Glaucoma and OSD: Finally better treatment options

TWIN CITIES
OCULAR SURFACE
DISEASE SYMPOSIUM

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DISEASE SYMPOSIUM

Disclosures

- Allergan, Inc
- Shire, Inc
- Katena
- BioDLogics
- Aril / Blythe Medical
- Johnson and Johnson Vision, Inc
- Bio-Tissue

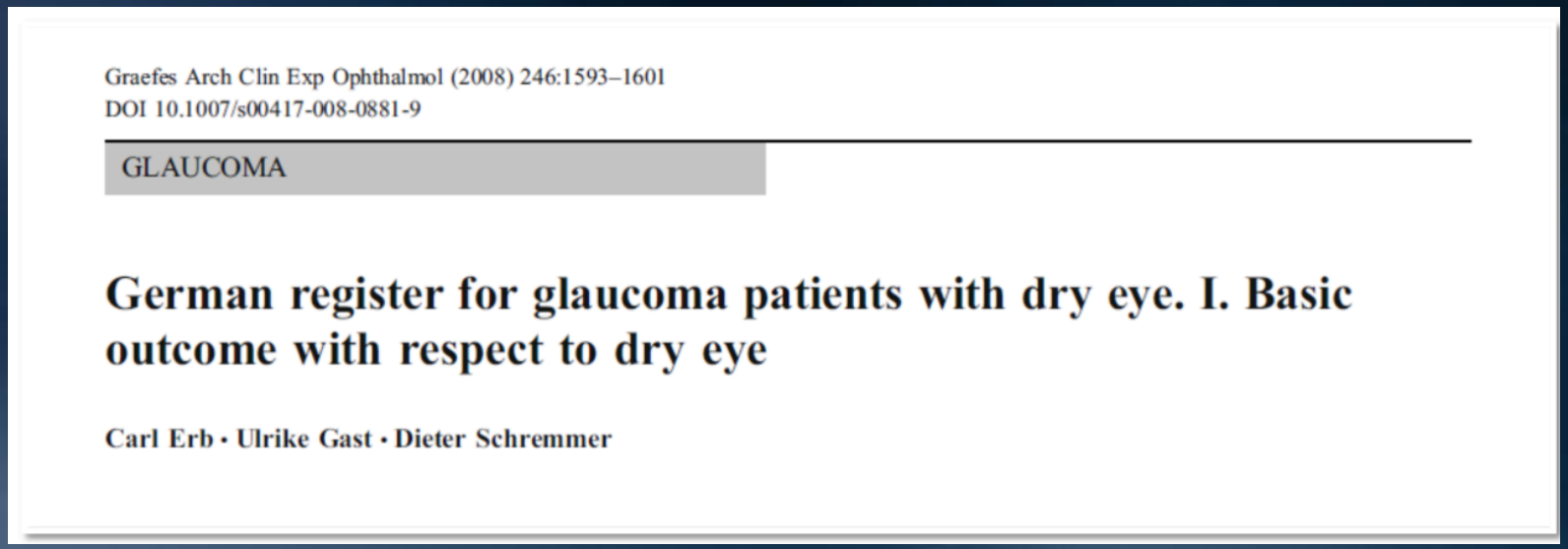
Pressing Question

- Does anyone consider the ocular surface when treating glaucoma?

Statistics

- Ocular surface disease is highly prevalent in general population
  - Ranges from 5% to 30% in patients >50 years
- As many as 60% of patients with glaucoma or OcHTN may have OSD
  - 1/3 will have severe form
- Patients with glaucoma and OSD are 12x more likely to have symptoms related to their drops

Statistics



Graefes Arch Clin Exp Ophthalmol (2008) 246:1593–1601
DOI 10.1007/s00417-008-0881-9

GLAUCOMA

German register for glaucoma patients with dry eye. I. Basic outcome with respect to dry eye

Carl Erb · Ulrike Gast · Dieter Schremmer

- 20,506 glaucoma patients
  - 52.6% concomitant diagnosis of dry eye
- Incidence of dry eye increases with age
- More women develop dry eye and glaucoma
- Impact of glaucoma duration significant

Pressing Question

- Does anyone consider the ocular surface when treating glaucoma?

Pressing Question

- Should we consider the ocular surface when treating glaucoma?

Case Study

- CD, 63 year old Caucasian female
- Referred to me for dry eye evaluation and continuation of care
- Medical History
  - Rheumatoid Arthritis
  - Hypertension
  - Heart Disease
  - Asthma
- Ocular History
  - Glaucoma

Case Study

- Medications
  - Coreg
  - Lasix
  - Albuterol
  - Mobic
  - Plaquenil
  - Travatan Z, Alphagan P, Lumigan

Case Study

- Patient c/o irritated, red, painful eyes x 6 months
- BCVA ~20/30 OD, OS
- IOP 15/14 mm Hg
- No relief with
  - Lotemax
  - Restasis
  - Punctal plugs
- All drops sting

Case Study

- Slit lamp exam
  - Diffuse SPK OU
  - TBUT < 5 seconds OU
  - Moderate injection OU

Case Study

- What next?

Why are glaucoma and ocular surface disease related?

Is it the preservatives?

- Development of OSD related to type, number, and duration of drops
- Studies show higher prevalence of OSD-like dry eye or allergy in patients treated long-term
  - Rises as number of topical meds increase

- Rise has been linked to preservatives and not the active substances

- EW Leung, FA Medeiros, RN Weinreb, "Prevalence of ocular surface disease in glaucoma patients", J Glaucoma, 17, 350–355 (2008). PMID: 18703943.
- C Erb et al., "German register for glaucoma patients with dry eye. I. Basic outcome with respect to dry eye", Graefes Arch Clin Exp Ophthalmol., 246, 1593–1601 (2008). PMID: 18648841.
- RD Fechtner et al., "Prevalence of ocular surface complaints in patients with glaucoma using topical intraocular pressure–lowering medications", Cornea, 29, 618–621 (2010). PMID: 20386433.
- GC Rossi et al., "Dry eye syndrome-related quality of life in glaucoma patients", Eur. J. Ophthalmol., 4, 572–579 (2009). PMID: 19551671.
- DC Broadway et al., "Adverse effects of topical antiglaucoma medication. II. The outcome of filtration surgery", Arch Ophthalmol., 112, 1446–1454 (1994). PMID: 7980134.

Preservatives

- All multi-dose ophthalmic preparations mandated by FDA to contain a preservative
  - Must maintain non-hazardous level of contamination

BAK

- Quaternary ammonium compound
- Works by dissolving bacterial cell membranes
  - Bacteriostatic and bacteriocidal
  - Prevents fungal and ameobal growth
- Prevents decomposition of active ingredients

- Cationic surfactant which increases space between epithelial cells

BAK

- Present in over 70% of ophthalmic preparations
- Adverse effects on ocular surface
  - Cornea
  - Conjunctiva
  - Eyelids

  - Trabecular meshwork?
  - Crystalline lens?

Corneal/Tear Film changes with BAK

- Detergent effect disrupts lipid layer
- Epithelial breakdown, decrease in epithelial cell density
- Can trigger apoptosis
- Damages microvilli
- Decrease aqueous production

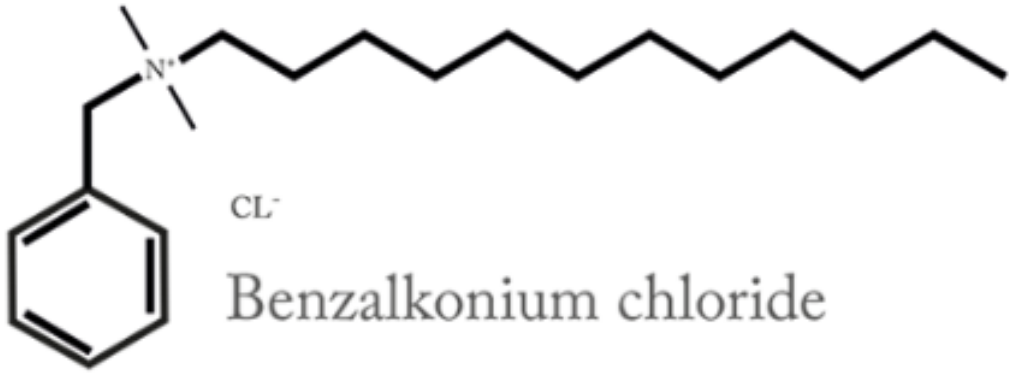
Conjunctival changes with BAK

- Reduces goblet cell density
- Follicular conjunctivitis
- Increases macrophages, fibroblasts, lymphocytes, and mast cells
  - may enhance the risk of external bleb scarring and filtration surgery failure
  - Cumulative duration significant risk factor for failure

Other potential issues with BAK

- Eyelids
  - Known skin irritant creating allergic/hypersensitivity reactions
    - Eczema
    - Blepharitis
- Crystalline lens
  - 3 different studies show there may be a correlation with cataract development
    - *Arch Ophthalmol. 2003;121(6):892-893*
- Trabecular Meshwork
  - Increased accumulation of inflammatory markers
    - Contributes to fibroblastic changes

BAK



Benzalkonium chloride

Loss of goblet cells

Tear-film instability

Ocular discomfort

Dry eye

Corneal nerve impairment

Induce/ enhance inflammation

Fibroblast activation in conjunctiva and subconjunctival space

Chronic inflammation

Ocular surface cell impairment

Corneal epithelium breakdown

Potential damage to deeper ocular tissues

Figure 1. The effects benzalkonium chloride can have on the ocular surface.

BAK

- Toxic effect is additive
- Dose-dependent effects on healthy ocular tissue
  - 0.0001% arrest of cellular growth takes place
  - 0.01% induces cellular apoptosis
  - 0.05 to 0.1% causes necrosis
- Dry eye patients may not produce enough tears to dilute the toxic effect

BAK

- Found in
  - Trusopt
  - Lumigan
  - Combigan
  - Xalatan
  - Simbrinza
  - Azopt
  - Timoptic
  - Vyzulta
  - Rhopressa

Are there better options?

BAK-free options

- SofZia
  - Used in Travatan Z
  - unique ionic buffer containing borate, sorbitol, propylene glycol, and zinc
  - Inactivated by enzymes when exposed to tear film
    - Break up into innate ingredients

SofZia

- Effective alternative to BAK?
  - Effects of SofZia-preserved travoprost and benzalkonium chloride-preserved latanoprost on the ocular surface – a multicentre randomized single-masked study (*2013, Acta Ophthalmologica)*
  - Study by Aihara et al showed less keratopathy and conjunctival hyperemia compared to travoprost with BAK
  - Less toxic than BAK but still has negative effects on cornea
  - Clinical trials have not demonstrated much difference in patient comfort compared to BAK

BAK-free options

- Purite
  - Found in Alphagan P
  - Breaks down upon contact with light into non-toxic natural tear components

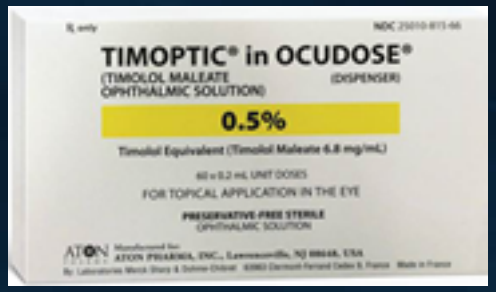
  - Brimonidine 0.15% produced less conjunctival lymphocytic infiltration than latanoprost, timolol, or dorzolamide
    - Noecker RJ, Herrygers LA, Anwaruddin R. Corneal and conjunctival changes caused by commonly used glaucoma medications. Cornea. 2004;23(5):490-496.

BAK-free Options

- Benzododecinium bromide (BDD)
  - Found in Timoptic XE
  - Quaternary ammonium compound
  - Toxic effects on conjunctiva

Current Non-Preserved Options

- Timoptic in Ocudose
  - timolol maleate 0.25% or 0.5%



- Zioptan
  - tafluprost ophthalmic solution 0.0015%

- Cosopt PF
  - dorzolamide-timolol ophthalmic solution 2%/0.5%

Current Non-Preserved Options

- ImprimisRx

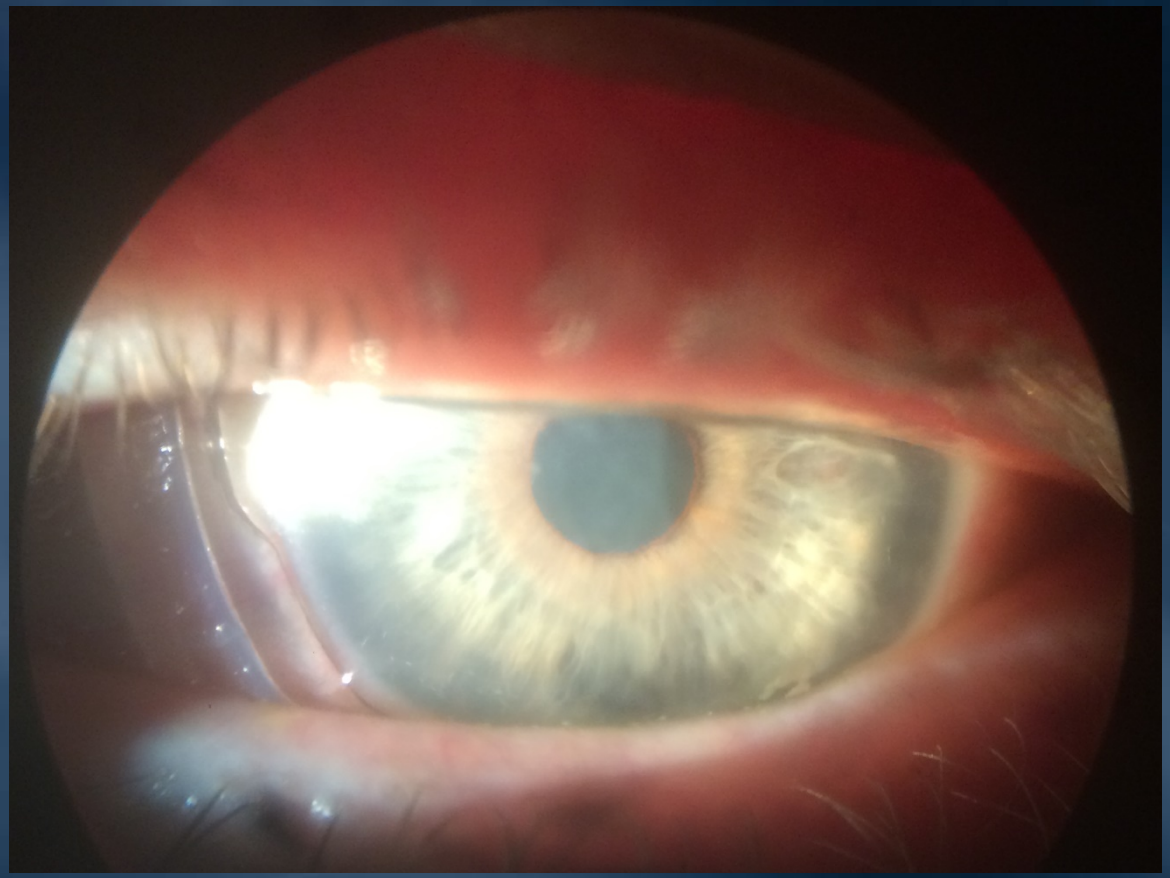
Preservative-Free Compounded Formulation	Size/Volume
Topical Medications *1gtts*	
☐ LAT PF (Latanoprost, 0.005%)*	7.5mL
☐ DOR PF (Dorzolamide, 2%)*	10mL
☐ TIM-LAT PF (Timolol/Latanoprost, 0.5/0.005%)*	5mL
☐ BRIM-DOR PF (Brimonidine/Dorzolamide, 0.15/2%)*	10mL
☐ DOR-TIM PF (Dorzolamide/Timolol, 2/0.5%)*	10mL
☐ TIM-DOR-LAT PF (Timolol/Dorzolamide/Latanoprost, 0.5/2/0.005%)*	5mL
☐ TIM-BRIM-DOR PF (Timolol/Brimonidine/Dorzolamide, 0.5/0.15/2%)*	10mL
☐ TIM-BRIM-DOR-LAT PF (Timolol/Brimonidine/Dorzolamide/Latanoprost, 0.5/0.15/2/0.005%)*	5mL
☐ TIM-BRIM-DOR PF (Timolol/Brimonidine/Dorzolamide, 0.5/0.15/2%)*	10mL
☐ TIM-BRIM-DOR-LAT PF (Timolol/Brimonidine/Dorzolamide/Latanoprost, 0.5/0.15/2/0.005%)*	5mL

Comparative Studies

- Horsley and Kahook
  - Replaced latanoprost with 0.02% BAK with Travatan Z
    - increased mean TBUT of 20 consecutive patients over 4 seconds
    - Reported improvement on symptoms according to OSDI
- Goldberg et al
  - Patients that switched to BAK-free medications needed fewer lubricant drops and reported improvement in dry eye symptoms
- Baudouin et al
  - patients receiving multiple drops >1 year had the greatest cellular changes to ocular tissue taken during trabeculectomy surgery

Case Study

- What next?

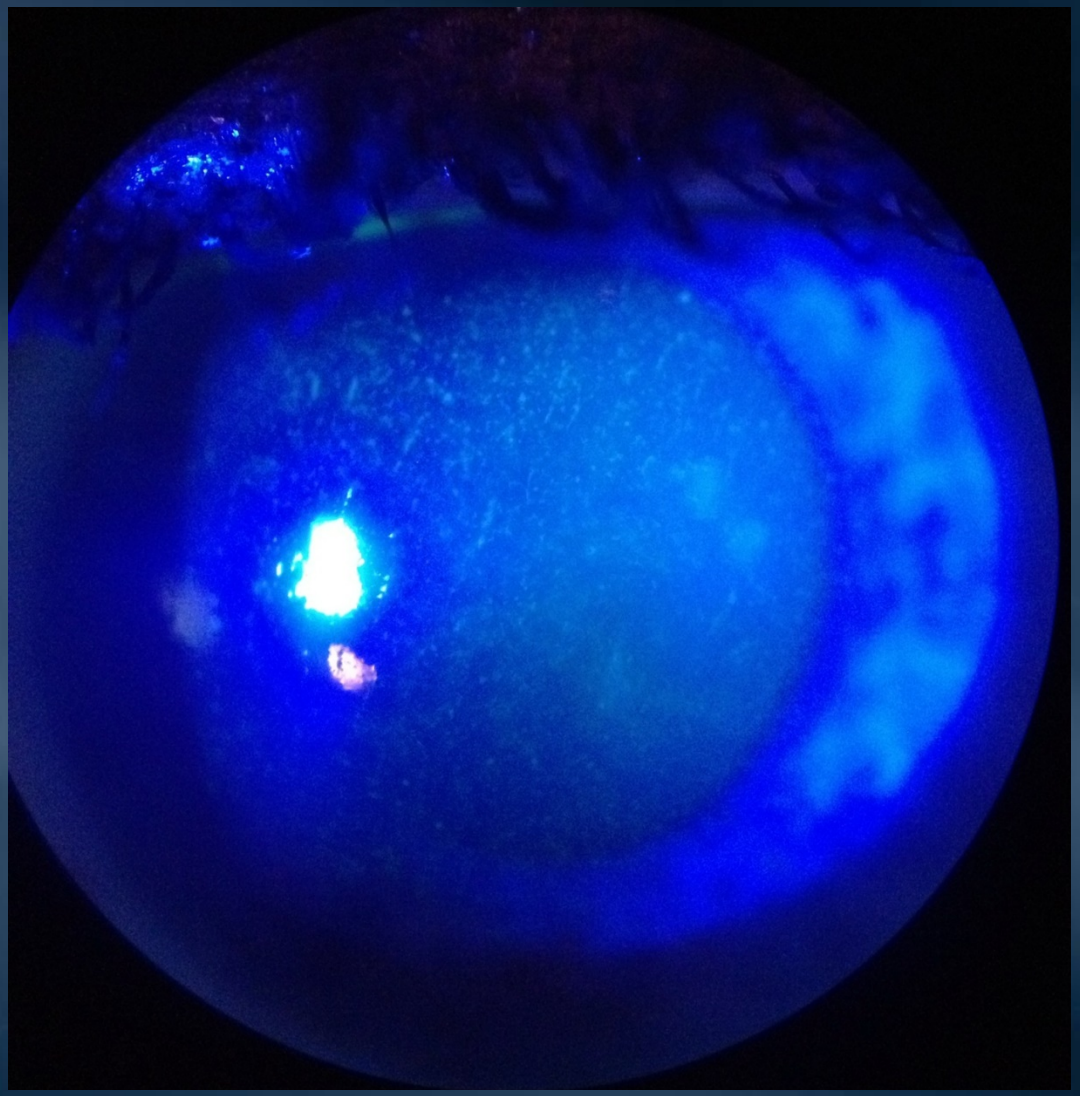


Case Study

- ProKera classic
- Tobradex BID OS
- RTO in 3-4 days

- Membrane dissolved, ring removed
- Clinical appearance

Case Study



THE AHA MOMENT

Case Study

- Discontinue Lumigan, add Zioptan QHS
- RTO x 2 weeks

- Patient reports better vision, better comfort
- IOP controlled
- Cornea clear

Case Study

- Has been controlled for several years
- Currently maintaining on Zioptan
- Ocular surface clear

Issues with non-preserved options

- Cost
  - Cosopt PF
    - 1 month supply: $164.40
  - Zioptan
    - 1 month supply: $190.97
  - Timoptic in Ocudose
    - 1 month supply: $453.37
  - latanoprost
    - 1 month supply: $12.00
  - Simple Drops (Imprimis Rx)
    - 1 month supply: $39 - $79/month

Issues with non-preserved options

- Dexterity concerns
- Potential for contamination

Standard of Care?

- Awareness
  - Patient complaints
  - Ocular surface
  - Duration
- OSD Treatments
  - Steroids
  - Artificial Tears

Practical Considerations

- The Ocular Hypertension Treatment Study observed that at least 40% of patients required treatment with two or more medications to reach target IOP

Final Thoughts

- BAK can be toxic to ocular structures
- Symptoms can alter quality of life
- Symptoms can decrease compliance

- BAK-free and preservative free products
  - Effective
  - Improve ocular tolerance
  - Improve compliance

Final Thoughts

- Consider dry eye testing for all glaucoma patients
  - Questionnaire
  - Signs vs. symptoms

Pressing Question

- Should we consider the ocular surface when treating glaucoma?

Thank you!

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