Ocular and Systemic Pain, and Drug Diversion

CDR Chris Cordes, OD FAAO
Staff Optometrist
Albuquerque Indian Health Center
United States Public Health Service

Disclosure Statement:
• Nothing to disclose

Course Description:
This course presents a review of pain, both ocular and systemic. It reviews ocular and local anesthesia and its relationship to pain management. It then discusses how systemic and topical pain management is used for ocular pain management. Finally, the course reviews the use of opioids and drug diversion and its components.

Course Learning Objectives:
- To understand the physiological pathways and components of ocular pain.
- To review how to manage ocular and systemic pain with both topical and systemic medications.
- To understand drug diversion.

PAIN
• An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.

Pain - Dictionary.com

PAIN and SUFFERING
• Pain is the physical sensations or signals (within your body) that tells you something is happening within your body in relation to an event or situation. Suffering is the interpretation or story that you tell yourself about the pain (i.e. thoughts, judgements, beliefs).

3 Types Nociceptor Pain Receptors
• Nociceptor - Mechanical
  • Respond to mechanical damage such as cutting, crushing or pinching
• Nociceptor Thermal
  • Temperature extremes especially heat
• Poly-modal Nociceptor
  • Respond to all kinds of damaging stimuli including irritating chemicals

Fast-Pain vs. Slow-Pain
• Fast Pain
  • A delta fibers
  • Small myelinated fibers
  • High velocities
  • Nociceptor
  • Sharp, pricking pain, easy to locate
• Slow Pain
  • C fibers
  • Unmyelinated fibers
  • Low velocities
  • Poly-modal
  • Dull, aching, burning sensation
  • Poorly localized
  • Persists for longer time period - more unpleasant

Ocular Pain - Trigeminal Nerve

Ocular and Systemic Pain, and Drug Diversion

CDR Chris Cordes, OD FAAO
Staff Optometrist
Albuquerque Indian Health Center
United States Public Health Service

Disclosure Statement:
• Nothing to disclose

Course Description:
This course presents a review of pain, both ocular and systemic. It reviews ocular and local anesthesia and its relationship to pain management. It then discusses how systemic and topical pain management is used for ocular pain management. Finally, the course reviews the use of opioids and drug diversion and its components.

Course Learning Objectives:
- To understand the physiological pathways and components of ocular pain.
- To review how to manage ocular and systemic pain with both topical and systemic medications.
- To understand drug diversion.
Ocular Pain

- Originates from nociceptors
- Activated by mechanical and chemical stimulations.
- Processed into Trigeminal Nerve Pathway

Local Anesthetics

- Drugs which produce reversible conduction blockage of nerve impulses.
- Completely reversible with no evidence of structural damage to the nerve fibers.
- Loss of sensation without loss of consciousness.
- Except Cocaine, all clinically used local anesthetics are synthetic and poorly water soluble, weakly basic and aromatic amines.

Ocular Pain Causes:

- Physical
  - Tachycardia
  - Hypertension
  - Peripheral Vasconstriction
  - Tachypnea
- Emotional
  - Poor Sleep
  - Anxiety
  - Uncooperativeness

Local Anesthetics - “CAINES”
Aromatic Ring

Aromatic rings (also known as aromatic compounds or arenes) are hydrocarbons that contain benzene, or some other related ring structure. Benzene, C₆H₆, is often drawn as a ring of six carbon atoms, with alternating double bonds and single bonds.

Ester Linkage

In an ester molecule, the bond connecting the atom doubly bonded to oxygen and the oxygen atom bearing the alkyl or aryl group is called the ester bond or ester linkage.

Hydrocarbon Chain

A hydrocarbon chain is a molecule that consists of entirely hydrogen and carbon. They are the simplest of the organic compounds and may be a liquid, gas, or solid. There are many types of hydrocarbon chains, including alkanes, alkenes, alkynes, cycloalkanes, and arenes. They can be branched, linear, or cyclical.

Tertiary Amine Group

- Tertiary amine (3° amine): An amine in which the nitrogen atom is directly bonded to three carbons of any hybridization which cannot be carbonyl group carbons. In organic chemistry, amines are compounds and functional groups that contain a basic nitrogen atom with a lone pair.

Mechanism of Action

- Prevent both generation and conduction of nerve impulses.
- Work on cell membrane.
- Block the transient increase in membrane permeability to sodium ions which normally occurs during depolarization of the membrane.
- Specific binding site located within voltage-gated sodium channel.
- Greater the hydrophobicity, greater affinity for binding.

Duration of Action

- Proportional to the time in contact with the nerve tissue.
- As hydrophobicity increases, so does potency and duration.
- As lipid solubility increases, the potency also increases, however, so does the toxicity.
- Ester compounds are topical and rapidly hydrolyzed.
- Amine compounds are injected and processed by the liver.

Topical Anesthetics

- Topical Anesthetic efficacy is determined by their ability to suppress corneal sensitivity.
- There is a point at which no further increase in activity of the drug occurs: maximum effective concentration.
- Increasing dosage above maximum effective concentration only increases risk.
- Optimum Effective Concentration can be less than maximum.
- In general, 0.5% is less irritating, the maximum effective concentration of 1.0%.
- TOPICAL APPLICATION OF TWO OR MORE LOCAL ANESTHETICS DOES NOT PRODUCE AN ADDITIVE EFFECT.

Ocular Anesthetics

- Tetracaine 0.5% and 1.0%
- Ester of para-aminobenzoic acid (PABA)
- Onset of action: 10-20 seconds
- Lasts for 10-20 minutes
- Use for cataract surgery
- Should NOT be injected.
- Reported 1% can last up to 1 hour and be used for cataract surgery.
- Should NOT be injected: patient and potentially toxic over 1.5mg/kg.
- Adverse Reactions:
  - Stinging
  - Greater corneal compromise (microvilli, cell membrane)
  - Allergy

- Proparacaine 0.5%
- Ester of para-aminobenzoic acid (PABA)
- Onset of action: 10-20 seconds
- Lasts for 10-20 minutes
- Does not penetrate into the cornea or conjunctiva as well as tetracaine.
- Unpreserved solutions may be corrosive to the conjunctiva.
- Discard discolored solutions of Proparacaine.
- Adverse Reactions:
  - Irritating or stinging
  - Hypersensitivity
  - Corneal thickness changes.
Ocular Anesthetics

- **Benoxinate 0.4%**
  - Ester of para-aminobenzoic acid (PABA)
  - Similar duration and effect as Tetracaine and Proparacaine 0.5%
  - 10-20 minutes for 10-20 minutes

- **Advantages:**
  - Always combined with a vital dye (Sodium Fluorescein)
  - Sodium Fluorescein alone is good Pseudomonas aeruginosa medium
  - However in combination with Benoxinate it is bactericidal

- **Adverse Reactions:**
  - Stinging
  - Allergy - very low profile
  - Can increase or decreased corneal thickness +/- 10um

Adverse Drug Reactions/Side Effects

- Risk of those over 50 to get Superficial Punctate Keratitis
  - More risk for filamentary keratitis and corneal edema
  - Repeated administration of topical ocular anesthetics should be avoided. It significantly inhibits healing of the corneal epithelium.
  - Systemic absorption of topical anesthetics or injection of them, can cause CNS depression, hypotension, low/absent pulse which can result in respiratory failure
  - Allergic/hyperreactivity reactions are uncommon, but mainly with ester compounds. Amine compounds occur at a much lower rate.
  - Occur 5-10 minutes after instillation

Self Administration of Topical Anesthetics

- DON'T DO IT
  - Leads to infiltrative keratitis and loss of eye
  - Occurs from 6 days of usage to 6 weeks
  - Loss of corneal epithium
  - Inhibits healing of epithelial defects, loss of neovascularization
  - Stromal Edema
  - Descemet's Folds
  - Yellow-White Ring around area of diseased area

Adverse Drug Reactions/Side Effects

- No life threatening allergic responses to topically applied ocular anesthetic has ever been reported.
  - Injected medications have a very rare chance at anaphylactoid responses
  - Psychomotor Fainting can happen but mostly it is anxiety driven
  - Contraindications
    - Hypersensitivity
    - Liver Disease (injectable)
    - Systemic Anti-cholinesterase agents (high dosages of topical anesthesia)
    - Dry Eye Testing
    - Perforating Ocular Injury (BAK)
    - Cultures (lids/conjunctiva)

Ocular Pain Treatment

- **Peripherally Acting Agents**
  - Act on peripheral pain receptors
  - Block Cyclooxygenase Pathway

- **Anesthetic Agents**
  - Nociceptive signal interrupted
  - Sodium Channel Block in nociceptor

- **Centrally Acting Agents**
  - Works on Central Nervous System blocking both pain and emotional response
  - Opioids
  - Non-Steroidal Anti-Inflammatory
    - Inhibit prostaglandin E and inactivate cyclooxygenase
    - Analgesic mostly, not anti-inflammatory until 3-4 grams
    - GI disturbance is most common ADR
  - Non-salicylates
    - Ibuprofen
    - Motrin, Advil, etc.
    - Naproxen
    - Aleve
    - Celecoxib
    - Celebrex

- **NSAID's**
  - Work by inhibiting the cyclooxygenase enzymes (COX-1 or COX-2). In cells, these enzymes are involved in the synthesis of key biological mediators, namely prostaglandins, which are involved in inflammation, and thromboxanes, which are involved in blood clotting.

- **Classifications**
  - Sulfonamides
    - Ibuprofen or naproxen are good examples.  In small doses, they can be used to decrease pain and inflammation.
  - For differentiation is well known (ASA)
  - Non-salicylates
    - Most used for anti-inflammatory but also effective analgesics
    - Propionic Acid and COX-2 Inhibitor classes
    - Both have a Ceiling Effect - repeated/chronic use does not cause tolerance or addiction

- **Adverse Effects:**
  - Increased Attention, confusion, headache, GI risks
  - Avoid in renal Patients, Pregnancy and breast feeding

Non-Steroidal Anti-Inflammatory

- Sulfonamides
  - Ibuprofen or naproxen are good examples.  In small doses, they can be used to decrease pain and inflammation.
  - For differentiation is well known (ASA)
  - Non-salicylates
    - Most used for anti-inflammatory but also effective analgesics
  - Propionic Acid and COX-2 Inhibitor classes
  - Both have a Ceiling Effect - repeated/chronic use does not cause tolerance or addiction

- Adverse Effects:
  - Increased Attention, confusion, headache, GI risks
  - Avoid in renal Patients, Pregnancy and breast feeding
Acetaminophen

• Little or no anti-inflammatory properties
• Superior safety profile
• DO NOT EXCEED 4 grams daily
• 12-25 grams is fatal, 7.5 grams is overdose
• Use with caution in chronic alcoholics and preexisting liver conditions
• Safe in pregnancy and breastfeeding in proper dosages

Cycloplegia

• Inhibit the actions of acetylcholine on muscarinic sites –
  Atropine/Scolopamine
• Specificity on the Iris Sphincter Muscle and Ciliary Body
• Innervation originates at the Edinger-Westphal Nucleus
• Paraganglionic parasympathetic fibers travel within CNIII
• Proceeds to the Ciliary Ganglion and synapses with postganglionic fibers
• Enter the eye through short ciliary nerves
• Short ciliary nerves run to the muscarinic receptors (acetylcholine) in
  the Iris Sphincter and Ciliary Body
• Thus, decreasing the activity of the sphincter and ciliary body

Cycloplegics

• Atropine – Naturally occurring alkaloid from belladonna plant
• Homatropine – Partially synthetic, partial natural
• Scopolamine – Alkaloid from plants, shorter duration of action
  Angel’s Trumpet
• Cyclopentolate – Synthetic derivative of Tropic Acid, available in 2018
• Opioids

Opioids

• Opioids/Opiums
• Opium
• Heroin
• Codeine
• Oxycodone
• Hydrocodone
• Hydromorphone
• Hydromorphone
• Naloxone
• Methadone
• Morphine
• Fentanyl
• heroin
• Oxycodone
• Hydromorphone
• Hydrocodone
• Propoxyphene
• Hydromorphone
• Opioids work by binding to various receptors in the brainstem, brain
  and spinal cord, mimicking natural endorphins.
• Effect both the sensation (pain) and the emotional component.

Opioid ADR’s

• Nausea
• Sedation
• Confusion
• Constipation
• Cough Suppression
• Respiratory Depression
• Miosis
• Diplopia
• Addiction

DEA Schedule

• Schedule I
  • Schedule I drugs, substances, or chemicals are defined as drugs with no currently accepted
    medical use and a high potential for abuse. Some examples of Schedule I drugs are:
    Heroin, LSD, Ecstasy, Marijuana, and Peyote
• Schedule II
  • Schedule II drugs, substances, or chemicals are defined as drugs with a high potential
    for abuse, with use potentially leading to severe psychological or physical dependence.
    Some examples of Schedule II drugs are:
    Vicodin, Codeine, Methadone, Hydromorphone, and OxyContin

Opioid Strength Comparisons

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Strength (Code)</th>
<th>Normalized (300 mg)</th>
<th>Strength (Code)</th>
<th>Normalized (300 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>60 mg</td>
<td>38 mg</td>
<td>adolone</td>
<td>60 mg</td>
</tr>
<tr>
<td>Meperidine</td>
<td>50 mg</td>
<td>33 mg</td>
<td>Meperidine</td>
<td>50 mg</td>
</tr>
<tr>
<td>Morphine</td>
<td>25 mg</td>
<td>17 mg</td>
<td>Morphine</td>
<td>25 mg</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>5 mg</td>
<td>4 mg</td>
<td>Fentanyl</td>
<td>5 mg</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1 mg</td>
<td>1 mg</td>
<td>Hydromorphone</td>
<td>1 mg</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>15 mg</td>
<td>10 mg</td>
<td>Oxycodone</td>
<td>15 mg</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>10 mg</td>
<td>7 mg</td>
<td>Hydrocodone</td>
<td>10 mg</td>
</tr>
<tr>
<td>propoxyphene</td>
<td>20 mg</td>
<td>13 mg</td>
<td>propoxyphene</td>
<td>20 mg</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>20 mg</td>
<td>13 mg</td>
<td>Hydromorphone</td>
<td>20 mg</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>5 mg</td>
<td>4 mg</td>
<td>Fentanyl</td>
<td>5 mg</td>
</tr>
<tr>
<td>Methadone</td>
<td>20 mg</td>
<td>13 mg</td>
<td>Methadone</td>
<td>20 mg</td>
</tr>
</tbody>
</table>
DEA Schedule

• Schedule III

Schedule III drugs, substances, or chemicals are defined as drugs with a moderate to low potential for physical and psychological dependence. Schedule III drugs abuse potential is less than Schedule I and Schedule II drugs but more than Schedule IV. Some examples of Schedule III drugs are:

- Products containing less than 90 milligrams of codeine per dosage unit (Tylenol with codeine), ketamine, anabolic steroids, testosterone

• Schedule IV

Schedule IV drugs, substances, or chemicals are defined as drugs with a low potential for abuse and low risk of dependence. Some examples of Schedule IV drugs are:

- Xanax, Soma, Darvon, Darvocet, Valium, Ativan, Talwin, Ambien, Tramadol

• Schedule V

Schedule V drugs, substances, or chemicals are defined as drugs with lower potential for abuse than Schedule IV and consist of preparations containing limited quantities of certain narcotics. Schedule V drugs are generally used for antidiarrheal, antitussive, and analgesic purposes. Some examples of Schedule V drugs are:

- Cough preparations with less than 200 milligrams of codeine or per 100 milliliters (Robitussin AC), Lomotil, Motofen, Lyrica, Parepectolin

Optometry and Opioids (02/2020)

- Cannot RX: DC, Guam, HI, MD, MA, NY, PR, VI, CNMI
- Schedule III Limited: AL, FL, ME, NH, PA, TX, VT, WY
- Schedule II Limited: IN (Tramadol), MN, MS
- TX can administer Schedule II, FL APAP with Codeine and Tramadol

- Schedule II ONLY HYDROCODONE: AK, AR, AZ, CO, DE, GA, IL, KY, MI, NM, NJ, OH, OK, OR, RI, SC, UT, WI, WV, VA, WA, WY
- Schedule II Hydrocodone, Tramadol, Codeine CA
- Schedule IV Limited: CT, ID, IA, LA, KS, MO, ND, NH, NY, SD*, TN
- SD Limited to 30-day supply
- October 6th, 2014 - DEA reclassifies Hydromorphone

Drug Diversion

- https://www.deadiversion.usdoj.gov/
- The use of prescription drugs for recreational purposes
- The diverting of prescription drugs for other than their intended purpose.
- From CMS:

Drug diversion is the illegal distribution or abuse of prescription drugs or their use for purposes not intended by the prescriber. The diversion of prescription drugs may occur at any point as prescription drugs are distributed from the manufacturer to wholesale distributors, to pharmacies, and ultimately to the patient. Members of the medical profession may also be involved in diverting prescription drugs for recreational purposes, relief of addictions, monetary gain, self-medication for pain or sleep, or the alleviation of withdrawal symptoms.

Drug Diversion – REPORT IT!

- Local law enforcement and local fraud alert networks
- DEA, for reporting theft or loss of controlled substances: http://www.deadiversion.usdoj.gov/antiphony/disposal
- U.S. Department of Health and Human Services, Office of Inspector General (HHS-OSG) by e-mail at OPIOsis@oig.hhs.gov
- Telephone at 1-800-HHS-TIPS (1-800-447-8477)
- TTY: 1-800-377-4950

Drug Diversion – Turn ins

- https://apps.deadiversion.usdoj.gov/pubdispsearch/spring/main?execution=e1s1
Case Study
• 48 yo Native American Male- Assaulted with Fist x 3 days ago
• Lost Glasses (i.e. never got them)
• All entrance testing normal
• Refraction:
  • OD:
    -6.00
    -2.50x177
    20/25
  • OS:
    -6.50
    -1.75x010
    20/25

Acetaminophen and NSAID
• Alternating OTC medications consistently found to provide adequate acute pain relief
• Start with either at initial dosage
• Alternate every 2 hours with minimal dosage
• 500mg Extra Strength Tylenol to Start (6am)
• 200mg Ibuprofen (8am)
• 325mg or 500mg Tylenol (10am)
• 200mg Ibuprofen (Noon)
• 325mg or 500mg Tylenol (2pm)
• 200 mg Ibuprofen (4pm)
• 325mg or 500mg Tylenol (6pm)
• 2500 mg Tylenol, 800 mg Ibuprofen or 2000mg Tylenol 1000mg Ibuprofen

Any NSAID
• Naproxen BID
• Ibuprofen 400mg, 600mg, 800mg TID
• Acetaminophen 150/325mg q6-8 hours
• Should be your "workhorse" medication for any acute short term pain relief.

ICE PACKS
• Don’t forget about ICE!
• Every 2 hours for 15-20 minutes for 72 hours.

A bit of everything...
• 76 year old Pueblo Male presents with Swollen Left Upper Eyelid (May 2015)
• Established patient, multiple co-morbidities
  • Diabetes, Chronic Pain (opioid management), Hypertension, Neuralgia, Sleep Apnea, Obesity and Asthma

URTI Background
• The upper respiratory tract includes:
  • Mouth
  • Nose
  • Throat
  • Sinus
  • Ear (middle ear)
  • Larynx (voice box)
  • Trachea (windpipe)
• Often referred to as “colds”
• Viral or bacterial

Follow-up
• Patient returns to the ER, stating no improvement in URTI
• Patient is given 2 grams of Intramuscular Steroid
• Stopped taking Augmentin
• Patient is now on Steroids

CASE HISTORY
• 76 year old Pueblo Male presents to the ER/Urgent Care
• Upper Respiratory Infection
• Augments
• Prednisone 40mg PO
Treatment

- Started on Augmentin 875/125mg BID x 14 days
- Can alter based on allergies
- Prefer less total dosages (BID)
- Started on Acyclovir 800mg 5x/day x 7 days (formulary)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Initial Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zovirax (Acyclovir)</td>
<td>800mg 5x/day PO</td>
</tr>
<tr>
<td>Famvir (Famciclovir)</td>
<td>500mg tid PO</td>
</tr>
<tr>
<td>Valtrex (Valacyclovir)</td>
<td>1000mg tid PO</td>
</tr>
</tbody>
</table>

Follow-up

- Patient returns for 2 day follow up
- Pre-Septal is looking better
- Zoster looks the same, definitely not worse
- Pain is WORSE
- Already taking Gabapentin, Percocet daily
- Capsaicin Cream: Pharmacy/Quick Order
- Amitriptyline 25mg PO TID

Over the next 6 Weeks

- Severe Post Herpetic Neuralgia
- Cannot sleep at times
- Cannot function daily
- Taking all medications
- Pre-Septal Resolved in 7 days
- Eventually referred to pain management clinic
- Steroids—can/did make it worse?
- Small Studies can be beneficial
- Large Studies can make it worse

Conclusion

- Work with your Pharmacist
  - ***if you don’t have one, work to get one!***
  - Sometimes modern medicine is pushed for answers
  - Get background information:
    - Case history
    - Recent medications

Thanks!

Feel free to email
Christopher.Cordes@ihs.gov
Friend me on Facebook, etc.