymes
  - Mycophenolate an alternative

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**Questions?**
Truth or Dare

- PRA causes cataracts.
- Cataracts are an inert opacity of the lens.
- Cataracts should be removed even if the retina is non-functional.

Cataracts and Complications

- Failure occurred in untreated eyes at a rate 65 and 255 times higher than in medically and surgically treated eyes respectively.
- Failure 4x higher in medically treated only compared with those surgically treated
- Success in Groups 1 (untreated) and 2 (medical treatment) = comfortable, non-inflamed, non-glaucomatous
- Success in Group 3 = all of the above + visual.

Cataract Complications

- Uveitis – Severe or persistent low grade
- Infection (gingival/dental, bladder, skin, etc.)
- Retinal detachment
- Secondary glaucoma
- Accidental injury
Medical Therapy

- Topical NSAIDs/Steroids (Even long after surgery)
- Mydriatics – Prevent posterior synechiae
- Prevent infections – Be aware of sources
- “Nutritional Support” – Is that possible?
  - Optixcare Eye Health®, OcuGloRx®, others

TOPOCAL KINOSTAT® CLINICALLY PREVENTS CATARACTS IN DIABETIC DOGS

Robert J. Munger and the Kinostat Trial Study Group, M. Wyman², M. Paulos³ and P. F. Kador²,³

¹Animal Ophthalmology Clinic, Dallas, Texas, ²Therapeutic Vision, Inc. Omaha, ³College of Pharmacy, University of Nebraska Medical Center, Omaha, Nebraska, USA.

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Kinostat® Proof of Concept

- Veterinary Ophthalmology, 13:363-8, 2010
- 40 naturally occurring diabetic dogs
- Kinostat™ (28 dogs) or Vehicle (12 dogs): 1 drop t.i.d. for 1 year
- Owners documenting each application
- Exams at 0, 1, 2, 3, 6, and 12 months
Comparison of Cataract Progression In Dogs Treated With Kinostat vs. Vehicle For 12 Months

Vehicle
- 0 Months
- 12 Months

Kinostat
- 0 Months
- 12 Months

Cataract Score (mean ± SEM)

n = 12     n = 12           n = 28    n= 28

p = 0.000002    p = 0.000018

Placebo Group

Initial                   1 month           3 months               6 months

18 of 24 eyes (9/12 dogs) developed cortical or mature cataracts after 12 months

Kinostat™ Group: Unchanged lens (0)

Initial                   1 month           3 months               6 months

38 of 56 eyes (15/28 dogs) had no change after 12 months
12 of 56 eyes (6/28 dogs) developed cortical or mature cataracts
14 of 56 eyes (7/28 dogs) developed vacuoles
### Kinostat®
**Topical Aldose Reductase Inhibitor**

**Study 2 (Phase 3 Clinical Trial) INAD 11-785**
- 9 month masked, placebo-controlled multi-center (11) study
- 100 diabetic dogs - 33 treated with placebo and 67 treated with Kinostat® (anticipated from 180 recruited)
- Sept. 2012 FDA granted MUMS designation (Animal Orphan Drug)
- March 2015 FDA approved toxicity study

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### Kinostat® Phase 3 Clinical Trial

**Primary Objective:**
Compare the incidence of Grade 2 or higher cataracts at 9 months between treatment with topical Kinostat® and treatment with placebo. The primary endpoint is the incidence of Grade 2 or higher cataracts at 9 months.

**Hypothesis:**
The success rate observed in the Kinostat® treated group will be statistically significantly different from and numerically greater than the success rate observed in the placebo group.

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### Treatment

- 120 animals were randomized to the experimental group and 60 to the control (placebo) group (2:1 topical Kinostat® : placebo ratio) as generated by the study statistician.
- The study used a stratified blocked random allocation scheme so that the number of patients assigned to each treatment allocation (topical Kinostat® or placebo in a 2:1 ratio) is approximately balanced over time.
- 179 dogs were randomized on the Kinostat® trial. Dog CA-06 was never randomized.
52 Dogs Excluded or DNF

- 17 - Owner decision
- 15 for other reasons (including 7 dogs whose cataracts were consistent with aging in consultation with the FDA: OH-21, OH-23, FL-21, FL-22, CA-20, CA-28, CA-41).
- 10 died
- 6 were dosing non-compliant
- 2 were visit non-compliant
- 2 were lost to follow-up

Kinostat® Multicenter Clinical Trial

- 127 dogs – 11 centers across US (Double masked with 1/3 placebo and 2/3 on Kinostat™)
- Newly diabetic dogs with < 360° equatorial vacuoles
- Applied OU – t.i.d.
- Exams by Diplomates of the American College of Veterinary Ophthalmologists at 1, 2, 3, 6, and 9 months
- Those not developing cataracts by 9 months given Kinostat™ with mandatory evaluations every 6 months

Statistics

- Statistical analysis by stratified logistic regression (stratified by site)
- Primary Endpoint is the incidence of ≥ Grade 2 cataract
  (Failure = dog with ≥ Grade 2 cataract in one or both eyes at any time point up to 9 months and success is < Grade 2 cataract development in either eye at 9 months.
- Results (p-value 0.0169):
  - Placebo: 36.4% had cataracts by 9 months (n = 16/44)
  - Kinostat™16.9% had cataracts by 9 months (n = 14/83)
9 Month Comparison of Kinostat Clinical Efficacy in Preventing Lens Changes Diabetic Dogs

The placebo group is 2.18 times more likely to develop cataracts than the drug group stratified by site.

A.O.C. Experience

- 32 dogs enrolled (First enrollment 4/13/12 with last enrollment 8/4/14)
- 20 advanced to long term treatment after 9 months
- First dog enrolled was long term at > 3 years (44 months) – Died due to osteosarcoma (9/16)
- 7 remained on long term (others died, were noncompliant, or "just did not want to do it any more")

Noncompliance Example

- “Kirby” – MN Labrador retriever born 10/05/08; diabetes diagnosed Feb. 2013 (~5 years old)
- On study 4/23/13 – 2/13/14 with no cataracts, normal intraocular pressure (16-17 mmHg OU), and became noncompliant during the long-term extension
- 8/31/15 – Presented with progressive vision loss with pupils resistant to dilation, lens induced uveitis and hypotony (IOP 7-8 mmHg), and mature cataracts OU, positive menace response; normal electroretinogram and ocular ultrasound
- 9/10/15 - Bilateral phacoemulsification with IOLs
Conclusions

- Kinostat® brings a new paradigm to veterinary ophthalmology.
- Owners will “soon” have an economical alternative to cataract surgery in their diabetic dogs.
- Prevention of cataracts during insulin regulation prevents lens induced uveitis even if cataract surgery is contemplated for later.
- Average dog develops DM between 7-9 years of age and lives 36 months after onset.
- Prevention of cataracts will reduce the risks of lens induced uveitis, secondary glaucoma, and other complications in diabetic dogs.

FDA Approval Still Pending

They are requiring additional studies.
SIGH!
Glaucoma
New Insights Into an Old Problem

Glaucoma Alternatives
What do I do now? Frustrations at the hand of the leading cause of blindness in animals.
Glaucoma Myth

Long term medical therapy is possible in most cases we encounter in veterinary medicine.

NOT!!!

Glaucoma Facts

- Primary angle closure is progressive and is the most common glaucoma we treat
- Irreversible changes occur fast with secondary glaucoma
- Owners should be advised early of the type of glaucoma and sequelae
- Screening IOPs not necessarily effective
- Check any red eye

Aqueous Outflow Dynamics in Dogs and Cats

Aqueous produced in the ciliary processes ➔ between iris and lens ➔ into anterior chamber ➔ out through iridocorneal angle ➔ ciliary cleft
Aqueous Outflow Dynamics in Dogs and Cats

- Overproduction of aqueous does not occur
- Any impairment of flow can lead to glaucoma
- Increased cells or fibrin, inflammatory scarring (synechiae), anatomical alterations – goniodysgenesis, angle closer, ciliary cleft abnormalities

Gonioscopy - Anatomy

Canine Angle

Feline Angle

Abnormal Iridocorneal Angles

Narrow Angle

Goniodysgenesis
Ciliary Cleft - HRUS

- High resolution ultrasound of the anterior segment alone to visualize microanatomy (corneal thickness, iris, anterior lens, iridocorneal angle, and the ciliary cleft)
- Ciliary cleft drains the iridocorneal angle and may be abnormal when the angle is normal

HRUS Microanatomy

Case Report – “Ringo”

- 4 yo MN DSH, episcleritis (mild) in OD with ocular hypertension, normal iridocorneal angle
- Episcleritis resolved but developed ocular hypertension/glaucoma marginally controlled
- Enucleation of buphthalmic, blind, glaucomatous eye 5 years later. OS remains normal.
- Pathology report: “The glaucoma was open angle and appeared to be related to scarring of the deeper outflow channels.”
Case 2: Mini Crowe

- Mini Crowe – 10 yo, FS Boston terrier; normal gonioscopy OU, cataracts - mature OD; immature OS
- Dilation for ERG (IOP = 18 mmHg pre- and post-dilation in OD)
- OD normal ciliary cleft on HRUS
- OS - Dilation for ERG (IOP pre-dilation 21 mmHg; post-dilation 26 mmHg)
- Closed ciliary cleft with normal iridocorneal angle
- Boston Terrorist!

HRUS of Ciliary Cleft: Mini Crowe

Case 2: Mini Crowe

- Cataract surgery performed OD only 4/26/12: visual with IOL and normal IOP 9 months post-op
- OS: No progression of immature cataract at last exam; IOP normal on NeoPolyDex drop q.d.
Case 3: Petunia Parker Initial Exam

- 7 year-old FS cocker spaniel
- Presented for incipient anterior and posterior cortical cataracts – not impacting vision
- IOP slightly greater in OS (23 mmHg) than OD (21 mmHg) on presentation; normal iridocorneal angle OU
- After dilation IOP in OD decreased to 18 mmHg and was 24 mmHg in OS
- Cataract surgery not yet indicated; RDVM to monitor IOPs

Case 3: Petunia Parker + 8 Weeks

- RDVM documented elevated IOP in OS (26-28 mmHg); started Cosopt™ t.i.d. and IOP decreased to 14-18 mmHg
- Recheck with AOC: IOP = 14 mmHg in OD and 20 mmHg in OS
- HRUS performed OU: Ciliary cleft normal in OD and closed in OS

Case 3: Petunia Parker HRUS

- [HRUS images showing ciliary cleft status in OD and OS]
Medical Glaucoma Therapy

- Carbonic Anhydrase Inhibitors – Oral and topical (Safe for most cases)
- Miotic agents (Prostaglandin F2 alpha analogs (Xalatan, Travatan), pilocarpine, etc. – contraindicated where pupillary block is imminent (lens luxation, uveitis, etc.)
- Hyperosmotics (Oral glycerin; IV mannitol)
- Beta blockers – Not very effective except for delaying onset in fellow eye

Treatment Plan

- Control IOP
- Assess type and cause of glaucoma
- If primary angle closure - medical therapy will fail at some point
- Discuss surgery options – Eye visual or blind?
- Secondary – control cause
- Delay onset in second eye
- Monitor second eye!

Control IOP

- Carbonic anhydrase inhibitors
- Prostaglandin F2-alpha analogs (Travoprost - Travatan®, latanoprost - Xalatan®, bimatoprost - Lumigan®): Apply 1 gtt. 1-2 times daily
- Hyperosmotic therapy - Oral glycerin or IV mannitol
**Carbonic Anhydrase Inhibitors**
- Acetazolamide: 3-5 mg/lb b.i.d.-t.i.d.
- Methazolamide: 1-2 mg/lb b.i.d.-t.i.d.
- Dorzolamide (Trusopt®) 2% ophth. soln.: 1 drop t.i.d.
- Brinzolamide (Azopt®) 1% ophth. soln.: 1 drop t.i.d.
- Dorzolamide 2% + Timolol 0.5% (Cosopt®): 1 drop t.i.d.

**Hyperosmotic Agents**
- Glycerin USP Pure - Give 1/3 cc p.o. with equal volume of water, milk, or melted ice cream. Withhold water for 1.5 hrs. Repeat q. 8 h.
- Mannitol 5-20% IV - 0.5-2g/kg (Riskier and more involved)

**Prostaglandin Analogues**
- Latanoprost®, Travoprost®, and Lumigan® ophthalmic solutions
- Act to increase aqueous outflow + ?
- Increase iridal, eyelid and eyelash pigmentation in man and primates
- Use with caution in uveitis & lens luxation – potent miotics
Delay Onset Fellow Eye

- Timolol 0.5% - 1 gtt. twice daily
  or
- Compounded demecarium bromide
  0/125% q. 12–24 hours
  with
- Dexamethasone 0.1% - 1 gtt. once daily

Surgical Options

- Visual Eye
  - Ahmed valve and other shunts
  - Diode cyclo-photocoagulation (CPC)
    - trans-scleral or endolaser
  - Future – SALVO /Brown (MicroOptx) shunt – VIGOR Trial
  - Fast – Cryo-

- Blind Eye
  - Enucleation
  - Intraocular prosthesis
  - Intravitreal injection of gentamicin

Glaucoma Shunts

- Ahmed valve shunt most commonly used in veterinary medicine
- Shunts often become scarred limiting time of glaucoma control – unpredictable (some last years)
- May be used in staged or combined procedures (CPC + shunt or CPC following scar resection)
- Express® shunts designed for temporary relief – expensive (We need an alternative!)
- Brown shunt (VIGOR) from MicroOptx may be the alternative. Shunts to tear film.
Cyclophotocoagulation (CPC)

- Destruction of the ciliary processes by laser energy (diode laser targets pigmented tissue)
- Trans-scleral vs. Endolaser (ECP)
- Causes inflammation (Trans-scleral > ECP)
- Initial postoperative pressure spike (Yikes!)

Diode Endolaser CPC

- Superior to trans-scleral laser of ciliary body
  - More precise (targeted) – ciliary processes visualized
  - Less destructive of other tissues (less inflammation)
- More expensive - equipment, supplies, and surgical time
- Often combined with lens extraction
  - (DOUBLE YIKES!)

Diode Endolaser CPC
Factors Affecting Tonometry

Extrinsic Factors
- Excitement
- Squinting/struggling
- Compression of neck
- White coat syndrome
- Sedation

Intrinsic Factors
- Corneal scarring, edema – thicker cornea
- Uveitis
- Lens luxation
- Ciliary cleft status

Additional Issues and Case Examples
Discussed as Time Allows
Mia – 7-month-old ♀ DSH

Before

After

Initial ℞: Famciclovir (90 mg/kg)b.i.d., Doxycycline p.o., Idoxuridine (IDU) 0.1% b.i.d., Erythromycin oint. t.i.d. → became inappetent and febrile and lids remained reactive
Reduced Famyclovir to 125 mg b.i.d. (70 mg/kg) and appetite returned
Stopped IDU and Doxycycline → fever (related to doxycycline?) resolved and lids less reactive (possible reaction to IDU)
Sometimes less is more

Antiviral Therapy

- Idoxuridine 0.1% - 1 drop to the eyes every 5 minutes for 30 minutes for the initial treatment only to saturate the corneal tissues; then administer 1 drop t.i.d.
- Cidofovir 0.5% - compounded to a 0.5% solution inartificial tears from the IV solution and has been shown to be efficacious when administered twice daily. Blepharitis is a potential complication!
- Ganciclovir gel 0.15% (Zirgan®) – 1 gtt. b.i.d.
- Famciclovir (A prodrug of Penciclovir) – Wide range of doses up to is 90 mg/kg t.i.d. for 21 days. (We most commonly use 125 – 250 mg, b.i.d.)
Topical Antibiotics for Cats

- Medications containing neomycin or polymyxin B have been known, albeit rarely, to cause anaphylaxis and even death in cats when administered topically to the eyes.
- Can their use be justified? Rarely!
- Erythromycin or chloramphenicol would provide coverage against Chlamyphila felis and Mycoplasma as well as some common secondary bacteria and thus are not only accepted medical practice but a superior choice for initial topical antibiotics in most ocular disease in cats.

Questions?
Thanks For Coming!

I don’t care what your horse says. I’ll drink with you any time!