Opioid Toxicity

Per Sjögren
Section of Acute Pain Management and Palliative Medicine
National Hospital, Copenhagen, Denmark

March 12, 2010

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

Sjörgen et al, Palliat Med 2008
Opioid effects

Wanted effects
- analgesia
- sedation
- anti-dyspnoe
- anti-salivation

Unwanted effects
- respiratory depression
- sedation
- constipation
- itching
- nausea/vomiting
- dry mouth
- sweating
- dizziness
- 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 attempts 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>Alloodynia</td>
<td>3%</td>
<td>0%</td>
</tr>
</tbody>
</table>
Long-term consequences of opioid treatment

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

Savage, J Pain Symptom Manage 1999  
Mitchell et al., Nat Neurosci 2000  
Mao, Pain 2002  
Saprua et al., Eur J Pain 2005  
Feuch et al., J Pharmacol Exp Ther 1995  
Aho et al., J Clin Endocrinol Metab 2000

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 myoclonic 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., Anesthesiology 1990
De Conno et al., Pain 1991
Sayer et al., Pain 1993
Sayer et al., Pain 1994
Beneci and Piercen, Pain 1997
Kronenberg et al., Pain 1998
Sayer et al., Acta Anaesth Scand 1998
Mercadante et al., JPSM 2003
OIH in non-cancer pain

- Methadone maintenance therapy (+cold pressor test/-
electrical and mechanical stimuli)
- Opioid withdrawal (reversibility after 6-12 month)
- 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

Dworz et al., Pain 2003
Cooman et al., J Pain 2003
Pud et al., Drug an Alcohol Depend 2006
Joly et al., Anesthesiology 2005
Guinard et al., Anesthesiology 2006
Ayer et al., Pain 2003
Chu et al., J Pain 2006
Ram et al., Pain 2008
Chu et al., Chu J Pain 2008

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>
</table>
| Chu et al., J Pain 2006 | 6 patients (0 to median 75 mg/day in 1 month) | Longitudinal (before-after) | +cold pressor test (CTh and CTo)
|                 |                     |                      | Seat stimuli                                    |
| Ram et al., Pain 2008 | 35 patients on opioids vs 37 patients on non-opioids | Cross-sectional | - cold pressor
|                 |                     |                      | DNIC was decreased with opioids                 |
| Chen et al., Pain 2009 | 1) Healthy controls (N=61) 2) Chronic pain patients on non-opioids (N=41) 3) Chronic pain patients on non-opioids plus opioids (+ morphine 30 mg/day) (N=67) | Cross-sectional | 4) decreased HPTD and exacerbated temporal summation (TS)
|                 |                     |                      | Higher opioid dose correlated with lower HPTD and higher TS |
Morphine metabolism and high dose OIH

Oral Morphine
(UDP-glucuronyl-transferase)
(UGT2B7)

M-3-G 55-65%
M-6-G 10-15%
Unchanged morphine 8-10%

M3G: antinociception and neurotoxicity in animals

- M3G has no μ-agonist activity
- M3G antagonizes morphine and M6G?
- M3G plays a role in tolerance?
- Neurotoxic potency: M3G>Morphine>M6G

Yaksh and Harty, J Pharmacol Exp Ther 1987
Smith et al., Life Sci 1996
Gaug et al., Pain 1984
Sazdak et al., Eur J Pharmacol 1993
Laphorecki et al., Life Sci 1984
Mechanisms of OIH

- Activation of the μ-receptor stimulate the excitatory amino acid neurotransmitter system
- Activation of the NMDA receptor system
- Descending facilitation (cholecystokinin and dynorphin releases substance P and glutamate)
- Glycinergic and GABA inhibition (strychnine-like)
- Opioid receptors coupled to excitatory intracellular second messenger systems
- A low dose OIH and a high dose OIH (e.g. naloxone resistance)

Treatment of OIH

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

Svobodová et al., Pain Med 2005
Tapper et al., Pain 1984
Joly et al., Anesthesiology 2005
Filer et al., Anesthes Analg 2002
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

Cognitive dysfunction in cancer

- Cerebral metastases
- Electrolyte derangement (e.g. hypercalcemia)
- Metabolic disturbances (e.g. uremia and anemia)
- Humoral factors (TNF, cytokines ect)
- Emotional distress (e.g. anxiety and depression)
- Other symptoms/conditions (e.g. pain and fatigue)
- Antineoplastic treatment (e.g. ”chemobrain”)
- Palliative treatment (e.g. opioids)

Cull et al., Br J Cancer 1995
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
Exclusion criteria in controlled studies of cancer patients in long-term opioid treatment

1. Metabolic and electrolyte disturbances
2. Cerebral metastasis
3. Other neurological and/or physical dysfunctions interfering with the tests (e.g. dementia, head injury)
4. Use of psychotropic drugs other than opioids
5. Alcohol/drug abuse
6. Anticancer treatment recently (3-4 weeks)
7. Acute progression of disease

Opioids and cognition

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Opioid treatment (route and dose)</th>
<th>Assessment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sjogren and Banning, Pain 1989</td>
<td>Cross-over Controlled</td>
<td>Oral/equivalent, Dose=210-300mg</td>
<td>CRT</td>
<td>No-difference</td>
</tr>
<tr>
<td>Bruera et al., Pain 1989</td>
<td>Controlled Longitudinal</td>
<td>Oral/Dose increase</td>
<td>FTT, Memory, Arithmetic</td>
<td>Difference</td>
</tr>
<tr>
<td>Bannister and Sjogren, Clin J Pain 1990</td>
<td>Healthy controls Cross-sectional</td>
<td>Oral, Dose=168mg</td>
<td>CRT</td>
<td>Difference</td>
</tr>
<tr>
<td>Bannister et al., Acta 1992</td>
<td>Controlled, Cross-sectional</td>
<td>Oral, Dose=150mg</td>
<td>CRT</td>
<td>Difference</td>
</tr>
<tr>
<td>Varini et al., Lancet 1995</td>
<td>Controlled, Cross-sectional</td>
<td>Oral, Dose=200mg</td>
<td>Driving ability</td>
<td>No-difference</td>
</tr>
<tr>
<td>Clemons et al., Cancer Treat Rev 1996</td>
<td>Controlled Cross-sectional</td>
<td>Oral, Dose=304mg</td>
<td>Arithmetic, Stroop-Colour-Word</td>
<td>Difference</td>
</tr>
<tr>
<td>Chrupat et al., IPSM 1999</td>
<td>Cross-over Double-Bind</td>
<td>Oral/morphine vs oral M5T, Dose=120 mg</td>
<td>CRT</td>
<td>No-difference</td>
</tr>
<tr>
<td>Sjogren et al., Pain 2000</td>
<td>Controlled, Cross-sectional</td>
<td>Oral, Dose=120/40mg</td>
<td>CRT, FTT, PASAT</td>
<td>No-difference</td>
</tr>
<tr>
<td>Kambjö et al., Pain 2005</td>
<td>RCT, double-blind cross-over</td>
<td>Long-term oral opioid vs supplemental morphine doses</td>
<td>Prose recall, Digit span, TMT, FTT</td>
<td>Difference</td>
</tr>
</tbody>
</table>
Driving ability in cancer patients receiving long-term morphine analgesia
Vanho et al., The Lancet 1995

- 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
Sjogren et al., Pain 2000

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

<table>
<thead>
<tr>
<th>Group</th>
<th>KPS</th>
<th>Pain</th>
<th>Opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (N = 40)</td>
<td>KPS A</td>
<td>-</td>
<td>- Opioids</td>
</tr>
<tr>
<td>Group 2 (N = 19)</td>
<td>KPS B</td>
<td>-</td>
<td>- Opioids</td>
</tr>
<tr>
<td>Group 3 (N = 19)</td>
<td>KPS B</td>
<td>+ Pain</td>
<td>- Opioids</td>
</tr>
<tr>
<td>Group 4a (N = 31)</td>
<td>KPS B</td>
<td>+ Pain</td>
<td>+ Opioids</td>
</tr>
<tr>
<td>Group 4b (N = 21)</td>
<td>KPS B</td>
<td>- Pain</td>
<td>+ Opioids</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 treatments</th>
<th>Study intervention</th>
<th>Assessments</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruera et al., Pain 1989</td>
<td>An open-label controlled study</td>
<td>Cancer patients (n=40) on oral and parenteral opioids</td>
<td>A dose increase of 30% in 20 patients</td>
<td>ESAS FTT Arithmetic Reverse memory Visual memory</td>
<td>Pain relief Increased sedation and nausea Significant impairment of all cognitive tests</td>
</tr>
<tr>
<td>Kamboj et al., Pain 2005</td>
<td>Randomized, placebo-controlled, double-blind, cross-over study</td>
<td>Cancer patients (n=14) on long-term opioids</td>
<td>Supplemental morphine doses</td>
<td>IVAS HADS Prose recall Digit span STM FTT</td>
<td>Pain relief Antisocial and attentional impairment Attention deficits</td>
</tr>
</tbody>
</table>
...but remember that there are remedies for cognitive dysfunction!

Management opioid induced cognitive dysfunction

1. Co-administrating 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
Other therapeutic strategies to manage cognitive dysfunction

- Psychostimulants
- Other drugs e.g. antidepressants
- Hydration
- Oxygen supply
- Sleep management

Methylphenidate 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 7 days, cross-over day 4</td>
<td>28 patients</td>
<td>Methylphenidate 10mg 5mg 10</td>
<td>ESAS Sleep</td>
<td>Improvement of pain, activity and drowsiness</td>
</tr>
<tr>
<td>Bruera et al., 1992</td>
<td>Randomized, double-blind, cross-over 3 days, cross-over day 3</td>
<td>19 patients</td>
<td>Methylphenidate 10mg daily</td>
<td>ESAS FTT Arithmetic Memory</td>
<td>Improvement of drowsiness, confusion, FTT, arithmetic and memory</td>
</tr>
</tbody>
</table>
Modafinil for attentional and psychomotor dysfunction in advanced cancer: a randomized, controlled, double-blind, cross-over trial

Lundorff et al., Palliat Med 2009

• **Aim:** To evaluate the cognitive effects of single-dose Modafinil

• **Methods:** 28 cancer patients (fatigue>50mm on ESAS) received Modafinil 200 mg or placebo and 4 days later they crossed over to the alternative treatment

• **Assessment:** FTT, TMT and ESAS were measured before and 4.5 hours after tablet intake

• **Results:** FTT (dom) and TMT as well as depression and drowsiness measured on ESAS improved statistically significantly on modafinil

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 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
6th Research Congress of the European Association for Palliative Care

Glasgow, UK
10-12 June 2010

EAPC Research Network