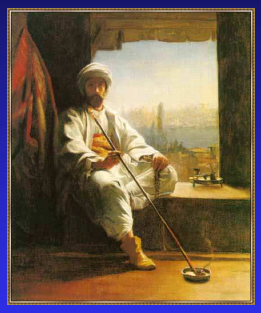
Opioid Toxicity



Per Sjøgren
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

Skorpen et al, Palliat Med 2008

Opioid effects

Wanted effects

- analgesia
- sedation
- anti-dyspnoe
- anti-salivation

Unwanted effects

- respiratory depression
- sedation
- constipation
- itching
- nausea/vomitting
- dry mouth
- sweating
- diziness
- 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

Side effect	Prevalence	Treatment attempts of side effects
Dryness of mouth	64%	9%
Constipation	63%	81%
Nausea/vomitting	46%	46%
Sweating	39%	2%
Cognitive dysfunction	37%	7%
Sedation	33%	8%
Confusion	17%	9%
Myoclonus	12%	0%
Allodynia	3%	0%

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 1993
Mitchell et al., Nat Neurosci 2000
Mao, Pain 2002
Sjøgren et al., Eur J Pain 2005
Fecho et al., J Pharmacol Exp Ther 1995
Abs 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”

Ballantyne and Shin, Clin J Pain 2008

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., 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

OIH in non-cancer pain

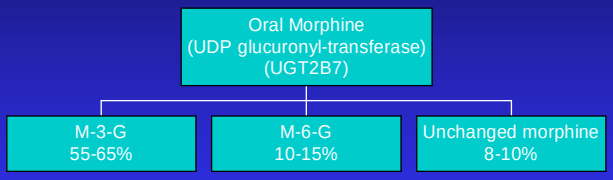
- Methadone maintenance therapy (+cold pressor test/-electrical and mechanical stimuli)
- Opioid withdrawal (reversibility after 6-12 month)
- Perioperative exposure to opioids (high intraoperative remifentanil increased wound hyperalgesia)
- Experimentel opioid exposure (remifentanil infusion; +cold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

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 chronic non-cancer pain: QST testing

Studies	Patients	Design	Outcomes
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 CTol) -heat stimuli
Ram et al., Pain 2008	73 patients on opioids vs 37 patients on non-opioids	Cross-sectional	- cold pressor DNIC was decreased with opioids
Chen et el., Pain 2009	I: Healthy controls (N=41) II: Chronic pain patients on non-opioids (N=41) III: Chronic pain patients on non-opioids plus opioids (> morphine 30 mg/day) (N=67)	Cross-sectional	III: decreased HPTh and exacerbated temporal summation (TS) Higher opioid dose correlated with lower HPTh and higher TS

Morphine metabolism and high dose OIH



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 Ther1987
Smith et al., Life Sci 1990
Gong et al., Pain 1993
Suzuki et al., Eur J Pharmacol 1993
Lipkowski et al., Life Sci 1994

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)

Vorobeychik et al., Pain Med 2008
Sjøgren et al., Pain 1994
Joly et al., Anesthesiology 2005
Eilers et al., Anesth Analg 2001

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

Kurita et al., Support Care Cancer 2009

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

Study	Design	Opioid treatment (route and dose)	Assessment	Results
Sjøgren and Banning, Pain 1989	Cross-over Controlled	Oral/epidural, Doses:210/80mg	CRT	No-difference
Bruera et al., Pain 1989	Controlled Longitunal	Oral/dose increase	FTT, Memory, Arithmetics	Difference
Banning and Sjøgren, Clin J Pain 1990	Healthy controls Cross-sectional	Oral, Dose=168mg	CRT	Difference
Banning et al., Acta 1992	Controlled, Cross-sectional	Oral, Dose=150mg	CRT	Difference
Vainio et al., Lancet 1995	Controlled, Cross-sectional	Oral, Dose=209mg	Driving ability	No-difference
Clemons et al., Cancer Treat Rev 1996	Controlled Cross-sectional	Oral, Dose=104mg	Arithmetics, Stroop-Colour-Word	Difference
Christrup et al., JPSM 1999	Cross-over Double-blind	Oral morphine vs. oral MST, Dose=120 mg	CRT	No-difference
Sjøgren et al., Pain 2000	Controlled, Cross-sectional	Oral, Doses=120/40mg	CRT, FTT, PASAT	No-difference
Kamboj et al., Pain 2005	RCT, double-blind, cross-over	long-term oral opioids + supplemental morphine doses	Prose recall, Digit span, TMT, FTT	Difference

Driving ability in cancer patients receiving long-term morphine analgesia

Vainio 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

Sjøgren et al., Pain 2000

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

Group 1 (N = 40)	KPS A	- Pain	- Opioids
Group 2 (N = 19)	KPS B	- Pain	- Opioids
Group 3 (N = 19)	KPS B	+ Pain	- Opioids
Group 4a (N = 31)	KPS B	+ Pain	+ Opioids
Group 4b (N = 21)	KPS B	- Pain	+ Opioids

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

Studies	Design	Patients and treatments	Study intervention	Assessments	Results
Bruera et al., Pain 1989	An open-label controlled study	Cancer patients (n=40) on oral and parenteral opioids	A dose increase of 30% in 20 patients Stable doses in 20 controls	ESAS FTT Arithmetics Reverse memory Visual memory	Pain relief Increased sedation and nausea Significant impairment of all cognitive test
Kamboj et al., Pain 2005	Randomized, placebo-controlled, double-blind, cross-over study	Cancer patients (n=14) on long-term opioids	Supplemental morphine doses	PVAS HADS Prose recall Digit span TMT FTT	Pain relief Ante- and retrograd memory impairment Attention deficits

...but remember that there are remedies for cognitive dysfunctioning !

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

Studies	Design	Patients and treatments	Study drug	Assessments	Results
Bruera et al., 1987	Randomized, double-blind, cross-over 7 days; cross-over day 4	N=28 Oral opioids	Methylphenidate 10mg+5mg+0	ESAS Sleep	Improvement of pain, activity and drowsiness
Bruera et al., 1992	Randomized, double-blind, cross-over 5 days; cross-over day 3	N=19 Continuous s.c. infusions	Methylphenidate 10mg daily	ESAS FTT Arithmetics Memory	Improvement of drowsiness, confusion, FTT, arithmetics and memory

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