Opioids induced hyperalgesia: A real clinical problem or just an experimental phenomenon?

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Opioid Induced Hyperalgesia (OIH)

- OIH: A state of increased 'sensitivity to pain' as a result of and during opioid therapy.
- Localized or diffuse.
- Spontaneous and/or evoked.

OIH – studied in three clinical conditions

- Acute postoperative pain.
- Patients with cancer pain (end of life).
- Chronic non-malignant pain.
OIH – studies in three clinical conditions

- Acute postoperative pain.
- Patients with cancer pain (end of life).
- Chronic non-malignant pain.

I.T fentanyl at operation increases postoperative morphine requirements

- 60 women underwent caesarean section.
- I.T. 0.5% bupivacaine + either 25 µg fentanyl or NaCl.
- Postoperative analgesia: i.v. morphine PCA.
- A 63% increase in morphine requirements in the fentanyl group was noted during the first 24 postoperative hours.

Cooper et al., Br J Anaesth 1997.

Additional evidence for post-operative OIH

- High (versus low) dose of I.V. fentanyl during surgery resulted in increased early postoperative pain and opioid consumption (hysterectomy, n=60; 4-16 hours). ¹
- Intraoperative remifentanil infusion resulted in increased post-operative I.V. PCA morphine requirements (major abdominal surgery; n=50; first 24 hours). ²

¹ Chia et al., Can J Anaesth 1999.
² Guignard et al., Anesthesiology 2000.
Intraoperative remifentanil induces postoperative experimental hyperalgesia

(N=75; abdominal surgery; high versus low remifentanil dose)

- High-dose remifentanil decreased mechanical pain threshold
- High-dose remifentanil increased area of hyperalgesia
- Hyperalgesia blocked by small-dose ketamine

Joly et al., Anesthesiology 2005

OIH – studies on acute post-operative pain

- Intraoperative opioid administration results in increased postoperative pain, both clinically and experimentally.
- However, those changes are noticeable only subsequent to discontinuation of the acute (intraoperative) opioid treatment.
- Therefore they likely represent acute withdrawal rather than true OIH.

OIH – studies in three clinical conditions

- Acute postoperative pain.
- Patients with cancer pain (end of life).
- Chronic non-malignant pain.
In a few case reports, patients with terminal cancer reported the exacerbation of existing pain and/or new widespread diffused pain in response to escalating doses of I.T. opioid administration.

A gradual tapering-off of the opioids resulted in the resolution of such pain exacerbation.

Unfortunately, these reports are sporadic, and clinical trials are still lacking.


OIH studies in three clinical conditions

- Acute postoperative pain.
- Patients with cancer pain (end of life).
- Chronic non-malignant pain.

Patients with chronic pain (n=224)
- Opioid treated (n=142)
- Non-opioid (n=82)

Psychophysical tests:
- Punctuate pain threshold (von Frey)
- Pressure pain threshold (algometer)
- Heat pain threshold (TSA)
- Tonic heat pain intensity (46.5°C; 60 sec.)

Reznikov et al Br J Clin Pharmacol. 2005
No evidence for OIH in opioid vs. non-opioid treatment

Table 1

<table>
<thead>
<tr>
<th>Pain threshold (mmHg)</th>
<th>Opioids</th>
<th>Non-opioids</th>
<th>Statistical analysis difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facet block</td>
<td>104 (96-112)</td>
<td>110 (98-122)</td>
<td>0.06 (0.00-0.12)</td>
</tr>
<tr>
<td>Intramuscular</td>
<td>120 (110-130)</td>
<td>128 (118-138)</td>
<td>0.04 (0.00-0.08)</td>
</tr>
<tr>
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<td>140 (130-150)</td>
<td>150 (140-160)</td>
<td>0.03 (0.00-0.06)</td>
</tr>
<tr>
<td>Intrathecal</td>
<td>160 (150-170)</td>
<td>170 (160-180)</td>
<td>0.02 (0.00-0.05)</td>
</tr>
</tbody>
</table>

BPS 0-10 numerical pain scale

* Equivalent to 69.6 7.0 (4-464 mg) of oral morphine

Reznikov et al., Br J Clin Pharmacol. 2005

No evidence for OIH in “strong” vs. “weak” opioid treatment

Table 2

<table>
<thead>
<tr>
<th>Pain threshold (mmHg)</th>
<th>Weak opioids (n=10)</th>
<th>Strong opioids (n=15)</th>
<th>Statistical analysis difference (95% CI)</th>
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</thead>
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<td>Facet block</td>
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BPS 0-10 numerical pain scale

Reznikov et al., Br J Clin Pharmacol. 2005

The Cold Pressor Test (CPT)

- Experimental model of cold-induced pain in humans
- Immersing a limb in ice-cold water (1.0 0.5°C)
- Three outcome measures:
  - Latency to pain onset (~10 sec)
  - Tolerance to limb withdrawal (~30 sec)
  - Maximal pain intensity (VAS ~ 80)
Additional evidence for OIH in patients with CNMP

- A multi-disciplinary pain rehabilitation program, which included cessation of opioid use resulted in:
  - Elevation of heat pain thresholds at the end of the program as compared to baseline.
  - Slightly reduced clinical pain intensity at the end of the program.
- These findings suggest that experimental OIH has clinical relevance in patients with CNMP who consume opioids.
- However, two points should be taken into consideration:
  - First, correlations between experimental pain, clinical pain, and opioid dosage were not measured.
  - Second, the program encompassed additional components of rehabilitation which might have contributed to the changes in both clinical and experimental pain.

Hooten et al., Pain Med 2008
Hydromorphone therapy: is there a correlation between hyperalgesia and analgesia? A study on patients with neuropathic (radicular) pain

- N=29
- Mean pain duration 70.2 - 107.4 months
- Mean hydromorphone dose 11.6 - 4.8 mg, (4 to 20 mg)

Change in clinical pain intensity in response to hydromorphone therapy

Change in experimental heat pain intensity in response to hydromorphone therapy

Dolnikov et al., Pain Physician 2012
A reverse correlation between hyperalgesia and analgesia

Dolnikov et al., Pain Physician 2012

\[ r = -0.592, p = 0.001 \]
\[ r = 0.467, p = 0.009 \]
\[ r = -0.389, p = 0.037 \]

OIH - conclusions

- Intraoperative opioid administration can lead to alterations in sensitivity to pain, but they seem to represent opioid withdrawal rather than true OIH.
- Only anecdotal reports point to true OIH in patients with cancer at the end-of-life.
- A few studies suggest that OIH has clinical significance in patients with CNMP and that experimental OIH and clinical pain correlate with each other.
- However, we are still facing methodological questions with regards to the preferred method for reliable demonstration of OIH.

Suggested clinical criteria for diagnosing OIH

2. No evidence for underlying disease progression.
3. No evidence for either clinical or pharmacological opioid withdrawal (i.e. symptoms and signs of opioid withdrawal; increased pain as a result of end-of previous opioid dose effect).
4. No evidence for opioid tolerance: to be tested clinically by decreased pain in response to an adequate opioid rescue dose.
5. Decrease in pain intensity in response to a reduction in opioid dose (gradual dose reduction might be required to avoid abstinence syndrome).
6. No evidence for addictive behavior.
Thank you
ALTERATION IN PAIN PERCEPTION IN OPIOID ADDICTS

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ICOI Boston, June 2014

Opioids - pain intensity

Chronic opioids addicts (OA's) - sensitive to pain

IS THAT SO?
Anticipated response to cold pain in theory

Addiction

- A persistent dysfunctional use of a substance
- A chronic disease with pharmacological, genetic, psychosocial elements
- Initially, impulsively and positive reinforcement → → a compulsive behavior even when faced with negative consequences
- The pleasurable feelings provide positive support → → the behavior is repeated → → a reward is reached

Addiction and Pain

- High prevalence of moderate and severe chronic pain – (~50% vs. 19%)
- High rates of medical and psychiatric disorders
- Greater use of medication
- Treatment for acute pain relief is ineffective
Addiction and Pain (cont.)

- Neurobiology of addiction = pain
- Multidimensional phenomena which cannot be fully explained by its neurophysiological bases
- In both - sustained exposure to the stimulus induces changes in the CNS
- Examining sensitivity to pain in addicts provides information as for the consequences of chronic exposure to opioids

Response to cold pain in OA's

<table>
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<tr>
<th>Study</th>
<th>Sample</th>
<th>Significant findings in OA's</th>
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<tr>
<td>Martin &amp; Iglis (1965)</td>
<td>Former OA's vs. control</td>
<td>Tolerance↓</td>
</tr>
<tr>
<td>Ho &amp; Dole (1979)</td>
<td>MMP vs. control</td>
<td>Threshold↓</td>
</tr>
<tr>
<td>Compton et al. (1994)</td>
<td>OA's vs. cocaine abusers</td>
<td>Tolerance↓</td>
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<tr>
<td>Liebmann et al. (1997)</td>
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<tr>
<td>Pud et al. (2006)</td>
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<td>Tolerance↓</td>
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Rather than being less sensitive to pain – opioid addicts are hyperalgesic.
• 60 OA’s (heroine, methadone, both; 50 M / 10 F)
• Attended for a 4-week detoxification program
• 70 healthy controls (38 M / 32 F)
• Cold pressor test on admission, 7 & 28 days after detox.
Is opioid-induced hyperalgesia reversible? A study on active and former opioid addicts and drug naïve controls
Roi Treister, Elon Eisenberg, Eli Lawental, Dorit Pud
Journal of Opioid Management 2012, 8(6) 343-50

Summary of these studies

- OA’s reduced tolerance time while intoxicated
- This may results from -
  1) Altered neural mechanisms
  2) Pain avoidance behavior and low frustration → deny of pain → denial impossible → a tendency to overreact → terminate the painful stimulus
- No signs of recovery 4 weeks after detox. → but within one year of detox. → OIH may be reversible but requires a long period of opioid abstinence
What causes hyperalgesia in OA’s?

‘specific theory’

OA’s have an altered nociceptive system
Supportive evidence:
• Former opioid users have a "vulnerable" nociceptive system - small opioid doses trigger hyperalgesia (Celerier et al., 2001)
Hypothesis:
• The altered nociceptive system predispose to addiction → delay in the ability to stop opioid use

What causes hyperalgesia in OA’s?

‘non specific theory’

The long term opioid exposure per se
Supportive evidence:
• Identical hyperalgesia in long term opioid-treated chronic pain patients with no history of addiction (Ram et al., 2008; Chen et al., 2009; Hay et al., 2009; Suzan et al., 2013)
• Animal studies - chronic exposure to opioids induces hyperalgesia

OIH is not associated with a particular population but with the long-term use of opioids

Opponent Process Theory
(Celerier et al., J. Neurosci. 2001)
Summary and Clinical implications

- Hyperalgesia in OA's is not expected
- It arises from long-term exposure to opioid drugs
- Expect high rates of chronic pain among OA's
- Expect difficulties with managing acute pain in OA's
- Analgesics will be less effective
- Individuals using opioids without pain may develop hyperalgesia
- Any “new” pain will be magnified in intensity

Recommendations for acute pain management in MMP

- Continue the usual verified dose of methadone maintenance therapy
- Use non-pharmacologic & conventional analgesics (including opioids) to relieve pain
- Use higher short acting opioid (e.g., remifentanyl) doses at shorter intervals
- Write continuous scheduled dosing orders rather than “as-needed” orders
- Avoid using mixed agonist and antagonist opioids - it may cause an acute withdrawal syndrome.
- Non-opioids (NSAID's, acetaminophen) & adjuvant analgesics (TCA) may be co-administered to decrease the total amount of opioid provided
- Have naloxone available

Characteristics of hyperalgesia in OA's

- Modality dependent –
  was not found in electrical or mechanical stimulation
  (Doverty et al., 2001; Hay et al., 2009)

- Not associated with alldynia –
  difficult to recognize and measure
  (Angst & Clark, 2006; Hay et al., 2009)

Conclusions and future directions

- Opioids have the potential to activate both pro-nociceptive and anti-nociceptive pathways
Clinical Implications of OIH

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Disclosure of Conflict of Interest
None

OPIOID THERAPY

Analgesia  Hyperalgesia

Addiction  Side Effects
Does opioid dose adjustment change clinical pain score?

An analysis of a subgroup of over 100 chronic pain patients
Opioid Dose Change and Pain Score (Effect of Gender and Age)

Opioid-Induced Hyperalgesia

OPIOID

DESENSITIZATION (TOLERANCE)  SENSITIZATION (INCREASED PAIN)

PRONOCICEPTIVE
REPEATED OPIOID EXPOSURE  
\[ \rightarrow \]  
A PATHOLOGICAL PAIN STATE

Altered Heat Pain Threshold

Exacerbated Temporal Summation of Second Pain (Windup)
**OPIOID TREATMENT**

![Diagram showing cellular mechanisms and opioid-induced hyperalgesia](image)

**Category I**
- Low dose
  - Initial titration phase

**Category II**
- High dose; Long-term use
  - Little change after dose titration
  - Change in pain pattern (location, quality, etc.)

**Analgesia (tolerance)**
- Opioid Rotation
- Adjunctive Medication
- NMDAR Antagonist

**Hyperalgesia**
- Dose Decrease
- NMDAR Antagonist
- Adjunctive Medication
Clinical Issues

Is methadone a better choice?

Is Suboxone an effective analgesic?