Opioid Induced Hyperalgesia
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Disclosures

- Receive consultant fees from Alere, INSYS, XenoPort, Zogenix and Nektar.
- Speaker bureau fees from Teva, Iroko, Salix, Purdue, Depomed, XenoPort and Mallinckrodt.
After completing this educational activity, participants will be better able to:

- Discuss the mechanisms of opioid-induced hyperalgesia.
- Describe clinical examples of hyperalgesia.
- Discuss possible strategies to address and treat opioid-induced hyperalgesia.
- Demonstrate objective pain assessment measuring tools.

Opioid analgesics

- Opioids have risen steadily for chronic pain
- Among the most common Rx
  - >250 million prescriptions in the US
- Duration of treatment varies
  - Post-op pain → days to weeks
  - Cancer pain → more sustained
  - Chronic pain conditions like OA or back pain → possibly Rx for decades → with controversial evidence supporting long-term effectiveness
- Concerns remain about dependence, addiction, adverse side effects and need for dose escalation
Opioid Induced Hyperalgesia- OIH

- There is accumulating evidence that opioid therapy might not only be associated with the development of tolerance, but also a hypersensitivity condition referred to as opioid-induced hyperalgesia (OIH)
- Studies in pain patients, opioid addicts, postsurgical patients and volunteers suggests that exposure to opioids may be associated with an increased sensitivity and perception of pain
- Some chronic pain patients need escalating doses of opioids to maintain adequate analgesia
  - But each escalation seems less beneficial???

OIH: Defined

- A state of nociceptive sensitization caused by a paradoxical response upon exposure to specific or certain amounts of opioids
- Type of pain experienced may be same as underlying pain, but usually different
- May represent a distinct, definable, and characteristic phenomenon that could explain treatment failure or loss of opioid efficacy in some cases.
Clinical Presentation

- OIH is a condition manifested clinically as hyperesthesia (dramatically ↑ sensitivity to painful stimuli) and/or allodynia (pain elicited by a normally nonpainful stimulus)
- May be accompanied by other signs of opioid toxicity such as myoclonus, delirium and seizures
- Characterized by decreasing efficacy of the drug that cannot be overcome by increasing dose
  - Increasing dosage would worsen pain
  - Pain improved by reducing or eliminating opioid

Do exogenous opioids suppress the endogenous opioid system, leading somehow to increased sensitivity?

- Basic science evidence of OIH in numerous animal models and clinical evidence established in multiple human studies
- Although the precise mechanism of OIH has not been elucidated, it is thought to be an imbalance of pronociceptive and antinociceptive processes.
- Occurrence in humans at low doses used clinically still controversial
  - Might one be genetically susceptible to OIH?
**OIH Mechanisms:**

- Pathophysiologic theories
  - Central glutaminergic dysfunction
    - NMDA receptor activation (similar mechanisms to tolerance?)
  - Spinal dynorphins = excitatory neuropeptides released with exogenous opioid exposure
    - Sensitization of primary afferent neurons from enhanced production/release of excitatory neurotransmitters and the suppressed reuptake of inhibitory neurotransmitters
  - Descending facilitation- hyperexcitable nociceptive processing

**Clinical Evidence**

- In former opioid addicts
  - A number of studies examined pain sensitivity in opioid addicts maintained on methadone using cold pressor, electrical, & pressure pain models
  - ↑ sensitivity to cold pressor pain in these pts compared with matched or healthy controls
- Other studies fail to show hyperalgesia in other pain models (electrical/thermal)
- Suggestive that OIH develops differently for different types of pain
- Multiple observations support OIH hypothesis but many limitations with these studies
Perioperative Opioid Exposure

- 2 prospective controlled clinical studies reported increased post-op pain despite increasing opioid dose
- Others have shown no significant difference in post-op pain sensitivity based on perioperative/intraoperative opioids
- These observations provide mixed support for hypothesis of development of OIH after acute perioperative opioid exposure

OIH in Healthy Volunteers

- Several studies examined development of OIH in humans after short-term exposure to opioids
  - Remifentanyl infusions
- Multiple investigations provided direct evidence for development of OIH in humans using models of secondary hyperalgesia and cold pressor pain
  - Antagonist induced hyperalgesia
OIH in Chronic Pain Patients

- OIH may be important in managing chronic pain patients
- Hay et al – pts with chronic pain rx with opioids and methadone-maintained pts >> hyperalgesic by cold pressor test, but no aldynia
- Cohen et al – opioid dose and duration of rx directly correlated with pain intensity and unpleasantness scores compared with pts not receiving opioid rx
- Concluded that results bolster preclinical and experimental pain models demonstrating enhanced pain perception in pts receiving opioids

OIH Most Commonly Seen…

- In patients receiving high opioid doses
- There are multiple case reports and some studies; however, there has not been any systematic evidence
- Many reports involve intrathecal administration of morphine, raising the possibility that metabolites, such as M3G that is known to cause neuroexcitation, could contribute to hyperalgesia
- High dose OIH does not seem to be modified by opioid antagonists
  - Suggesting NMDA, glycine …

Treating OIH

- Reduce, rotate or completely taper opioid
  - Rational polypharmacy
- Diminish hyperexcitability
  - AEDs, Ads
  - NMDA antagonists
    - Ketamine, Dextromethorphan
    - Namenda, Methadone
    - Alpha 2 agonists
- Multiple published reports have shown that opioid rotation to methadone significantly improved or resolved suspected OIH


Ketamine

- Perioperative administration of low-dose ketamine might modulate the expression of OIH or analgesic tolerance
  - it reduces postoperative wound hyperalgesia after acute intraoperative opioid exposure.
- However, the clinical significance of these benefits still needs to be demonstrated in larger prospective studies and in chronic pain patients
Gabapentin improves cold-pressor pain responses in methadone-maintained patients

- Individuals on methadone maintenance (MM) are demonstrated to be hyperalgesic to cold-pressor pain in comparison to matched controls and ex-opioid addicts.
- Interestingly, opioids induce hyperalgesia via many of the same neuro-inflammatory and central sensitization processes that occur with the development of neuropathic pain.
- Changes in cold-pressor pain threshold and tolerance following a 5-week trial of GPN (titrated to 2400mg/day) were evaluated.
- Utilizing change scores from baseline, significant improvements in cold-pressor pain threshold and pain tolerance were observed at both peak and trough methadone levels (p<0.05).
- These results support that GPN, as prescribed for the treatment of neuropathic pain, is effective in decreasing OIH in patients who are abstinent and stable in methadone treatment.


Buprenorphine

- Buprenorphine shows an enhanced ability to treat hyperalgesia experimentally induced in volunteers compared to fentanyl.
- As mentioned, spinal dynorphin (a known kappa receptor agonist) increases during opioid administration contributing to OIH.
- Buprenorphine is a kappa receptor antagonist and may be unique in its ability to treat chronic pain and mitigate OIH.

Summary

- Clinicians should suspect OIH when opioid treatment effect seems to wane in the absence of disease progression, particularly if found in the context of unexplained pain or diffuse allodynia unassociated with the original pain, and increased levels of pain with increasing dosages.
- Treatment involves reducing the opioid dosage, tapering them off, or supplementation with NMDA receptor modulators.

Lee M, Silverman S. Pain Physician 2011; 14:145-161

We Need to Know!

- What are the time courses and magnitude of opioid tolerance and hyperalgesia in patients treated with opioids?
- How likely are they to occur?
- Do different opioids or dosage regimens alter the probability of OIH/tolerance?
- To what degree does OIH limit the utility of opioids for chronic pain?
THANK YOU

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