

# Opioid Rotation and other Analgesic Strategies

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ABRA Annual Scientific Meeting  
15th November 2013



# Background

- Experience from Paediatric perspective.
- Much of the 'evidence' is from adult practice.
- This talk is to explore the rationale for some of the regimes that are used and to generate discussion of people's experiences.

# Outline

- Opioids- the mainstay of burns pain management
- The problems with opioids and potential management strategies
- Adjuvant therapies to help with these strategies

# Burns Pain management

- Opioids remain the mainstay of treatment
- Initial management is usually bolus (IV or IN)
- Followed by intravenous infusion- Morphine  
(later converted to oral opioid)
- In major burns the patient is usually sedated on (P)ICU – therefore Midazolam/ Propofol
- (Next step would be to add a Ketamine infusion)

# Problems with Opioids

- Common Side effects- Nausea/ vomiting, reduced gut motility, itch
- Tolerance
- Opioid induced hyperalgesia (OIH)

# Tolerance vs. OIH

- Tolerance is defined as increasing doses of a particular opioid being required to achieve the same analgesic effect.
- OIH is described as increasing pain in patients receiving high, increasing doses of opioids AND the appearance of pain with characteristics different from those of the original pain syndrome.

# OIH

- May be accompanied by neuroexcitatory features- agitation, multifocal myoclonus, seizures and delerium.
- Clearly more than a simple opioid tolerance phenomenon
- Some pathophysiological overlap

# Pathophysiology of OIH

- Poorly understood and great variation in the literature.
- Non-opioid channels, neurotransmitters and receptors have been implicated. (NMDA/ glutamate likely play a critical role.)
- Generally thought to result in the activation of descending pain facilitation (pronociceptive) pathways.

# Clinical and Management implications of OIH

- Recognition is important
- First line management is to increase the dose and evaluate for increased efficacy (Tolerance)
- If pain or other symptoms worsen with increased dose then OIH is likely

Lee M. Silverman SM. Hansen H. Patel VB. A comprehensive review of opioid induced hyperalgesia. *Pain Physician*: March/ April 2011; 14: 145-161



# Clinical and Management implications of OIH

## Options

- Decrease or eliminate opioid
- 'Switch' or 'Rotate' opioids
- Utilise specific agents that are involved in the NMDA/ glutamate receptor systems
- Utilise combination therapies (e.g. COX II inhibitors)

# Opioid Switch/ Rotation

- Well recognised in Cancer pain and chronic pain management
- Cochrane review (2004)
- Equipotent doses have not been established
- Less commonly described in acute pain

Mercadante S, Bruera E. Opioid switching: A systematic and critical review. *Cancer Treatment Reviews* 2006; **32**: 304-315

Quigley C. Opioid switching to improve pain relief and drug tolerability. *Cochrane Database of Systematic Reviews* 2004, Issue 3. Art No.: CD004847



# Opioid rotation

## Theories

- Incomplete cross tolerance between different opioids
- Different intrinsic activities
- Action on other receptors e.g. methadone with weak NMDA receptor properties
- (Allows the body to clear M-3-G)

Mercadante S. Opioid Rotation for Cancer Pain, Rationale and Clinical Aspects. *Cancer* 1999; **86**: 1856-66

Ross JR et al. Clinical Pharmacology and Pharmacotherapy of Opioid Switching in Cancer Patients. *The Oncologist* 2006;11:765-773



# Morphine metabolites

Morphine-6-Glucuronide

- mu receptor agonist

Morphine-3-Glucuronide

-no significant opioid receptor affinity

But implicated in tolerance, hyperalgesia,  
myoclonus, irritability

Molecular mechanisms still disputed

Christrup LL. Morphine metabolites. *Acta Anaes Scand.* 1997; **41**: p116-22

Vaughn CW, Connor M. In search of a role for the morphine metabolite Morphine-3-Glucuronide. *Anaest Analg.* 2003; **97**: p311-2



# Opioid rotation

## Examples

- Anecdotal PICU
- Child Case reports in Burns management
- Morphine to Fentanyl associated with more failures. Rapid fentanyl tolerance a problem
- Methadone theoretically a good option.

Arnold JH, Truog RD, Scavone JM, Fenton T: Changes in the pharmacodynamic response to fentanyl in neonates during continuous infusion. *J Pediatr* 1991;119:639-43.

Mercadante S, Bruera E. Opioid switching: A systematic and critical review. *Cancer Treatment Reviews* 2006; **32**: 304-315

Williams PI, Sarginson RE, Ratcliffe JM. Use of methadone in the morphine-tolerant burned paediatric patient. *British Journal of Anaesthesia*. 1998; **80**: 92-95



# Opioid rotation in burns

## Our experience

- Timing
- Which drugs?
- What dose?

# Ketamine

- Non-competitive antagonist at NMDA receptor
- Long history of ketamine use in burns management- traditionally in anaesthetic doses for procedures

# Ketamine

Established in practice in lower doses  
(0.1mg/kg) as

-opioid sparing

-helping to prevent NMDA-mediated  
tolerance and hyperalgesia

Subramaniam K. et al. Ketamine as Adjuvant Analgesic to Opioids: A Quantitative and Qualitative Systemic Review. *Anesth Analg.* 2004; **99**: 482-95

Shimoyama N. et al. Ketamine attenuates and reverses morphine tolerance in rodents. *Anaesthesiology.* 1996; **85**: 1357-66

Joly V. et al. Remifentanyl-induced postoperative hyperalgesia and its prevention with small-dose ketamine. *Anesthesiology* 2005; **103**: 147-55

Visser E, Schug S,. The role of ketamine in pain management. *Biomed Pharmacother* 2006; 60: 341-8



# Ketamine

## Cochrane review (2010)

*'Ketamine in subanaesthetic dose (that is a dose which is below that required to produce anaesthesia) is effective in reducing morphine requirements in the first 24 hours after surgery. Ketamine also reduces postoperative nausea and vomiting. Adverse effects are mild or absent.'*

So how best to give it?

Single dose? Infusion? With NCA/ PCA?

# Ketamine- Benefit shown with

- A. Pre-incisional IV/ IM bolus
- B. IV bolus at wound closure
- C. Continuous (or repeat bolus ) Peri-operative ketamine
- D. Post-operative PCA-MK (with or without intra operative bolus)

**No benefit in increasing dose  $>30\text{mg}/24\text{ hrs}$**

# Gabapentin

- Anticonvulsant with license for neuropathic pain
- Mechanism not fully defined, but involves inhibition of central sensitisation to pain. (Known to bind pre-synaptic calcium channels involved in hypersensitivity)
- Indirectly inhibit NMDA receptor over activation

# Gabapentin

- Evidence in Burns pain management is scarce and conflicting
- 1x RCT, Case control studies/ series
- 300-1200mg tds
- (children start at 10mg/kg increasing to 60mg/kg)
- Recent study questions efficacy

Rimaz S et al. Effect of Gabapentin on Morphine Consumption and Pain after Surgical Debridement of Burns Wounds: A Double-Blind Randomized Clinical Trial Study. *Arch Trauma Res.* 2012;**1**(1):38-43.

Cuignet O, Pirson J, Soudon O, Zizi M. Effects of gabapentin on morphine consumption and pain in severely burned patients. *Burns.* 33(1):81-6, 2007 Feb.

Grey P, Williams B, Cramond T. Successful use of gabapentin in acute pain management following burn injury: a case series. *Pain Medicine* 2008;**9**(3): 371-6

Wibbenmeyer L, Eid A, Liao J, Heard J, Horsfield A, Kral L, Kealey P, Rosenquist R. Gabapentin is Ineffective as an Analgesic Adjunct in the Immediate Postburn Period. *J Burn Care Res.* 2013 Mar 18.



# Pregabalin

- Equivalent efficacy as gabapentin, but at lower doses (therefore reduced side effects)
- Lower doses because of higher bioavailability (90% vs. 33-66%). Rapidly absorbed (1h vs. 3)
- Pregabalin plasma [ ] linear at higher doses.
- Pregabalin BD dosing
- Pregabalin FDA approved and NICE recommended

# Pregabalin

- RCT
- Adults with >5% BSA burns with moderate/high scores on 'hot' or 'sharp' pain on NPS
- 28 days titrated to maximum dose
- Significant reduction in pain, itch and procedural pain.
- No difference in opioid consumption

Gray P, Kirby J, Smith MT, Cabot PJ, Williams B, Doecke J, Cramond T. Pregabalin in severe burn injury pain: a double-blind, randomised placebo-controlled trial. *Pain*. 2011 Jun;152(6):1279-88.



# Clonidine

- Alpha-2 agonist
- Analgesic, sedative, anxiolytic
- Has a place for these reasons in ICU setting
- Case reports supporting use managing burn pain in children.

Lyons B. Casey W. Doherty P. McHugh M. Moore KP. Pain relief with low-dose intravenous clonidine in a child with severe burns. *Intensive Care Medicine*. 22(3):249-51, 1996 Mar.



# Summary

- Opioids remain the mainstay of burns pain management.
- Tolerance and OIH are problems associated with high dose (prolonged) opioid therapy
- Opioid rotation is one option in managing these difficult problems
- Adjunct therapy with ketamine and gabapentioids are helpful

# What are other people's experiences?



Thank you

