Megatrends in Optometry: Evidence Based Medicine - Evaluating Risk VS Benefit in Ocular Disease Management

Bruce E. Onofrey, OD, RPh, FAAO
Professor, U. Houston University Eye Institute

EVIDENCE BASED MEDICINE
- Rational care requires a scientific approach to patient management
- Sound clinical research should be the basis for therapeutic decisions
- Know the Disease: Pathophysiology
- Know the patient: Histories
- Know the therapy: Pharmacology

QUESTIONS?
KEEP IN TOUCH
EYEDOC3@AOL.COM or BONOFREY@OPTOMETRY.UH.EDU

WHAT IS THE BEST WAY TO REDUCE STROKES?

THE TREND
Stroke Prevention IT’S EVERYBODIES BUSINESS – WHY?

• Leading cause of disability
• Third leading cause of death
• Financial and emotional economies
• Modifying risk factors to prevent first stroke (primary prevention) or recurrent stroke (secondary prevention)

TOPICS
- MANAGING THE STROKE PATIENT (THE PC OD)
- LAB TESTING
- GLAUCOMA STUDIES
- NSAID’s and GLAUCOMA
- ANTIBIOTICS AND DRUG RESISTANCE
- MANAGEMENT OF SCLERITIS
- ANTI-INFLAMMATORY MANAGEMENT IN DRY EYE

• Managing the Stroke Patient (The PC OD)
• Lab Testing
• Glaucoma Studies
• NSAID’s and Glaucoma
• Antibiotics and Drug Resistance
• Management of Scleritis
• Anti-Inflammatory Management in Dry Eye

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CHECK PRESSURESSSSSS!!

LIFESTYLE CHANGES/BP
Metabolic syndrome
- Weight loss
- Support dietary changes
- Exercise, daily activity levels
- Educate, motivate

TOBACCO CESSATION
- Patient education and support-not criticism
- Provide TX information
- Co-benefit: Reduces risk of eye disease (AMD)

CONSIDER IN-OFFICE TESTING YOUR CLUELESS DIABETICS

Diabetes Mellitus
- Don’t just examine eyes-discuss ways to minimize morbidity
- Tight diabetes control
- 40% - 60% of type 2 DM have hypertension
- Aggressive hypertension management can lead to increased glc/ION risk? (Perf. Pres)

Atrial Fibrillation
- Can lead to thrombus formation
- Warfarin (Coumadin) therapy
- Reduces relative risk of stroke by 70% - 80% in highest-risk groups
- SYMPTOMS INCLUDE HX OF TIA’S – BE VIGILANTE

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Asymptomatic Carotid Artery Stenosis
- Carotid endarterectomy
- WATCH FOR TIA’S/CHECK CAROTID PULSES/BRUIT’S-Look for Hollenhorst plaques
- evidence of ischemia, ie uniteral low IOP, Unilateral GLC, diplopia, etc
- ASK THE RIGHT QUESTIONS
Sleep Apnea
- Oximetry – measures oxygen saturation
- Polysomnogram – sleep study test
- CPAP – continuous positive airway pressure: RED EYE
- Increased risk of glaucoma
- NO OPIATES

Stress
- Offer ways to improve stress levels (be a source of information)
- Knowledge reduces stress-Talk to patients about reducing risk

Estrogen Therapy
- Research on this topic is changing its use
- Advised against in patients with history of stroke without a medically compelling reason
- BE ALERT TO TIA SIGNS AND SYMPTOMS IN PATIENTS ON HORMONE REPLACEMENT THERAPY-ASK ABOUT SYMPTOMS

NEW FOR YOU!!!
- Fun with Herpes
  AN ORAL FOR ALL
  ZIRGAN FOR ALL
  KNOW YOUR HEDS
  SCOPE STUDY - CYCLOSPORIN A IS OK

THE TREND
RATIONAL USE OF LAB TESTS IN OPTOMETRY-WHY
- Verify DX
- Medico-legal documentation
- Evaluate effectiveness of therapy-TA
- Monitor for drug side-effects – CAI-CBC
- Don’t need to do tests-can ask PCP to order tests-Must be able to explain why the test needs to be done
- Need to be able to interpret the results accurately

New for you
TETRACYCLINE FOR ALL
INFLAMMATION
**Important Lab/clinical Tests**
- TA: ESR/CBC/CRP/TA biopsy
- Uveitis: ESR, RF, ANA, RPR, VDRL, TB skin test, chest xray/ACE levels
- Infectious keratitis: Culture scraping on blood/chocolate—special tests include Sabourauds and Ecoli plate
- Conjunctivitis: Chlamydia/diff-quick
- MRI/MRA/CT Scans
- Abnormal bleeding?

**Bleeders: Clin. info**
- #1
  - Ecchymosis of lids
  - bruising on arms
  - Multiple, recent episodes of epistaxis
  - (+) Hx trauma
  - (-) anticoagulant TX
- #2
  - Same + topical CAI use

**Cont’d**
- Intrinsic pathway: factors VIII, IX, X, XII
- Liver (Vit K) factors: I, II, V, VII, IX, X
- PT: Protime: Measures extrinsic system and coumadin activity
- INR: Latest way to standardize the PT
- PTT: Measures intrinsic system: Used to measure heparin activity

**KNOW YOUR PATHOPHYSIOLOGY—EXAMPLE: A TALE OF TWO BLEEDERS**
- 50 y/o hispanic male presents to acute care eye clinic with complaint of “bleeding eyes”
- VA w/o correction 20/25 OD, OS
- IOP 16 OU
- Pupils: 4mm, +3RX, RD, (-) APD

**How does the body prevent hemorrhage? Hemostasis—THE PHYSIOLOGY**
- 1. Small vessels: Vasoconstriction
- 2. Larger vessels: Clot formation

**THE TESTS**
- BLEEDING TIME
- CBC
- INR
- LIVER PANEL

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**BLEEDER #1 : Significant Lab Results**

- CBC: Generally Normal
- INR = 1
- Hepatic: Alk Phos 281 VH, Bilir.1.8H Alt (SGPT) 55H (OFF THE SCALE)
- Glucose: Normal
- Bleeding time: 23 minutes
- ESR: 36H

**Cause of hemorrhage?**

1. Hepatic failure
2. Reduced platelets
3. Renal failure
4. Leukemia
5. Drug induced aplastic anemia

**Bleeding time**

- Very simple test
- 1-9 minutes normal
- Over 15 minutes is definitely abnormal
- NOT DIAGNOSTIC-Doesn't tell WHY the person bleeds abnormally

**WHAT'S NEW IN GLAUCOMA?**

- AIN'T TECHNOLOGY GREAT
  - We have those fancy machines-the GDX and a new Cirrus OCT, as well as a CBS, FBI, JFK ETC

**BUTTTT....The REAL Advancement isn’t technological ie drugs and equipment, IT’S...IT’S... (WAIT FOR IT)**

- KNOWLEDGE !!
- ie. INDIVIDUALIZED RISK ASSESSMENT
The impact of clinical research on current glaucoma management

- Who we treat and who we watch
- Initial drug selection / maximizing drug combinations / max medical therapy
- How we (most accurately) assess disease progression
- The relationship between IOP and BP in GLC patients
- Evaluating and resolving similar studies with differing outcomes (sponsor bias?): Parrish (XLT) vs Noecker (LX)

Live and die by studies—both good and bad

OHTS:
- Risk factors of getting glaucoma 5 yrs

EMGT:
- Identified risk factors for progression
- TX reduces risk of progression 15%/min drop

AGIS:
- Target IOP below 18

ABRAN:
- Minimize diurnal fluctuation

NTG:
- Must lower IOP a min of 30%

LASE:
- C/D > 0.6 is 93% sensitive & 96% specific for POAG

DPP:
- Diastolic perfusion pressure and glaucoma

THE MEGA-TREND
Managing Glaucoma by the Numbers

THE MEGA-TREND
LIES, DAMN LIES AND STATISTICS

- According to OHTS:
  - TX all oc. Hypertensives reduces glaucoma prevalence by 50%
  - From 10% to 5% in 5 years
  - NNT = 22-42
  - Important message: determination of relative risk—TX decision is more objective

POAG Endpoints by Central Corneal Thickness and Baseline IOP (mmHg) in Observation Group

POAG Endpoints by Central Corneal Thickness and Baseline Vertical C/D Ratio in Observation Group

Central Corneal Thickness (microns)

Central Corneal Thickness (microns)

* through 8 Nov 2001
The OHTS Lesson

- Treating all ocular hypertensives is not safe/effective or cost effective
- Pachymetry is important
- Conversion best determined by Optic Nerve (Nerve fiber layer) changes HOLD THAT THOUGHT
- TX is optional if risk is acceptable
- IF NFL changes or disc changes TX-DON’T wait for VF changes (thank Harry Quigley)

EMGT: Does TX Help
Best measure of Progression

- Lower IOP Lower risk
- VF vs Disc evaluation
- If TX-What target IOP? Look at AGIS

Lower IOP Stabilizes Glaucoma Progression

Additional Support (AGIS):
“The AGIS data support the suggestive evidence from earlier studies that achieving low levels of intraocular pressure slows the progression of glaucomatous optic neuropathy”


Low Pressures Should Be Maintained Over 24 Hours

Risk Associated With Diurnal IOP Variations

LALES Study
C/D Ratio as screening tool

- Los Angeles Latino Eye Study
- Comprehensive evaluation for predictors of eye disease in this population
- 6,357 latinos over 40Y/O
- Vertical C/D > 0.6 cutoff for gle screening
- 92.3% sensitive for gle
- 95.3% specificity for gle
Ocular Perfusion Pressure and Glaucoma Progression

Low ocular perfusion pressure has been shown to be strongly associated with the prevalence of glaucoma progression in multiple population-based surveys.


BP – IOP = Ocular Perfusion Pressure (OPP)

BP is mean arterial pressure, diastolic BP, or systolic BP.

Perfusion Pressures

• Mean arterial pressure (MAP) = 2/3 diastolic + ½ systolic
• Mean Arterial OPP = MAP - IOP
• Systolic OPP = Systolic - IOP
• Diastolic OPP = Diastolic - IOP

Ocular Perfusion Pressure and Glaucoma Progression:

• Baltimore Eye Survey (AA and Caucasian)1
  Excess of POAG in subjects with lowest category of Ocular Perfusion Pressure (OPP)
• Egna-Numarkt Study (Caucasian)2
  Lower Diastolic Ocular Perfusion Pressure (DOPP) associated with marked, progressive increase in frequency of POAG
• Barbados 4 yr Eye Study (African-Caribbean)3
  4-year risk of developing glaucoma increased dramatically at lower perfusion pressure
• Proyecto Ver (Hispanic)4
  Found lower Diastolic Perfusion Pressure (DPP) associated with increased risk of POAG

OPP and Glaucoma Progression: Population Studies


OPP: Barbados 9-year

• Cohort study of African-Caribbeans residing in Barbados, West Indies
• 9-year risk of developing glaucoma increased dramatically at lower perfusion pressure

**Barbados Eye Study Conclusions**
- Correlates indicating increased risk of GLC progression (in order of significance)
  - Low mean perfusion pressure
  - Family HX of GLC
  - Corneal thickness
  - Elevated IOP
  - Age
  - Increased Systolic BP was a protective factor

**Thessaloniki Eye Study**
- Performed HRT in 263 subjects
- Excluded those subsequently identified with glaucoma
- Patients with DBP < 90 as a result of systemic anti-HTN treatment had larger C:D ratios and cup areas on HRT compared to normals with DBP < 90 and HTN patients with BP ≥ 90

**POAG Risk Factors 9-year BES**

**FINALLY, how does perfusion pressure data effect drug selection and treatment methods?**
- What’s happening to IOP at night?
- What drugs work well on a 24-hour cycle (particularly during sleep)?
- Which drugs maximize 24 hour IOP control with minimal effect on BP?
- First, the LIU studies from Weinrebs GLC lab

**Glaucoma Medications and their effects on Ocular Perfusion Pressure (OPP)**
- 27 Patients treated with BID timolol 0.5%, BID brimonidine 0.2%, TID dorzolamide 2% or QHS latanoprost 0.005% for six weeks, followed by a 4-week washout period between different treatments
- 24-hour IOP monitoring in habitual position
- 24-hour systemic blood pressure monitoring

**GOAL:** Based upon drug effect on IOP and BP find the best mono therapeutic agent and best drug combination
Diastolic Ocular Perfusion Pressure (DOPP) Results

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Timolol</th>
<th>Brimonidine</th>
<th>Dorzolamide</th>
<th>Latanoprost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean 24-Hour DOPP (mm Hg)</td>
<td>50.7</td>
<td>52.0</td>
<td>46.2</td>
<td>55.9</td>
<td>56.4</td>
</tr>
</tbody>
</table>

Significant reduction in DOPP (p < 0.0001)

Significant improvement in DOPP (p < 0.0001)

* Reduction in DOPP is a risk factor for glaucoma progression


Relationship between Nocturnal Hypotension and OPP

- Low BP at night, coupled with high IOP in supine position, compromise OPP
- Use systemic BP meds in the AM to minimize nocturnal hypotension
- Use IOP lowering drugs that lower IOP during BOTH the diurnal and nocturnal period (CAI’s and prostaglandins)
- Avoid IOP meds that lower systemic BP at night (beta blockers, alpha agonists)


Think holistically

- Consider measuring perfusion pressures
- Monitor those at greatest risk-low BP/over-aggressive BP control
- Nocturnal hypotension can produce NA-ION
- Talk with PCP

CONCLUSION:
In primary open-angle glaucoma patients, diclofenac significantly enhances the hypotensive effect of latanoprost (approx 25% below treatment baseline) without influence on timolol efficacy. Because non-steroidal anti-inflammatory drugs are widely employed in medical practice, supplementary ophthalmologic checks should be scheduled during the co-administration of these compounds and prostaglandin analogues.

The influence of diclofenac ophthalmic solution on the intraocular pressure-lowering effect of topical 0.5% timolol and 0.005% latanoprost in primary open-angle glaucoma patients.

Purpose: To verify the influence of a non-steroidal anti-inflammatory drug ophthalmic solution on intraocular pressure reduction induced by 0.5% timolol and 0.005% latanoprost eyedrops in patients affected by primary open-angle glaucoma.

Costagliola C, Parmeggiani F, Antinozzi PP, Caccavale A, Cotticelli L, Sebastiani A. Department of Ophthalmology, University of Ferrara, Ferrara, Italy. costaciro@libero.it

PURPOSE: To verify the influence of a non-steroidal anti-inflammatory drug ophthalmic solution on intraocular pressure reduction induced by 0.5% timolol and 0.005% latanoprost eyedrops in patients affected by primary open-angle glaucoma.

CONCLUSION: In primary open-angle glaucoma patients, diclofenac significantly enhances the hypotensive effect of latanoprost (approx 25% below treatment baseline) without influence on timolol efficacy. Because non-steroidal anti-inflammatory drugs are widely employed in medical practice, supplementary ophthalmologic checks should be scheduled during the co-administration of these compounds and prostaglandin analogues.
**Proposed mechanism of synergism of NSAID and Xalatan**

- NSAID inhibits endogenous prostaglandin cmpds
- Lowered prostaglandin levels stimulate an increase in prostaglandin tissue receptors.
- Increased tissue sensitivity to exogenous prostaglandins

**QUICK QUIZ!!**

- How does bacterial resistance develop?
  - A. Rapid reproduction leads to spontaneous mutation
  - B. Bacteria have a mid-life crisis, buy a sports car, new clothes, new shoes, become a blonde, and mutate
  - C. They intentionally mutate
  - D. I SAID “What the heck is for dinner”.

**RESISTANCE IS NOT FUTILE!! or spontaneous**

- Resistance is not a passive process—it is an active defensive process that is stimulated by bacterial stress
- Lex A protein inhibits mutation genes
- Cipro use produces cleavage of the Lex A protein that suppresses the activation of mutagenic genes.
- Polymerases are released that stimulate rapid mutations that lead to production of drug resistant bacteria—a defensive mechanism of the bacteria. Resistant bacteria do not bind cipro to DNA gyrase.
- By dosing fluoroquinolone with a cmpd that inhibits Lex A protein cleavage, mutagenesis and subsequent resistance was eliminated

**Fluoroquinolone (Cipro) use stimulates mutation in E.coli**

**THE TREND:**

**Reducing Bacterial Resistance**

How do bacteria become resistant and what are you going to do about it?!!

**Episcleritis and scleritis: clinical features and treatment results.**

Jabs DA, Mudun A, Dunn JP, Marsh SJ.

Department of Ophthalmology, The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA. dajabs@jhmi.edu

PURPOSE: To evaluate the clinical experience with episcleritis and scleritis at a tertiary care eye center, drugs.
CONCLUSIONS: Scleritis is a severe ocular inflammation, often associated with ocular complications, and nearly always treated with systemic medications. Nearly 60% of these patients will need oral corticosteroids or immunosuppressive drugs to control the disease.

AUTOIMMUNE DISEASE

- Episcleritis VS Scleritis
- Differential DX of Scleritis-Underlying systemic disease is common-Can I use a topical steroid? If systemic, what TX has greatest safety/efficacy?
- 4 types of scleritis
  - Anterior diffuse
  - Anterior nodular
  - Necrotizing anterior-97% syst. Disease (Avoid topical steroids-scleral melting)
  - Posterior-----High flow vs low flow??

Mythoponolate mofetil (Cellcept) therapy for inflammatory eye disease.

Thorne JE, Jobs DA, Oezl FA, Nguyen OD, Kempen JH, Dunn JP.

Department of Ophthalmology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA. jthorne@jhmi.edu

RESULTS: Of the 84 patients treated with mycophenolate mofetil, 61% had uveitis, 17% had scleritis, 11% had mucous membrane pemphigoid, and 11% had orbital or other inflammatory disease. Forty-three percent of patients treated with mycophenolate mofetil had been treated with at least one other immunosuppressive drug previously. The median dose of prednisone at the start of mycophenolate mofetil therapy was 40 mg, and 82% of the patients were considered a treatment success, as judged by the ability to control the inflammation and taper prednisone to ≤ or =10 mg daily.

CONCLUSIONS: These data suggest that mycophenolate mofetil may be an effective corticosteroid-sparing agent in the treatment of inflammatory eye disease with a manageable side effect profile.

Cellcept

- T-cell inhibitor
- Used to prevent transplant rejection
- Start with 500mg BID
- Go to 1000mg BID if necessary
- GI upset most common
- Monitor renal and hepatic function

Dry eye-Management of INflammation is IN

Stern et al. Cornea. 1998:17:584

- Who would have ever thought steroids would be indicated for dry eye management
- It’s simple logic
- Dry eye = injury = inflammation
**Dry Eye Disease: An Immune-Mediated Inflammatory Disorder**

- Neurogenic inflammation
- T-cell activation
- Cytokine secretion into tears

**Interrupted Secretomotor Nerve Impulses**

Tears Inflame Ocular Surface

Cytokines Disrupt Neural Arc

**Inflammation disrupts normal neuronal control of tearing**

**Dry Eye Disease: An Immune-Mediated Inflammatory Disorder**

Topical nonpreserved methylprednisolone therapy for keratoconjunctivitis sicca in Sjogren syndrome.

March P, Pflugfelder SC.

Ocular Surface and Tear Center, Bascom Palmer Eye Institute, Department of Ophthalmology, University of Miami School of Medicine, Florida 33136, USA.

CONCLUSIONS: These findings indicate that topical nonpreserved methylprednisolone is an effective treatment option for patients suffering from severe keratoconjunctivitis sicca who continue to experience bothersome eye irritation despite maximum aqueous enhancement therapies. They also suggest that inflammation is a key pathogenic factor in this condition.

**The Bad 3 ’s**
- DRY
- DROWSY
- DILATED

**The Good 3 ’s**
- DROOL
- DIARRHEA
- DAMP

**Parasympathomimetics**

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Salagen
Indications/Dosage forms
- Indications:
  - Advanced, non-responsive Sjogrens
- Dosage form:
  - 5mg tablets

Evoxac: New and improved pilocarpine
- Parasympathomimetic
- Better tolerated
- 30mg TID
- No titration necessary
- NEVER in asthmatics

THE END
Thank you for your hospitality and attention