New knowledge on opioids – does it matter in clinic?

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Interindividual variability in response to opioids

- Pharmacokinetics: absorption, distribution, metabolism and elimination
- Pharmacodynamics: drug concentration at the target sites, number and morphology of receptors and downstream events
- Genetic factors: pain sensitivity and response to opioids. There is still no clear evidence that genetic markers can predict opioid efficacy or side effects in palliative care patients

Skorpen et al, Palliat Med 2008

Opioid effects

Wanted effects
- analgesia
- sedation
- anti-emetic
- anti-diarrhea

Unwanted effects
- respiratory depression
- sedation
- constipation
- itching
- nausea/vomiting
- dry mouth
- sweating
- diarrhea
- sleep disturbance
- difficult micturition
- mood changes
- hallucinations/delirium
- myoclonus/seizures
- hyperalgesia/allodynia
- cognitive dysfunction

Unwanted effects of side effects

- respiratory depression
- sedation
- constipation
- itching
- nausea/vomiting
- dry mouth
- sweating
- diarrhea
- sleep disturbance
- difficult micturition
- mood changes
- hallucinations/delirium
- myoclonus/seizures
- hyperalgesia/allodynia
- cognitive dysfunction

Pain management of opioid treated cancer patients in hospital settings in Denmark

Lundorff et al., Acta Anaesthesiol Scand 2008

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Prevalence</th>
<th>Treatment of side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dryness of mouth</td>
<td>64%</td>
<td>9%</td>
</tr>
<tr>
<td>Constipation</td>
<td>63%</td>
<td>81%</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>46%</td>
<td>46%</td>
</tr>
<tr>
<td>Sweating</td>
<td>39%</td>
<td>2%</td>
</tr>
<tr>
<td>Cognitive dysfunction</td>
<td>37%</td>
<td>7%</td>
</tr>
<tr>
<td>Sedation</td>
<td>33%</td>
<td>8%</td>
</tr>
<tr>
<td>Confusion</td>
<td>17%</td>
<td>9%</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>12%</td>
<td>0%</td>
</tr>
<tr>
<td>Allodynia</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Hyperalgesia</td>
<td>17%</td>
<td>9%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>13%</td>
<td>6%</td>
</tr>
<tr>
<td>Sweating</td>
<td>12%</td>
<td>1%</td>
</tr>
</tbody>
</table>
Long-term consequences of opioid treatment

- Physical dependence
- Tolerance development
- Opioid-induced hyperalgesia (OIH)
- Addiction
- Cognitive dysfunction
- Dysfunction of the immune and reproductive systems

Opioid-induced hyperalgesia (OIH)

"OIH is broadly defined as a state of nociceptive sensitization caused by exposure to opioids"

Chu et al., Clin J Pain 2008

Terminology

- Opioid-induced paradoxical pain
- Overwhelming pain syndrome
- Opioid hyperalgesia
- Opioid-induced pain sensitivity
- Opioid-induced abnormal pain sensitivity
- Opioid-induced abnormal pain
- Opioid-induced hyperalgesia

OIH and tolerance

"Repeated opioid administration results not only in the development of tolerance (a desensitization process), but also in a pronociceptive process (a sensitization process)"

Collectively, both desensitization and sensitization from prolonged opioid therapy may contribute to an apparent decrease in analgesic efficacy"

The clinical problem

“Decreased effectiveness of the opioid therapy raises the difficult question, whether it is a sign of tolerance development, OIH, progression of the tissue injury or a combination of these factors”

Angst and Clark, Anesthesiology 2006

OIH in cancer pain

- Generalized allodynia (touch-evoked pain)
- Amplifying pre-existing pain
- Accompanied by myofascial jerks
- Segmental distribution during spinal therapy
- Escalating the dose aggravates symptoms (dose dependent or on/off)
- Cessation/rotation alleviates OIH
- OIH was described with different types of opioids

- Parkinson et al., Anaesthesiology 1990
- De Conno et al., Pain 1991
- Sjøgren et al., Pain 1993
- Sjøgren et al., Pain 1994
- Bruera and Pereira, Pain 1997
- Kronenberg et al., Pain 1998
- Sjøgren et al., Acta Anaesth Scand 1998
- Mercadante et al., JPSM 2003
- Doverty et al., Pain 2001
- Compton et al., J Pain 2003
- Pud et al., Drug an Alcohol Depend 2006
- Joly et al., Anesthesiology 2005
- Guignard et al., Anesthesiology 2000
- Angst et al., Pain 2003
- Chu et al., J Pain 2006
- Ram et al., Pain 2008
- Chu et al., Clin J Pain 2008

OIH in non-cancer pain

- Methadone maintenance therapy (+cold pressor test—electrical and mechanical stimuli)
- Opioid withdrawal (reversibility after 6-12 months)
- Perioperative exposure to opioids (high intraoperative remifentanil increased wound hyperalgesia)
- Experimental opioid exposure (remifentanil infusion; +cold pressor test)
- Chronic non-cancer pain patients on opioids

- Donnelly et al., Pain 2007
- Compton et al., J Pain 2003
- Ong et al., European Journal of Pain 2006
- Ong et al., Anesthesiology 2006
- Ong et al., Pain 2006
- Ong et al., Clin J Pain 2004
OIH in chronic non-cancer pain: QST testing

<table>
<thead>
<tr>
<th>Studies</th>
<th>Patients</th>
<th>Design</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chu et al., J Pain 2006</td>
<td>6 patients (0 to median 75 mg/day in 1 month)</td>
<td>Longitudinal (before--after) + cold pressor test (CTh and CTol) + heat stimuli</td>
<td>OIH was decreased with opioids</td>
</tr>
<tr>
<td>Ram et al., Pain 2008</td>
<td>73 patients on opioids vs 37 patients on nonopioids</td>
<td>Cross-sectional cold pressor</td>
<td>OIH was decreased with opioids</td>
</tr>
<tr>
<td>Chen et al., Pain 2009</td>
<td>I: Healthy controls (N=41) II: Chronic pain patients on nonopioids (N=41) III: Chronic pain patients on nonopioids plus opioids (&gt; morphine 30 mg/day) (N=67)</td>
<td>Cross-sectional III: decreased HPTh and exacerbated temporal summation (TS)</td>
<td>Higher opioid dose correlated with lower HPTh and higher TS</td>
</tr>
</tbody>
</table>

Mechanisms of OIH

- Activation of the NMDA receptor system
- An imbalance between the opioid-dependent analgesic systems and the NMDA-dependent pronociceptive systems
- Activation of the μ-receptor stimulates the excitatory amino acid neurotransmitter systems (substance P and glutamate)
- Glycinergic and GABA inhibition (strychnine-like)
- μ-receptor agonists (e.g. M4-G) may induce OIH in knockout mice
- Metabolites without μ-receptor activity may also induce OIH (via microglia in the spinal cord)

Treatment of OIH

1. Reducing the opioid dose whenever possible
2. Opioid rotation
3. Co-administering adjuvant analgesics e.g. ketamine or gabapentin
4. Administering the opioid by an alternative route?
5. Administration of an opioid-antagonist? (high/low dose OIH)

Conclusions

- OIH may emerge as distinct, definable, and characteristic phenomenon that may explain loss of opioid efficacy in some cases
- However, OIH may also be of tremendous significance for opioid therapy
- The mechanisms of OIH is not clear, but it OIH resembles neuropathic pain
- In OIH there may exist a modality-specific sensitivity to painful stimuli
- However, OIH may not be detected by "standard" psychophysical tests
Addiction – ICD-10

A cluster of behavioural, cognitive and physiological phenomena, which may develop after repeated use and that typically include:
- A strong desire to take the drug
- Difficulty in controlling the use
- Persisting in the use despite harmful consequences
- A higher priority given to the drug use than to other activities and obligations
- Increased tolerance
- Intentional physical withdrawal state

Addiction – Portenoy’s criteria

Portenoy’s criteria: 19.3%

Prevalence of addiction in a multidisciplinary pain centre

232 patients with pain (235 non-cancer, 17 cancer) were screened for addiction by the treating physician and nurse and filled in the PMQ. 74% were treated with opioids.

PMQ had acceptable construct and criterion validity and high reliability.

Why is it important to identify and treat addiction?

- Uncontrolled opioid use may lead to increased tolerance and high opioid doses with increased risk of adverse effects (e.g. cognitive dysfunction, side effects, tolerance, OIH, etc.)
- Addiction leads to psychological and social instability and maladaptive behaviors (e.g. non-compliance with treatment programs)
- Conclusion: Treatment of both the pain and the addiction problem is necessary
Opioids and cognition

Four clinical relevant situations:

- Stable long-term treatment
- Dose increase
- Supplemental opioid doses (on demand)
- Wean off

Cognitive domains in opioid treated cancer patients

- Attentional capacity
- Information-processing speed and working memory
- Short-term memory
- Psychomotor speed

Driving ability in cancer patients receiving long-term morphine analgesia

Kamboj et al., Pain 2005

- The morphine group: 24 cancer patients treated with stable doses of slow-release morphine tablets (mean daily dose: 209 mg)
- The control group: 25 cancer patients taking no analgesics
- Conclusion: "Long-term analgesic medication with stable doses of morphine does not have psychomotor effects of a kind that would be clearly hazardous in traffic"
Neuropsychological performance in cancer patients: the role of oral opioids, pain and performance status

Sjøgren et al., Pain 2000

130 cancer patients were consecutively included and divided in the following categories:

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>KPS</th>
<th>AKPS</th>
<th>Pain</th>
<th>Opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>40</td>
<td>A</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Group 2</td>
<td>19</td>
<td>B</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Group 3</td>
<td>19</td>
<td>B</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Group 4a</td>
<td>31</td>
<td>B</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Group 4b</td>
<td>21</td>
<td>B</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Conclusions

1. The use of long-term oral opioid treatment did not affect any of the neuropsychological tests.
2. Patients being in KPS B had statistically significantly slower CRT than patients being in KPS A.
3. Pain itself deteriorated the performance of PASAT.

The effects of opioid dose increase and supplemental opioid doses on cognition

<table>
<thead>
<tr>
<th>Studies</th>
<th>Design</th>
<th>Patients and treatment</th>
<th>Study assessments</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruera et al., 1989</td>
<td>Open-label, controlled study</td>
<td>Patients on oral and parenteral opioids</td>
<td>ESAS, FTT, Arithmetics, Reverse memory</td>
<td>Pain relief, increased sedation and nausea, Visual memory significant impairment of all cognitive tests</td>
</tr>
<tr>
<td>Kamboj et al., 2005</td>
<td>Randomized, placebo-controlled, double-blind, crossover study</td>
<td>Patients on long-term opioids, supplemental morphine doses</td>
<td>PVAS, HADS, Prose recall, Digit span, TMT, FTT</td>
<td>Pain relief, Ante-and retrograde memory impairment, Attention deficits</td>
</tr>
</tbody>
</table>

Management opioid induced cognitive dysfunction

1. Co-administering adjuvant analgesics
2. Reducing the opioid dose whenever possible
3. Circadian modulation with the opioid
4. Administering an alternative opioid
5. Administering the opioid by an alternative route
6. A combination of 4 and 5
### Psychostimulants in opioid-induced cognitive dysfunction and sedation

<table>
<thead>
<tr>
<th>Studies</th>
<th>Design</th>
<th>Patients and treatments</th>
<th>Study drug</th>
<th>Assessments</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruera et al., 1987</td>
<td>Randomized, double-blind, cross-over</td>
<td></td>
<td>Day 4</td>
<td>N=28</td>
<td>Oral opioids</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Methylphenidate 10mg+5mg+0</td>
<td>ESAS</td>
<td>Improvement of sleep, activity, and drowsiness</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bruera et al., 1992</td>
<td>Randomized, double-blind, cross-over</td>
<td></td>
<td>Day 3</td>
<td>N=19</td>
<td>Continuous s.c. infusions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Methylphenidate 10mg daily</td>
<td>ESAS</td>
<td>Improvement of sleep, activity, and drowsiness, confusion, FTT, arithmetics, and memory</td>
</tr>
<tr>
<td>Lundorff et al., Palliat Med 2009</td>
<td>Randomized, double-blind, cross-over</td>
<td></td>
<td>(day 4)</td>
<td>N=28 (fatigue&gt;50mm on ESAS)</td>
<td>Single-dose modafinil 200 mg or placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ESAS, FTT and TMT and ESAS</td>
<td>Improvement of FTT, TMT, ESAS, depression, and drowsiness</td>
</tr>
</tbody>
</table>

### Conclusions

1. The cognitive effects of stable long-term oral opioid treatment seem to be modest.
2. Driving ability seems to be preserved in patients treated with stable doses of opioids.
3. Pain and poor performance status seem to impair cognitive function.
4. Dose increase as well supplemental opioid doses may temporarily deteriorate cognitive function.
5. Psycho-stimulants may counteract cognitive dysfunction and sedation, however, more studies are needed.