THE PAIN GAME
EXPLORING OCULAR PAIN AND INFLAMMATION

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Recent Optometric Legislation

- April 2013 - Florida
  - Rx oral drugs
  - Comanagement
  - Minor procedures
- May 2013 - Georgia
  - Oral steroids
  - Hydrocodone
  - Use appropriate drug distribution modalities
- April 2014 - Tennessee
  - Injectable anesthetics
- Hydrocodone Update

I Think There is Something in My Eye

Photo Courtesy of Tom Joly, MD, PhD
Basics

- Anatomy
- Ocular Anatomy
- Clinical Manifestations
- Treatment
- Control
- Cause---------> Effect

Anatomy of Pain

- COX enzymes play a key role in inflammation and pain.
  - COX-1 is involved in maintenance of GI mucosa
  - COX-enzyme signals pain and inflammation

The Inflammatory Cascade

- Mast Cell
- Membrane Stabilization
- Tryptase
- Heparin
- Chymase
- Membrane Phospholipid
- Phospholipase A2
- Arachidonic Acid
- Cyclooxygenase
- Cysteine-related molecules
- Prostaglandins
- Thromboxane A2 (TXA2)
- Leukotrienes (LTB4, LTD4, LTE4, LTA4)
- Lipooxygenase
- Hydroperoxides

Pain - One in a Million

- Pain receptors are specific to location and stimuli
  - Sharp immediate pain: A-delta fibers
  - Prolonged unpleasant burning pain: mediated by smaller unmyelinated C fibers
- These lay dormant until stimulated and are often sensitized by inflammation

Nociceptors

- In all peripheral tissue
- Distribution will vary
- Stimulated by:
  - Heat
  - Energy
  - Trauma
  - Emotion?
  - Chemicals
    - Bradykinins
    - Serotonins
    - Histamines
    - GABA
    - Capsaicin
    - Prostaglandins

Modern Pain Perspective

- When a nerve cell communicates with another it uses just a millionth of the energy that a digital computer expends to perform an equivalent operation.
- Reliability - a signal travelling from one cortical cell to another typically has only a 20 percent possibility of arriving at its ultimate destination
Pain - Remember ME

- Various stimuli may signal a specific pattern of neuronal response based on a learned response
  - Think “suspicious coincidences” (Horace Barlow) as seen in the visual cortex

Common Painful Ocular Conditions

- Allergic conjunctivitis
- Angle closure glaucoma
- Conjunctivochalasis
- CL Related Pain
- Dacryoanexitis
- Dacryocystitis
- Dry eye disease
- EKC
- Episcleritis
- Foreign bodies
- Headache
- Hordeolum
- Optic neuritis
- Orbital cellulitis
- Preseptal cellulitis
- Pterygium
- Refractive Surgery
- Scleritis
- Trauma
- Uveitis

Importance of History

- History
  - Medical
  - Family
  - Social
  - Any drug allergies
- DOFDAR
  - Tell me about your pain
    - Quality
    - Duration
    - Frequency
    - Reproducible factors
    - Associated features
Eyelids and Pain

- Typically inflammation induced
- Many capsaicin receptors

Eyelids

- Pain is often inflammation and swelling based
- Decrease swelling = decrease pain
  - Cold compress
  - Medrol Dosepak
  - Lotemax ung
**Corneal Pain Anatomy**

- Most richly innervated structure in the body
  - Densely supplied by sensory and autonomic nerve fibers
- Sensory nerves (the vast majority) come from the ophthalmic division of the trigeminal
  - Posses both sensory and efferent functions
  - Mechanical, thermal and chemical stimulation usually is perceived as pain

**Autonomic Nerve Fibers in Cornea**

- Sympathetic fibers from the superior cervical ganglion
- Parasympathetic fibers from the ciliary ganglion
- Corneal sensation is essential for maintaining the integrity of the ocular surface

**What Does it Look Like?**

- 70-90 nerve bundles enter the cornea at the level of the mid stroma (in all clock hours)
- Run anteriorly toward the central cornea
- Form plexiform arrangements
- Form a dense subepithelial plexus and penetrate Bowman’s membrane
  - Largest concentration of perforation sites in the mid periphery
  - Form a whirl like pattern in the central cornea (clockwise)
Corneal Sensitivity Changes

- Age considerations
- Contact lenses
- Ocular surface disease
- Previous infections

Insensitive Old People

- Corneal sensitivity decreases with age
  - Explain decreased tear production
  - When elderly complain of significant pain it should be taken seriously

Contacts

- Decrease corneal sensitivity
  - Decrease tear production
  - Sensory adaptation to mechanical abrasion
Dry Eye

• The king of chronic eye pain

Corneal Nerve Structure and Function in Patients With Non-Sjögren Dry Eye: Clinical Correlations

• Mean corneal sensitivity was significantly lower in the NSDD group as compared with the control group ($P = 0.014$).

• NSDD patients have both structural and functional alterations of subbasal corneal nerves and these changes are related to the severity of dry eye.

• Antoine Labbé$^1$ 2013 ARVO

The Relationship between Subbasal Nerve Morphology and Corneal Sensation in Ocular Surface Disease

• Corneal sensitivity was significantly decreased in dry-eye and glaucoma patients compared with controls. The density and number of subbasal corneal nerves were also significantly decreased in dry eye and glaucoma patients compared with controls.

• Labbe 2012 IOVS
**Neuropathy is end stage organ damage**

- Diabetics know this first hand
- All diabetics get dry eye, few complain about it.

**What’s Happening in Dry Eye**

- Sensory nerves may adapt to irritation by decreasing the frequency and intensity of action potentials
- With time this elevates pain threshold, and stronger stimuli is needed to evoke corneal sensation for basal and reflex tearing
- Corneal hypoesthesia likely plays a role in the pathogenesis of tear deficiency

**The Other Edge of the Sword**

- Long term exposure to low levels of prostaglandins from dry eye sensitize the receptors for pain
How do we attack this?

- Indirectly go after the immune modulation in the lacrimal gland
- What if we could directly address the nerve issue in the cornea?
  - How can we do this?

Refractive Surgery Considerations

- Do more nerves enter the cornea nasally?

- Initially several studies showed that nasal or superior LASIK flaps had no effect on corneal sensation

- Transient light sensitivity syndrome
Unilateral Herpes Zoster Ophthalmicus Results in Bilateral Corneal Nerve Alteration: An In Vivo Confocal Microscopy Study

- Patients with unilateral HZO demonstrated a profound and significant bilateral loss of the corneal nerve plexus as compared with controls, demonstrating bilateral changes in a clinically unilateral disease. Loss of corneal sensation strongly correlated with subbasal nerve plexus alterations as shown by IVCM.
- Hamrah - Ophthalmology 2012

Ciliary Body and Pain

- Pain receptors diffusely distributed
  - Localization very difficult
  - Similar to sinus pain
- Light sensitivity

Classification of Uveitis

- Anatomical / structural location
- Etiology
- Acute vs. Chronic
- Non-granulomatous vs. Granulomatous
- Unilateral vs. Bilateral
Clinical Signs

- VA
- Conjunctiva
- Cornea
- Anterior chamber
- Iris
- Pupil
- IOP
- Lens
- Vitreous
- Disc edema
- Macular edema
- Periphlebitis


Posterior Segment Pain

- Neovascular glaucoma
- Ocular ischemic syndrome
- Optic neuritis
- Posterior uveitis
- Pars planitis

21 Year Old AA Female
What About IOP?

- Angle closure
- Postoperative
- High IOP in non-seeing eyes

Best Drug

Topical Route

- Direct drug delivery
  - Higher concentrations
- Minimize or eliminate systemic side effects
Topical Pain Control
Anesthetics (not long term analgesics)

- Tetracaine
  - 10-20 min
- Benoxinate
  - Only in combos
  - 10-20 min
- Proparacaine
  - Diet Tetracaine
  - Poor penetration
  - VERY LITTLE CROSS SENSITIVITY TO TETRACAINE AND BENOXINATE

Corticosteroids

- Longer onset of action due to full system shut down
- Inflammation resolution tends to mirror analgesic effect
- Some tissues are not that prone to swelling

Early- and Late-Phase Inflammatory Mediators

- Mast Cell
  - Membrane Phospholipids
  - Histamine
  - Leukotrienes
  - Prostaglandins

- Phospholipase A₂ Activity
  - Arachidonic Acid

- Cyclic Endoperoxides
  - Prostacyclin (PGI₂)

- Hydroperoxides (5-HPETE)

- Leukotrienes (LTB₄, LTD₄, LTE₄, LTB₅)

- Thromboxane (TXA₂)

- TRYPTASE, CHYMASE

- PROTEASES

Corticosteroids

- Will control prostaglandins and leukotrienes
- STOPS THE INFLAMMATION CASCADE
- Suppresses inflammation
- Allows for reestablishment of the neural feedback loop

Steroid Efficacy

- Difluprednate > Prednisolone > Loteprednol > Dexamethasone > Fluorometholone

Percent of Subjects with Clearing of Anterior Chamber Cells (Grade 0 defined as ≤1 cell)
Mean Change from Baseline in Total Symptom Score*

*DThe total symptom score was the sum of pain/ocular discomfort, photophobia, blurred vision, and lacrimation. Each symptom was graded using a visual analogue scale that ranged from 0-100. Patients were asked to assess these symptoms by using a mark on a 100 mm line where 0 = absent, 100 = maximal.

Immunosuppression

NSAIDS

- Act peripherally - avoid CNS
- Very good pain control
- Low dose - analgesic
- High dose - anti-inflammatory
Most Feared Side Effect?

NSAIDS

- Very Safe
- Most of ophthalmology is still caught up in the hysteria of the generic voltaren saga.
- Diclofenac Paranoia

NSAIDS

- Inhibit prostaglandin synthesis
  - 1. irreversible inactivation of COX
  - 2. reversible competitive inhibition
  - Reversible non-competitive inhibition ("free radical trappin")
Unmanageable Pain and Photophobia with Steroids

**NSAIDS**

- The most underutilized drug class in optometry

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**Relative IC\(_{50}\)s: Rank - Order Greatest to Least Activity**

<table>
<thead>
<tr>
<th>Cyclo-oxygenase 2 (COX-2)</th>
<th>IC(_{50}) ((\mu)m)</th>
<th>Relative Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bromfenac</td>
<td>0.0075</td>
<td>4.10 X</td>
</tr>
<tr>
<td>Amfenac</td>
<td>0.0204</td>
<td>1.50 X</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>0.0279</td>
<td>1.10 X</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>0.0307</td>
<td>1.00 X</td>
</tr>
</tbody>
</table>

Ogawa, Senju. Accepted ASCRS 2007

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Indications for Topical NSAIDs

<table>
<thead>
<tr>
<th>Indication</th>
<th>Diclofenac 9.5%</th>
<th>Ketorolac 20%</th>
<th>Ketoprofen 0.4%</th>
<th>Naproxen 1.6%</th>
<th>Bromfenac 5.6%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-inflammatory</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td></td>
</tr>
<tr>
<td>Oral Pain</td>
<td>✅</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-refractive Oral Pain</td>
<td>✅</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raneophtholides</td>
<td>✅</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral itching</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhoidal Bleeding</td>
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</tbody>
</table>

All else fails

- Pressure patch
  - Corneal pain

Acetaminophen

- #1 stunner (mild to moderate pain)
- We have no idea how it works (probably CNS effects)
- No real GI effects
- Additive with other pain meds
- No cross reactions
- Not associated with Reye's syndrome (kids dying from NSAIDS)
Aspirin

• The Original NSAID
• Anticoagulant
• No mood altering effect
• Irreversibly acetylating COX
  – Most others are reversible competitive inhibitors
  – Watch asthma patients

NSAIDS

• All NSAIDS can cause GI problems and gastric bleeding all high/long term dosages

NSAIDS

• Studies have shown NSAIDS to have same analgesic effect as narcotics
  – Some studies show better pain control than morphine (what?.........)
• Almost all have a ceiling effect
Not all COX are the same

- COX-1
  - Constitutive variant
  - Mucus production and renal blood flow
- COX-2
  - Inducible
  - Sensitizes nociceptors

NSAIDS

- Have cross sensitivities with aspirin, ibuprofen, and other NSAIDS
- Can delay wound healing

Opioids
Opioids

• Best drug for severe acute pain
• Not used nearly enough by ODs
• Most are addictive and patients can develop tolerance
  – Addiction very unlikely with short term use
• Start all at q 4-6h
• All are compared to morphine for efficacy and potency

Opioids

• No ceiling effect

• Sympathomimetic - miosis, blurred vision, diplopia

Codeine

• Available with acetaminophen
• Most commonly used
• Works in 20 min, peaks at 2 hours
• The Greece of opioids
  – Less toxicity
  – Less addiction potential
  – Less sedation and constipation
Hydrocodone

- With acetaminophen (Vicodin, Lortab)
- 6X more potent than codeine with less sedation and constipation

Oxycodone

- Available with acetaminophen (Percocet)
- 10X effective than codeine
- Less side effects than codeine
- Higher addiction potential

Ultram (tramadol hydrochloride)

- Moderate to severe pain
- Non-narcotic opioid receptor agonist
- Pregnancy Category C
- 50-100mg q4-6 hours
- Side effects
  - Hallucinations
  - Fever
  - Nausea and vomiting
  - Seizure
  - Skin rash
  - Shallow breathing, weak pulse
Neurontin

- Recently failed study for ocular pain control after PRK (JCRS)
- Used for suppressing exaggerated pain and seizures

Non-Narcotics

- Skin patches
  - Lidocaine
  - Capsaicin
- Anticonvulsants
  - Lyrica
  - Neurontin
  - Tegretol
- Antidepressants
  - Cymbalta

Ciliary Spasm

- What about orals?
- Indirect control of pain
- Central nervous control works better than sight specific in the oral class
  - Opioids
Ciliary Spasm - Don’t Pressure Patch

Controlling Ciliary Spasm

- Limit light
- Decrease inflammation
- Steroids and NSAIDS
- Mydriasis (blocks acetylcholine)
  - Cycloplegia does not equate to mydriasis
  - How often do we use Atropine/homatropine?

Don’t Forget the Cycloplegics

- Comfort
- Break synechiae
- Stabilize blood-aqueous barrier
### Cycloplegic Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Max Effect (min)</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tropicamide 0.5, 1%</td>
<td>20-30</td>
<td>3-4 hours</td>
</tr>
<tr>
<td>Cyclopentolate 1, 2%</td>
<td>20-45</td>
<td>1 day</td>
</tr>
<tr>
<td>Homatropine 2, 5%</td>
<td>20-90</td>
<td>2-3 days</td>
</tr>
<tr>
<td>Scopolamine 0.25%</td>
<td>20-45</td>
<td>4-7 days</td>
</tr>
<tr>
<td>Atropine 0.5, 1%, 2%</td>
<td>30-40</td>
<td>1-2 weeks</td>
</tr>
</tbody>
</table>

### Non-Therapeutic Treatments

- Hot compress
- Sunglasses / Hats
- Stay indoors
- Low lighting
- Plus for near
- Patching

### Ciliary Spasm Tip

- Have patient look down and touch upper eyelid to assess pain
3rd Nerve Palsy
• Can be extremely painful
• Start with NSAIDS

Bandage Contact Lens
• Not used nearly enough
• Filamentary or severe punctate keratitis
• Allows a bridge for re-epithelialization and establishment of a normal glycocalyx

Diagnostic Approach
• Complete history, including contact lens use
• Presenting symptoms
• Physical examination
  – Slit Lamp exam
    • Signs
    • Rule out viral/fungal infections
    • Pay attention to the details
Corneal Infection

• Be careful of adding cycloplegic
  – Pain will indicate success of therapy

• Eyelid edema great indicator of infectious etiology

Chronic Pain

• Many types

• Often a chemical or physiological imbalance (not just Mucho Dolor Syndrome)

• We all see it on a daily basis
High IOP in Non-seeing Eyes

• Cyclo-cryo ablation
• Retrobulbar alcohol injection

Vaccines for HZO - Zostivax

• Zostivax is live attenuated herpes zoster (HZ) virus
  – 50% reduction in the incidence of HZ
  – 60% reduction in symptom severity in patients who developed HZ
  – 66.5% reduction in postherpetic neuralgia.

• Must have chicken pox as a child
• May help patients who’ve had HZO already


Thank you