Waterloo Wellington LHIN

Opioid-Induced Hyperalgesia (OIH)

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Objectives

- Define opioid-induced hyperalgesia (OIH)
- Discuss pathophysiology of OIH
- Recognize the clinical presentation of OIH
- Discuss treatment options
- Understand the nursing role in anticipating and managing OIH

Case – Mr. C

- 74 year old diagnosed 18 months ago NSCLC metastatic to bone, liver
- Followed by community HPC team
- Symptom constellation: fatigue, early satiety, cachexia, localized and progressive pain to right iliac crest, T-spine, right scapula, sacrum
- Previous radiation treatment to bone, refusing more at this time
- SR hydromorphone PO with b/t ~ 40mg /24hours – pain opioid responsive
- Dexamethasone 8mg added – unclear if response.

Case – Mr. C cont'd

- Oral opioid switched to continuous infusion, titrated every few days
- Over 3 weeks, dose titrated to hydromorphone 9mg/hr – total daily dose ~ 250mg or 500mg oral equivalent
- Developed insomnia, irritability, unsteadiness on feet – spouse reporting no hallucinations but general tremulousness, myoclonus
- Describes pain as "everywhere" – global severe pain, allodynia

Definition of Opioid Induced Hyperalgesia (OIH)

- A state of nociceptive sensitization cause by exposure to opioids…the nociceptor changes to now detect not only noxious stimuli, but also non-noxious stimuli

- Characterized by a paradoxical response whereby a person who is receiving opioids for the treatment of pain develops worsening pain in spite of, and because of, increases in the opiate

Definitions of OIH Continued…

- Diffuse pain or pain in different regions other than the site of injury/damage
- Where a mildly uncomfortable stimulus such as a pinch becomes disproportionately painful
- Differs from allodynia, which is where a non-painful stimulus (such as a gentle touch) becomes painful
- **OIH is a form of opioid toxicity**

Prevalence and Incidence

- Not known
- Often not recognized
- Often not distinguished from pain crisis
- Often recognized only after the patient is on very, very high doses of opiate and unresponsiveness to opioid therapy

Risk Factors

- More commonly seen in patients receiving high dose opioids rather than low or moderate doses
- Can occur with both short acting and long acting opiate preparations
- Parenteral administration (intravenous and subcutaneous) more common, but can occur with all forms of opiate administration including oral, transdermal and intrathecal

Pathophysiology

- The precise mechanism of OIH is not well understood, although there are a few theories…
- One theory suggests that neuroplastic changes, or a rewiring, occur in the peripheral and central nervous pathways leading to an over sensitization.

Pathophysiology….continued…

- Another theory suggests a degree of neuro-excitability, where certain opioids and their metabolites activate nerve receptors (N-methyl-D-asparate NMDA) causing an influx of calcium
- It is this influx of calcium which greatly enhances the excitability of the neuron and allows painful impulses to be transmitted more readily
- Limited data suggests genetic and other personal factors that influence pain sensitivity and response to analgesia
- May occur quickly over hours or days, therefore can occur with both acute and chronic pain situations

Assessment

- It is important to distinguish from ***opioid tolerance***: if pre-existing pain is undertreated or tolerance exists, then increasing the opioid dose would result in pain relief

- In OIH, further increasing the opiate will cause further pain or increased sensitivity

  - **In undertreated pain/tolerance, further opiate =** ↓ sensitivity to opioids and thus **pain relief**

  - **In OIH, further opiate =** ↑ sensitivity to opioids and thus **worsening pain**

Assessment

- Remember, OIH is a form of **opioid toxicity**:
  - Common severe signs include *myoclonus, delirium and seizures*
  - Other manifestations that can be overlooked, and therefore mask OIH include *insomnia and agitation*
- Suspect OIH when opioid treatment effectiveness wanes and there are:
  - Increases in pain, despite increase in opiate
    - Short interval increases required (10-fold) over days/weeks
  - Reports of diffuse pain and allodynia
  - No evidence of disease progression

Table 1. Differential diagnosis of neuropathic pain, opioid-induced hyperalgesia and opioid tolerance

	Neuropathic pain	Opioid-induced hyperalgesia	Tolerance
Definition	Pain initiated or caused by a primary lesion or dysfunction in the nervous system. Pain in the area of altered sensation	OIH is a paradoxical response to an opioid agonist, whereby instead of an analgesic or anti-nociceptive effect occurring, there is an increase in pain perception	Progressive lack of response to a drug thus requiring increased dosing
Nature of the pain	Pain sensations in the distribution of the damaged neurological structure; i.e. pain in the area served by the damaged nerve or neurological structure. The area of neuropathy may show hyperalgesia and/or allodynia	The original pain may be well controlled or exacerbated. OIH pain may be much more diffuse and cannot be explained by the neuro-anatomical distribution, i.e. in dermatomes. In the area of OIH there may be hyperalgesia or allodynia	Pain sensitivity is unaltered; the original pain may still be present or be well controlled
How fast can this phenomenon develop?	Usually a couple of weeks or months after nerve damage	May develop rapidly, within hours or days	Usually develops slowly in weeks or months
Benefits of increasing the opiod dose	With increasing doses of opioids, there is usually an increase in adverse effects but no improvement in analgesia	Single/acute dose may be experienced as beneficial, although increasing the total dose of opioids does not usually result in pain improvement. Patients can usually state that, for example, doubling the dose of opioids did not improve the pain and if anything made the pain worse	Increasing the dose has a beneficial effect for a longer time, i.e. patients start on a dose of fentanyl 25 μg/ hour and after a couple of weeks this increases to 37.5 μg/hour, still without adverse effect and with adequate control of pain
Quality of pain	Usually burning, lacerating or stabbing	Usually different from the original pain. May have a character of sensitivity to touch or slightly painful stimuli	Unaltered in comparison to the original pain condition
Pain sensitivity	Increased	Increased	Unchanged
Pain threshold	Decreased	Decreased	Unchanged
Opioid adverse effects	Usual opioid adverse effects, indicating overdosing	May be accompanied by other symptoms of neurotoxicity: agitation, delirium, multifocal myoclonus, seizures	Usual opioid adverse effects, indicating overdosing
Initial response to opioids	Pain improvement up to a certain level; further increase in the opioid dose does not result in better analgesia	The pain may initially respond to opioids; however, it may also immediately get worse after starting opioids	Pain usually responds well to opioids
Effect of dose reduction	The pain will increase	The pain will decrease	The pain will increase

Kenter, E. et al. (2010), p 96

Investigations and Diagnosis

- **Investigations:** if possible, rule out disease progression or new complications and treat accordingly

- **Diagnosis**: complete a thorough pain history including location, distribution, response to opioids previously and most recent opioid adjustments with total opiate administration

If increased opioid doses do not even partially relieve pain, then the dose should not be further increased !!

Pharmacological Treatment

- Reduce the opioid dose by tapering off systematically (25-30% every 24 hours) – there is no advantage to miniscule 5 or 10% reductions
- Sometimes, reduction in opiate may cause worsening symptoms initially
- Offer hydration to enhance renal secretions of active metabolites
- Opioid rotation and/or change route of administration
- Add in NMDA receptor adjuvants, if possible (e.g. methadone, ketamine) as these are less likely to cause OIH

Pharmacological Treatment

- Consider adjuvants such as steroids, nsaids, neuropathic-targeted medications (gabapentinoids, SNRI or TCA antidepressants)
- Intermittent sedation or palliative sedation therapy may be warranted if symptoms remain severe and persistent
- DO NOT use naloxone to reverse opiate toxicity unless significant narcotization exists
    - This could cause opiate withdrawal accompanied by pain crisis and can precipitate seizure

Treatment: Communication with Family and Team

- May be mistaken for disease progression
- ***Consider family and health provider distress
- Essential to establish a plan and ensure that all team members understand and reinforce the approach:
  - Remain calm and supportive in the face of distress
  - Remember that more opioids will not help situation
  - Revisit goals of care and other treatment options: radiation therapy, adjuvants palliative sedation therapy

Treatment: Communication with Family and Team

- Education is the most important…it is critical that we knowledge transfer re: OIH between team members and help one another recognize symptoms, etc

- Educating the family is critical – knowledge around cause, what to expect, etc is important
(ensure patient confidentiality
is maintained)

Case – Mr. C cont'd

- Multiple increases in opioid infusion did not address pain.
- Patient and family very distraught
- Hyperalgesia identified and plan discussed in home – plan to introduce methadone and decrease infusion rate by 25% with bolus dose option
- Family and community team nervous, frightened, convinced that disease was rapidly progressing and patient was "dying"
- Admitted to hospice before methadone titrated or outcome of opioid reduction evaluated
- Sedation initiated, patient died within one week

Discussion & Questions?

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