The Pain Game: Exploring Ocular Pain and Inflammation
COPE 43956-PH

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Basics

• Anatomy
• Ocular Anatomy
• Clinical Manifestations
• Treatment
• Control
• Cause \( \rightarrow \) Effect

Anatomy of Pain

• COX enzymes play a key role in inflammation and pain.
  • COX-1 is involved in maintenance of GI mucosa
  • COX-2 enzyme signals pain and inflammation
The Inflammatory Cascade

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
  - Bradykinin
  - Serotonin
  - Histamines
  - GABA
  - Capsaicin
  - Prostaglandins
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
• Dacryoadenitis
• 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
- DOF DAR

- Tell me about your pain
  - Quality
  - Duration
  - Frequency
  - Reproducible factors
  - Associated features

Prescribing for Women

- Certain medications are OK in pregnancy
- Breast feeding
- Consult OB-GYN if necessary

Prescribing for Children

- Children 12 years old and older can be dosed as adults unless otherwise noted
- Look up dosage for child (mg/kg/day)
- Determine how many kg child weighs
  - 1 kg=2.2 lbs
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 afferent 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 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 hypoaesthesia 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

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

- Early-Phase Mediators
  - Phospholipase A2 Activity
  - Arachidonic Acid

- Late-Phase Mediators
  - Lipoxigenase Pathway
  - Cyclic Endoperoxides
  - Prostacyclin (PGI2)
  - Thromboxane A2 (TXA2)
  - Leukotrienes (LTC4, LTD4, LTE4)

- Early-Phase Mediators
  - HHT, MDA
  - Prostaglandins (PGF2α, PGD2)
  - Prostaglandins (PGE2)

- Late-Phase Mediators
  - Leukotrienes (LTC4, LTD4, LTE4)
  - Leukotrienes (LTC4, LTD4, LTE4)
  - Hydroperoxides (5-Heptadienal)
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)

- Durezol QID
- Pred Forte 8x/day
Mean Change from Baseline in Total Symptom Score*

*The 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
PLA2 = A key enzyme involved in the release of arachidonic acid from the cell membrane.

Inflammatory – Arachidonic Acid Pathway: Cyclo-oxygenase (COX) Enzyme

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 trapin")

Unmanageable Pain and Photophobia with Steroids
NSAIDs

• The most underutilized drug class in optometry

Relative IC50s: Rank – Order Greatest to Least Activity

<table>
<thead>
<tr>
<th>Cyclo-oxygenase 2 (COX-2)</th>
<th>IC50 (µm)</th>
<th>Relative Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bromfenac</td>
<td>0.0075</td>
<td>4.10 X</td>
</tr>
<tr>
<td>Aminfenac</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>

Indications for Topical NSAIDs

- Pro-Dwelling inflammation
- Dry eye
- Post-cataract surgery inflammation
- Post-cataract surgery edema
- Pterygium
- Pterygium incision (postoperative)
- Graft
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 NSAI DS)

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**

- 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, Loratab)
- 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

Ulram (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 (ICRS)
- 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>20-60</td>
<td>2-3 days</td>
</tr>
<tr>
<td>Scopolamine 0.05%</td>
<td>20-45</td>
<td>4-7 days</td>
</tr>
<tr>
<td>Atropine 0.5, 1, 2%</td>
<td>20-40</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
Corneal Infection

- Be careful of adding cycloplegic
  - Pain will indicate success of therapy
- Eyelid edema great indicator of infectious etiology

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

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