Clinical Resource Guide: Opioid-Induced Hyperalgesia

INTRODUCTION TO HYPERALGESIA

Hyperalgesia is described as an abnormally heightened sensitivity to pain. It is thought to occur due to interruptions or changes in how the nervous system processes pain. An example is feeling intense pain when touching a recently sunburned area of skin. While it is normal to feel pain after a burn, hyperalgesia causes your nervous system to overreact in response to the painful stimulus. Though there can be various causes of hyperalgesia, this document will focus on opioid-induced hyperalgesia or OIH. In OIH, pain significantly worsens despite opioid dose escalation attempts. Since pain is a commonly experienced symptom at end of life that is often managed with opioids, hospice patients are at greater risk. It is important to be aware of the clinical presentation and management of OIH.

Pharmacist Corner Objectives

1.) Learn to recognize the signs of hyperalgesia.
2.) Explore potential causes and mechanisms of OIH.
3.) Describe potential treatment methodologies to address OIH.

SIGNS OF OPIOID-INDUCED HYPERALGESIA

Opioid-induced hyperalgesia will typically present as extreme pain or a pain crisis, often **despite an opioid dose increase**. Patients may experience an increase in generalized pain extending beyond an injured body part and an enhanced pain response to stimuli. Paradoxically, increasing the opioid dose will further increase pain with OIH.

Patients with hyperalgesia:

- Have a diminished pain threshold with increased pain sensitivity.
- React more strongly. Pain feels more intense because pain receptors are firing more often than they would under normal conditions.

- Respond faster to pain signals. The body prioritizes pain signals, decreases response time and reacts faster in response to repeated pain signals.
- Continue to transmit pain signals that don't stop firing even after a painful event is over.

POSSIBLE CAUSES OF OPIOID-INDUCED HYPERALGESIA

The proposed mechanisms contributing to OIC are complex and involve chemical and molecular changes in the spinal cord and brain. Potential causes include:

1.) Activation of central glutaminergic system via increased glutamate available to NMDA receptors
2.) Toxic effect of opioid metabolites (e.g. morphine-3-glucuronide or hydromorphone-3-glucronide)
3.) Increase in spinal dynorphin activity
4.) Enhanced descending facilitation from the rostral ventromedial medulla
5.) Activation of intracellular protein kinase C

TREATMENT METHODS

Strategy	Comments
Opioid dose reduction	• Wean slowly, especially from high doses, to minimize withdrawal and adverse effects
Opioid rotation	• Consider a more appropriate opioid based on terminal diagnosis, comorbidities, or known organ dysfunction • Methadone has NMDA antagonist activity and is proven to reduce OIH symptoms • Buprenorphine is a kappa receptor antagonist which has been shown to mitigate spinal dynorphins and relieve hyperalgesia • Due to incomplete cross-tolerance among various opioids, the total daily dose of opioids may generally be reduced by approximately 25% when switching agents which is likely to improve OIH symptoms
Add non-opioid adjuvant	• Ketamine and dextromethorphan have NMDA antagonist activity • Additional adjuvants may include gabapentin, baclofen, acetaminophen, NSAIDs, steroids, clonidine, dexmedetomidine • Combining two or more non-opioid adjuvants may have a synergistic effect and be superior to a single agent
Add opioid adjuvant	• Adjuvant low-dose methadone may promote opioid receptor resensitization, incomplete cross-tolerance, and allow for an overall opioid reduction while blocking NMDA to minimize withdrawal and hyperalgesia symptoms simultaneously

SUMMARY

Opioid-induced hyperalgesia occurs when opioids paradoxically exacerbate pain. OIH should be considered in any situation where a patient is experiencing increasing pain that is not responding to increasing doses of opioids. Treatment methods aim to combat the chemical and molecular changes in the spinal cord and brain suspected to cause OIH.

References:

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