Opioid Induced Hyperalgesia

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Disclosures

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Learning Objectives

- Define and demonstrate evidence for the presence of OIH
- Define 2 likely mechanisms for OIH
- Recognize clinical clues for OIH in patients
- Formulate treatment options for patients with OIH
Outline

- DEFINITION
- DOES ITEXIST?
- WHAT IS IT?
  - Anatomical possibilities
  - Neurochemical possibilities
- CLINICAL PRESENTATION
- TREATMENT
**Definition**

- Opiate induced hyperalgesia (OIH) is best considered a state of nociceptive sensitization caused by exposure to opioids.

Chu 2008
Does OIH Exist

- Over 1500 articles related to OIH in humans and animals
- Animal studies, generally support the presence of OIH
- Human studies, some controversy, clinically relevant

Angst 2006, Fishbain 2009, Yi 2015
Does OIH Exist

HUMAN STUDIES

- Opiate addicts
  - Tends to support OIH
- Perioperative opiates
  - Mixed results
- Experimental exposure
  - Best evidence
- Controlled studies
  - Few
Opioid Addicts

- Former opiate addicts on methadone
- Found to have an increased sensitivity to cold pressor, though hyperalgesia to electrical or mechanical pain was weak or absent
- Confounded by
  - Effect of length of exposure
  - Pre-addiction quality of pain tolerance
  - Genetic predisposition

Perioperative Opioid Exposure

- Fentanyl and remifentanil exposure primarily, with mixed outcome
  - Preop exposure leads to increased postoperative opioid consumption, or peri-incisional wound allodynia and hyperalgesia (Joly 2005 Chia 1999)
  - Preop exposure vs naïve, undergoing GYN or GI surgery with no difference in postoperative consumption of opioids (Lee 2005 Hansen 2005 Cortinez 2001)
Acute Opioids Exposure in Healthy Volunteers

- Opiate exposure in volunteers that are opiate naïve
  - Brief hyperalgesia to mechanical, cold pressor, and electrical stimuli
  - Usually lasting 30-90 minutes and resolve by the next day

- Fishbain literature review (2009)
  - This is primary model showing any significant evidence for OIH in the human literature

Prospective Observational Studies in Chronic Pain Patients

- Chu (2006), with a small N and using MS at 75 mg per day max for 1 month, found significant hyperalgesia and analgesic tolerance in cold pressor model but not in heat model
Prospective Observational Studies in Chronic Pain Patients (cont’d)

- OIH with hydromorphone
  - 30 patients over 4 weeks
  - Hydromorphone to 24 mg per day max
    - Washout from other opiates
    - ER hydromorphone
  - Clinical and experimental pain response
    - OIH measured by CP and heat
- OUTCOMES
  - Analgesia and OIH concurrently
  - Dose dependent

Suzan et al 2013
What is MOA

- **Peripheral**
  - TRP-V1, cytokines, beta-2 adrenergic receptors

- **Spinal**
  - NMDA, dynorphin, cytokines, substance P, 5HT3
  - Dorsal horn is primary site of action

- **Supraspinal**
  - PAG with 5HT, NE, opioid
  - RVM with opioid “on” cells, 5HT
  - Anterior cingulate

- **Glial cell activation**

Glial Cell Activation
Glial Cell Activation (cont’d)

- Microglia > astrocytes
  - Activation causing cascade of events in both the brain and spinal cord

- Triggers
  - Nerve damage byproducts
  - Intracellular debris
  - Heat shock proteins
  - Inflammatory stressors
  - Opioids
  - ETOH

DeLeo 2004, Bianchi 2007)
Glial Cell Activation (cont’d)

- Activation releases
  - Proinflammatory cytokines (interleukin 1&6, TNF, ATP, NO, prostaglandins, substance P, etc)

- Increase neural activity due to
  - Upregulate AMPA, NMDA
  - Downregulate GABA and other modulating CNS activities

- Feedback loop
  - Ongoing activation of the CNS, including the “illness response”

Glial Cell Activation (cont’d)

- Appears to be independent of classic opiate receptors
  - Toll like receptor 4 (TLR4)
  - Nonstereoselective, unlike opioid receptors
  - Unique treatment options
- Mu receptor may not be involved in OIH

Alternative Mu Opioid Receptor

- **Mu opiate receptor 1 (MOR1), G-protein receptor with 7 domains**
  - Has standard inhibitory response, through decrease in Ca++, NO, and cAMP

- **MOR1K is G-protein receptor with only 6 domains**
  - Has atypical excitatory response, showing increase in Ca++, NO, and cAMP
  - Shown to cause OIH in mouse model

Diatchenko 2010, Folabomi 2015
Diffuse Noxious Inhibitory Control (DNIC)

- Endogenous pain inhibition
  - Pain inhibits pain

- Nociceptive input form C and A delta
  - Wide dynamic range neurons at DH inhibited
  - Inhibition originates from upper CNS centers
DNIC Measurement

- Pressure pain threshold (PPT)
  - First pressure noted

- Pain tolerance (Ptol)
  - Intolerable

- Second painful stimuli applied to distant location and PPT measured again
  - Delta of PPT under both conditions is DNIC
Clinical Presentation

- OIH IS NOT
  - Tolerance
  - Progression of lesion
  - Withdrawal pain
  - Medication effects
    - Generic
    - Formulation changes (oxycodone ER)
Clinical Presentation

- OIH (for hours to days) with either acute or chronic opioid dosing
- OIH may be more prone in mechanical pain rather than electrical or thermal (though methadone addicts don’t show this)
- OIH with high or low dose opioids (though larger doses were faster and longer)
- Route of administration not important
- Shorter half life tended to give more rapid tolerance and OIH
- Relative potency was not a factor
- Sensitization lasted long after direct OIH effects were resolved
- Pain at a site different than the original pain may be a marker for OIH. Generalized pain or flare of previously resolved pain

Angst and Clark 2006, Bekhit 2010
Clinical Presentation

- Rossback 1880

“When dependence on opioids finally becomes an illness of itself, opposite effects like restlessness, sleep disturbance, hyperesthesia, neuralgia, and irritability become manifest.”
Clinical Presentation

- Sleep reduced consistently
- Irritability
- Thoughts racing
- Physical agitation
  - Myoclonic jerking
  - Night time movements
- Distractible
- Impulsivity
Irritable Mania, DSM V Criteria

- Distinct period of abnormally and persistently elevated, expansive or irritable mood, lasting at least 1 week

- With 3 (or more) of the following symptoms have persisted (4 if the mood is only irritable) and have been present to a significant degree:
  - Inflated self-esteem or grandiosity
  - Decreased need for sleep (eg, feels rested after only 3 hours of sleep)
  - More talkative than usual or pressure to keep talking
  - Flight of ideas or subjective experience that thoughts are racing
  - Distractibility
  - Increase in goal-directed activity or psychomotor agitation
  - Excessive involvement in pleasurable activities that have a high potential for painful consequences

- Sufficiently severe to cause marked impairment in occupational or usual social activities or relationships
- The symptoms are not due to the direct physiological effects of a substance (eg, a drug of abuse, a medication, or other treatment)
Clinical Presentation

- Not to be given the dx of bipolar disease
  - Type I, II, III
- Looks like Cluster B, some obsessive or mixed mood
- Clinically associated with:
  - Family history of mood instability consistent with BAD
  - Personal mood instability
    - Personality d/o
    - Severe mood variability
    - Bipolar dx
Adjunctive Treatment

- NMDA receptor antagonists (NMDARAs)
  - Ketamine
  - Dextromethorphan
    - 3 RCTs with 1:1 MS and dextro, no different than MS alone
    - Nuedexa
  - Memantine
    - Open channel NMDARA

- GABA-A antagonist
  - Propofol

- Alpha-2 agonist
  - Clonidine
  - Dexmedetomidine

Opioid Treatment

- Opioid rotation
- Opioid reduction
- Methadone (levorphanol)
  - NMDA receptor antagonist
- Buprenorphine

TLR-4 Treatment

ANTAGONIST

- Ibudilast
  - Asthma and stroke tx, now AV411
- Amitriptyline
- Imipramine
- Cyclobenzaprine
- Naloxone/naltrexone
Glial Cell Inhibitors

REDUCE MIGRATION

- Minocycline (TCN derivative)
- Cannabinoids (CBR2 in particular)
Clinical Approach

- OIH as unintended clinical outcome
- OIH as tool
- OIH as club
Clinical Approach (cont’d)

- Identify
  - Sleep disturbance primary
    - Medicated?
  - Reported stimulation from the opiate
  - Irritability
    - Collateral, inconsistent history, staff reactions
  - Impulsivity
    - Medication, behavioral dysregulation
Clinical Approach (cont’d)

- Educate, enlist cooperation
  - Predict outcome
  - Curious about change in behavior with opiates
    - Collateral information supporting change in behavior
  - Not about opiate use per se
Clinical Approach (cont’d)

- **Rotate**
  - Oxycodone, fentanyl, hydrocodone
  - Oxymorphone
  - MS, hydromorphone, methadone, levorphanol
  - Buprenorphine
  - Tapentadol

- **Mood stabilize**
  - Lamotrigine, aripiprazole
  - Duloxetine

- **Stimulating agents to help DC of opioids**
  - Replacement
  - Bupropion, modafinil, atomoxetine
  - Dextroamphetamine, methylphenidate
Clinical Approach (cont’d)

- Opioid holiday
  - Tapering schedules
  - Effective “holiday” time unknown
  - Is OIH reversible
  - Pain management in the interim
  - PRN opiates
Summary

- OIH exists
- Varied mechanisms
  - Multiple mechanisms
  - Glial cell activation as common denominator?
- CNS is primary
  - Cord and brain
- Clinical appearance
  - Increasing pain with increasing opioid activation
- Treatment options
  - Rotation, education, replacement, holiday trial
THANK YOU