The Role of Ketamine in the Management of Complex Acute Pain

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Aim of the session

• Adverse effects of ketamine abuse
• Normal pain transmission
• Changes with persistent pain
• How to use ketamine
• Does it prevent persistent pain
Adverse Effects of Ketamine
Adverse Effects

• Clinical use often limited by dose dependent side effects

• Studies report short term results only

• Evidence for long term clinical efficacy and safety is lacking
# Adverse Effects

<table>
<thead>
<tr>
<th>Dizziness</th>
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<tr>
<td>Sedation</td>
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<td>Nausea</td>
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<td>Agitation</td>
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<td>Hallucinations</td>
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<td>Nightmares</td>
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Longer Term Adverse Effects

• Rat model (Olney et al 2002)
  – Hyperstimulant effect of repeated low dose ketamine

• Canine model (Schug et al. 2015)
  – Abnormal histological changes in neural tissue with intrathecal ketamine infusion

• Neuropathic pain clinic patients (Cvrcek et al. 2008)
  – 3 months of ketamine: dry mouth, dizziness, drowsiness
Long term Effects

• Cognitive and Emotional Function

• ‘Ketamine Cystitis’

• Chronic Abdominal Pain

• Hepatotoxicity

• Abuse potential
Bladder problems / ‘Ketamine Cystitis’

- Cause unknown
- Associated with abuse
- Over 3 months use/high doses
- Ulcerative cystitis, obstructive nephropathy
- 3 cases in palliative care
- 1 case in chronic pain (Bell 2012)
- Not seen in low-dose, short duration

Abuse Potential

• Most common abused drug in SE Asia

• Relationship between chronic pain and problematic drug use is complex

• Problematic drug use of prescription analgesic drugs is a major healthcare problem in Western countries
Abuse potential: Australia

• 15 x opioid prescription increase from 1992 to 2012

• Opioid related hospitalisation
  – Prescription drug use > Heroin abuse since 2001

• Opioid related deaths: 0.78 to 1.19 per 100,000 population in 10 years

How does Ketamine work?
The NMDA Receptor

• Ion channel complexes located centrally and peripherally in the nervous system

• Ligand gated ion channels (glutamate)

• Multiple functions in the nervous system
The NMDA Receptor

- Learning and Memory
- Cognitive functions
- Neural development / synaptoplasticity
- Addiction
- Psychiatric disorders
- Nociception
The NMDA Receptor

- Learning and Memory
- Cognitive functions
- Neural development / neuroplasticity
- Addiction
- Psychiatric disorders
- Nociception
NMDA receptor – spinal level

• Activation of the receptor clinically
  – Central Sensitisation
    • Hyperalgesia
    • Allodynia
  
• Amplification of nociceptive traffic towards higher brain centres

Petrenko AB, Yamakura T, Sakimura K et al (2014) Defining the role of NMDA receptors in anesthesia: are we there yet? Eur J Pharmacol 723: 29–37
Excitatory Synapses in Dorsal Horn

- Glutamate Release
- NMDA Activation

Sustained Hyperexcitability of the neurone
Sustained Hyperexcitability of the neurone

• Acute Pain States

• Chronic Pain States

• Opioid Induced Tolerance

• Hyperalgesia / Opioid Induced Hyperalgesia
NMDA Receptor Antagonists

• Ketamine
• Magnesium
• Dextromethorphan
• Anamantadine
• Memantine

NMDA Receptor Antagonists

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Ketamine

• First synthesized in the 1960’s
• Dissociative anaesthetic agent
• Low-doses used for pain relief
• Blocks NMDA receptor
Ketamine Action

• In low doses acts primarily as a non-competitive antagonist of the NMDA receptor

• Slow ‘off rate’ causing a prolonged tonic block

• Main role is an adjuvant in pain associated with central sensitisation
Central Sensitisation

• Severe Acute Pain

• Neuropathic Pain

• ‘Opioid Resistant’ Pain

Evidence for Ketamine?
Ketamine - evidence

- Preventative analgesia
- Peri-operative for acute post-operative pain
- Postoperative analgesia
- Postoperative analgesia, intravenous infusion
- Ketamine addition to PCA
- Opioid induced hyperalgesia
Role of NMDA receptor antagonists in preventative analgesia

• Preventative analgesia
  – Postoperative period
  – ↓Pain scores / ↓analgesic consumption
  – Relative (another Rx, no Rx, or placebo)
  – Effect observed beyond drug duration of action (>5.5 half lives)
  – Given pre-incision (pre-emptive) or intraop

Role of NMDA receptor antagonists in preventative analgesia

- Preventative analgesia
  - McCartney et al. 2004
  - 24 ketamine studies
  - 58% studies showed significant preventative effect

Role of NMDA receptor antagonists in preventative analgesia

• Preventative analgesia
  – McNicol et al. 2014
  – perioperative ketamine use for more than 24 h has a modest but statistically significant reduction in the incidence of persistent post-surgical pain
  – at 3 months and 6 months after operation
  – but not 12 months after surgery.

Perioperative ketamine for acute postoperative pain

- Laskowski (2011)

- 70 RCTs (ketamine bolus or infusion - subanaes)
- No RA
  - ↓ opioid consumption
  - Longer time to first analgesia
- 25/32 (78%) Treatment Group had less pain
- Thoracic, Upper GI, Major Ortho
- SEs:
  - less PONV but ↑ psychomimetic effects
  - No ↑ sedation

Ketamine & PCAs

• Mathews et al 2012 (5 RCTs n=243)
• Addition of ketamine to PCA
• Post thoracotomy
  – Opioid sparing
  – Improved analgesia
  – Better Respiratory outcomes
  – Better patient satisfaction

Low dose IV infusion for postoperative pain

- Jouguelet-Lacoste et al 2015

- 5 meta-analysis & 39 clinical trials (Nov 2013)
  - Reduces opioid consumption by 40%
  - Lowers pain scores
  - No major complications (≤ 48 hours)

Ketamine and Opioid induced hyperalgesia (OIH) & tolerance

• OIH
  – Nociceptive hypersensitivity caused by exposure to opioids.
  – Paradoxical $\uparrow$ dose $\Rightarrow$ $\uparrow$ pain
  – Acute: post-remifentanil

• Tolerance
  – Increasing dose of opioid is required to achieve same clinical effect
Ketamine and OIH & tolerance

• Wu 2015 (14 RCTs, n=729)
• Acute tolerance post remifentanil use
• Included ketamine (8), Mg (5) and amantadine (1) versus placebo
  – ↓ postoperative pain scores
  – ↓ opioid requirements
  – ↑ to first analgesic request
  – Better patient satisfaction

How to use Ketamine
Ketamine

• Used as a racemic mixture - Ketalar®

• Different concentrations
  – 10mg/ml
  – 50mg/ml
  – 100mg/ml
Ketamine

• Multiple routes
  – Bioavailability
    • IM – 93%
    • Intranasal 50%
    • Rectal – 25%
    • Oral – 20%

• Liver metabolism – norketamine (20% analgesia)
Patient Selection

• Indications for using ketamine
• **Neuropathic Pain** (inc. phantom limb)
• **Pathological Pain** (hyperalgesia, allodynia)
• **Poor opioid responsiveness**
• Patients with **previous opioid consumption**

Trial of Ketamine

• Intravenous (rescue) bolus
  – 2.5mg up to a maximum of 10mg

• Maintenance
  – IV infusion of 0.1 mg/kg/hour
  – Oral suspension 25mg 4 to 6 hourly
  – Max 450mg a day
Ketamine in complex patients

• Titrate as necessary
• May require gabapentinoid
• Decrease opioids first, avoid rebound hyperalgesia

• Don’t send them home with ketamine

• Chronic pain clinic follow up?
Can we use ketamine to prevent persistent post-surgical pain
Pharmacotherapy for the prevention of chronic pain after surgery in adults (Review)

Chaparro LE, Smith SA, Moore RA, Wiffen PJ, Gilron I
Pharmacotherapy for the prevention of chronic pain after surgery in adults

- Chaparro 2013
- Ketamine – 14 RCT, small numbers (n=1388)
- Perioperative ketamine compared to placebo significantly reduces the incidence of CPSP
- at 3 months only if infusion > 24 hours
- At 6 months (even if <24hrs) [10RCTs]
- Predominantly colorectal surgery
Ketamine, PPSP & thoracotomy

• Duale et al, 2009, n=86
  – All had PCA, plus ketamine or saline infusion for 24 hours
  – Less morphine 24 hours, lower pain scores
  – No differences in PPSP at 4 months

• Hu et al, 2014, n=78
  – All had PCA, plus ketamine or saline infusion for 72 hours
    no difference in pain scores
  – No difference in PPSP at 6 months

• Tena et al, 2014, n =104
  – All had thoracic epidural, plus IV ketamine, or epidural ketamine or saline
  – lower pain scores
  – No reduction in PPSP at 6 months
“...results with ketamine should be viewed with caution since most of the included trials were small (that is <100 participants per treatment arm), which could lead to an overestimation of treatment effect”
Conclusion

• Ketamine is a non-opioid analgesic that has an effect on acute and chronic pain

• May provide pain relief in carefully selected complex pain patients

• Complements other analgesic modalities

• Safe in analgesic doses

• Do analgesic effects translate into better functional outcomes? Facilitate rehabilitation?