The Management of Neuropathic Pain and the Use of Adjuvant Analgesia in Children

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Opioid induced tolerance and hyperalgesia

Opioid

mu-receptor

uncoupling

stimulation

Genes

activation

Protein Kinase-C

other neuromodulators

Inhibition of Ca channels: neurotransmitter release

Membrane Hyperpolarization (K+ channel)

NMDA-receptor


### NMDA-Receptor Channel Blocker

1. Membrane potential at resting level
   \(\rightarrow\) channel blocked by Magnesium

**Excitatory NMDA (N-Methyl-d-Aspartate) Receptor channel complex**

2. Membrane potential changed as a result of \(\uparrow\) excitation
   - Opioid-sensitivity
   - Central (dorsal horn) sensitization
   - Radiation of pain
   - Spontaneous pain
   - Hyperalgesia, allodynia

### Magnesium as Analgesic


- 13 RCTs, all but 2 reported reduced postop pain & analgesic requirements

- 8 RCTs spinal Mg: lower pain scores & analgesic requirements

- Administration: IV (severe hypo-Mg), PO (mild)
**Central Sensitization**


**NMDA-Receptor Channel Blocker**

3. Phencyclidin (PCP) - binding sites [uncompetitive NMDA receptor antagonists with moderate affinity]
- Ketamine
- Methadone
- Levorphanol
- (Dextrometorphan?)
NMDA-Receptor Channel Blocker

- **Central NMDA receptors**
  - NMDA receptors in supraspinal facilitatory sites (such as rostral ventromedial medulla, nucleus gigantocellularis) maintain non-inflammatory muscle pain in animal model by Silva LF, Desantana JM, Sluka KA. Activation of NMDA receptors in the brainstem, rostral ventromedial medulla, and nucleus reticularis gigantocellularis mediates mechanical hyperalgesia produced by repeated intramuscular injections of acidic saline in rats. J Pain. 2010 Apr;11(4):378-87.

- **Peripheral NMDA receptors**

Ketamine

- Dissociative anesthetic which has analgesic properties in sub-anesthetic doses.
- Racemic mixture [S(+)-enantiomer (Analgnesia, GA); R(-)-enantiomer (bronchodilatation, nightmares)]
- **Sedative-Hypnotic-Dissociative Dosing**
  - IV: 1-2 mg/kg/dose
- **Analgesic (subanesthetic) Dosing**
  - IV: 1-5 mcg/kg/min [=0.06-0.3 mg/kg/hr]
  - PO: 0.2-0.5 mg/kg TID-QID and PRN (sc, sl, intranasal, pr, spinally)
  - Adverse effects: intracranial hypertension, tachycardia, psychotomimetic phenomena (euphoria, dysphoria, vivid hallucinations) -> at low-dose??

Low-dose Ketamine

- Action which may contribute to analgesic effect: Müller S, Pain 1996. 68:435-6
  - Cholinergic transmission
  - Noradrenergic / serotonergic re-uptake inhibition
  - μ, δ, κ - opioid-like effect
  - Interactions with other Na-/Ca- channels
Ketamine

**Adult evidence:**
- 37 RCTs (n=2240): subanesthetic Ketamine effective in reducing morphine requirements in first 24 hours after surgery, reduces postoperative nausea and vomiting; Adverse effects are mild or absent.

**RCT (n=60):** Adult CRPS patients - 4 day low-dose (1.2-7 mcg/kg/min) infusion reduced pain scores week 1-11 (not 12) without functional improvement

**Metaanalysis:** NMDA antagonists (& mexiletine) have no consistent clinical relevant efficacy in neuropathic pain

**Pediatrics:** no RCT's, few case reports:
- Finkel JC, J Pain 2007; 8(6):515-21
  - n = 11, terminal cancer, age 3-17
- Starting dose: 0.1-0.2 mg/kg/hr (max 1 mg/kg/hr)
- Lorazepam 0.025 mg/kg BID
- n = 8/11: ↓ Pain; ↓ Opioid requirements (28-100%)
- No psychotropic side effects, no hallucinations

- 5-year-old girl, meningitis caused by malignant T-cell lymphoma with difficult to treat neuropathic pain. IV lidocaine (9.3–14 mcg/kg/min) and later ketamine (2 mcg/kg/min) in combination with fentanyl (0.8-1.2 mcg/kg/hr) provided good analgesia without significant side effects for the last 20 days of her life.

**Short-term ‘burst’ treatment with ketamine may have long-term benefit:**

**Prevents analgesic tolerance to TENS (in rats):**

**Low-dose: Effective rapid acting anti-depressant?**

**Anti-depressant mechanism: up-regulation of mammalian target of rapamycin (mTOR):**
Ketamine

- Steady-state oral/parenteral ratio unclear
- Bio-availability 93% IM/IV; 20% PO
- Ketamine -> norketamine
- Potency ketamine: norketamine 3:1 (anesthetic); 1:1 (analgesic)
- Plasma half-life: ketamine 1-3 hrs; norketamine 12 hrs
- Maximum blood concentration of norketamine: oral > IV


Subanesthetic-dose Ketamine-PCA

<table>
<thead>
<tr>
<th>Day</th>
<th>Rate</th>
<th>Bolus</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4 mg/hr [0.9 mcg/kg/min] plus</td>
<td>4 mg bolus</td>
</tr>
<tr>
<td></td>
<td>↑ 8 mg/hr [1.9 mcg/kg/min] plus</td>
<td>8 mg bolus</td>
</tr>
<tr>
<td>2</td>
<td>↑ 12 mg/hr [2.8 mcg/kg/min] plus</td>
<td>12 mg bolus</td>
</tr>
<tr>
<td>3</td>
<td>↑ 16 mg/hr [3.7 mcg/kg/min] plus</td>
<td>16 mg bolus</td>
</tr>
<tr>
<td>4</td>
<td>↑ 24 mg/hr [5.6 mcg/kg/min] plus</td>
<td>16 mg bolus</td>
</tr>
</tbody>
</table>

3 unsuccessful trials of decreasing/discontinuing dose

Day 8: Change to 40 mg PO PRN
Day 10: 40 mg PO TID [plus 40 mg PRN]
Day 14: Discontinued [changed to PRN only]

- Hypertonic at baseline, initially MAP increase by 10-15 mm/Hg
- Absent benzodiazepine -> no psychotropic adverse effects
Low-Dose Ketamine: Case Example

Case 2:
17-year-old
Hydromorphone PCA Start: Ketamine

Number of Hydromorphone PCA Boluses
55 -> 20/day [\(64\%\) over 3 days]

Opioid Use
71 mg/day -> 32 mg [\(55\%\) over 4 days]

Pain Score:
Bolus Response Hydromorphone: VAS 9/10 -> 7/10
Bolus Response Ketamine: VAS 9/10 -> 2/10
Usual Pain Scores: VAS 9/10 -> 2-3/10 [over 4 days]

Breakthrough Pain
↓↓↓

Function
↑↑

Case Report: Clark

Number of Hydromorphone PCA Boluses
55 -> 20/day

Opioid Use
71 mg/day -> 32 mg

Pain Score:
Bolus Response Hydromorphone: VAS 9/10 -> 7/10
Bolus Response Ketamine: VAS 9/10 -> 2/10
Usual Pain Scores: VAS 9/10 -> 2-3/10

Breakthrough Pain
↓↓↓

Case Report: Clark at Home

Methadone:
10 mg PO TID -> 12.5 mg PO TID -> 10 mg PO TID

Hydromorphone:
10 mg PO Q1h PRN (0-3/day)

Pregabalin:
300 mg TID

Amitriptyline:
50 mg QHS

Ketamine:
40 mg PO PRN Q1h (discontinued after 2 weeks)

Lidocaine Patches:
Discontinued after 3 weeks
Further Training

7th Annual Pediatric Pain Master Class | Minneapolis, MN | June 7-13, 2014

Center to Advance Palliative Care (CAPC) - Pediatric Palliative Care Leadership Center (PCLC) Training | Jul 10-12, 2013 | Dec 4-6, 2013

Education in Palliative & End-of-life Care [EPEC]: Become an EPEC-Pediatrics Trainer | San Diego, 2014