NMDA Receptor Antagonists:
Preventing windup pain

Presented by Lee Ellingson, MHS CRNA
Staff CRNA, Sanford Health-Meritcare
Objectives

- Review basic anatomy and physiology of pain responses.
- Analyze pathophysiological / chronic pain responses as related to NMDA receptor activation.
- Examine the longterm ramifications of NMDA receptor induction.
- Compare and contrast perioperative pharmacologic methods of antagonizing NMDA receptors: past, present and future.
Anesthesia-definition/goals

- Reversible Amnesia
- Reversible Loss of Responsiveness
- Reversible Loss of Skeletal Muscle Reflex
- Reversible Obtunding of Autonomic Reflexes
- Reversibility Analgesia
Brief history of anesthesia

- 1840s: Nitrous Oxide, Ether, Chloroform
- 1884: Cocaine in eye surgery
- 1898: Spinal anesthesia used in surgery
- 1930s: Intravenous anesthesia w/ barbiturates
- 1943: Lidocaine synthesized
- 1954: Halothane first used
- 1970s: Fentanyl and analogs
- 1980s: Epidural/Spinal narcotics
- 1990s: Ketorolac and Cox2 inhibitors
- 1990s: Preemptive use of local anesthesia
- 1995: NMDA receptor antagonism
- 2005: Dexmedetomidine
- 2010-----------→ Even more change
The CRNA and Change

Traditionalist  Mainstream Practice  Futurist
approaching recommendations for change (or non-change) with caution

fill in the blank

the lack of analgesic action of __________ is an undesirable property of this drug and limits its safe use as sole anaesthetic.
The answer is Halothane

NMDA Anatomy/Physiology

- NMDA (N-methyl D-aspartate)
- Ionotropic Glutamate receptor
  - Nonselective to cations (Na⁺, Ca²⁺, K⁺)
  - Ligand operated (glutamate & glycine)
  - Voltage dependent (blocked by Mg²⁺)
NMDA Anatomy/Physiology

- NMDA receptor activation
  - By co-ligands: glycine and glutamate
  - Subunits (AMPA and Neurokinin1) cause exit of blocking ion, Mg\(^{++}\), from NMDA ion channel.
  - Na\(^{+}\) & Ca\(^{++}\) enter while K\(^{+}\) exits; thus, producing membrane depolarization
NMDA Anatomy/Physiology

- NMDA receptors responsible for:
  - Neural plasticity
  - Learning and memory
NMDA Pathophysiology

- Excessive activation implicated in
  - Depressive/mood disorders
  - Schizophrenia
  - Alzheimers
  - Addiction
  - Oncogene induction
  - Chronic Pain
NMDA: Pathophysiology & Pain

- Repeated or constant noxious input primes the NMDA receptor for chronic pain states (central sensitization)
  - Windup pain
  - Opioid tolerance
  - Opioid induced hyperalgesia
  - Receptive field size increase
  - Pain threshold reduction
  - Longterm potentiation
Windup Pain

- Repeated noxious stimulus through C-fibers stimulates NMDA receptors in dorsal horn neurons in a progressively increasing manner.
  - Also termed Temporal Summation of Second Pain “TSSP”
  - Neural activity increases in a spontaneous “self-sustaining” manner
  - Hyper-excitability results
  - Central sensitization occurs at spinal and supraspinal levels
Opioid Tolerance

- Desensitization of Pronociceptive mechanisms.
- Patient requires escalating doses and more potent opioids
- Coadministration of NMDA antagonists prevents buildup of Morphine tolerance
- Coadministration of NMDA antagonists also prevents opioid withdrawal when decreasing doses.
Opioid Induced Hyperalgesia

- Sensitization of pronociceptive mechanisms
- Long term use of opioids may paradoxically cause increased pain sensitivity (hyperalgesia or allodynia)
- Escalating doses of opioids may actually further increase sensation of pain
Receptive field size expansion

- Spinal neurons activate a pain response to field normally outside site of injury.
Pain threshold alteration

- Increase in magnitude and duration of neural responses.
- Decrease in threshold so that even non-nociceptive stimulation may be painful (eg. Allodynia)
Windup and Chronic Pain

- Windup and Central Sensitization can lead to biochemical cascades:
  - Phosphorylation of NMDA receptors and ion channels
  - Transcription/Translation of genes
  - Changing phenotype of neurons
  - Increased excitability/sensitization

- This phenomenon reflects the neural plasticity of Long Term Potentiation.

Significance of Chronic Pain Syndromes

- Untreated acute postop pain can evolve into chronic pain syndromes
- 80% of patients experience postop pain with 86% of these reporting moderate to extreme pain.

*Are we doing our job?*

Gottschalk, A. Severing the Link between Acute and Chronic Pain: The Anesthesiologist's Role in Preventive Medicine. Anesthesiology: November 2004; 101: 1063-1065
Incidence of Chronic Pain one year after surgery

- 70% after amputation
- 50% after thoracotomcy
- 50% after mastectomy
- 25% after sternotomy
Chronic Pain Predictors

- **Difficult to predict which patient will develop a chronic pain syndrome**
  
  *However*

- **Early postoperative pain is the only significant predictor of persistent pain.**

Fear of experiencing pain is most common concern of surgical preop patients—59%

8% of these patients postpone surgery because of fear of pain.

Apfelbaum, J et al. Postoperative Pain Experience: Results from a National Survey Suggest Postoperative Pain Continues to Be Undermanaged. Anesthesia and Analgesia. 2003;97;534-540
The Bottom Line

- Chronic pain is associated with physiological and psychological consequences.
  - Mood swings
  - Depression
  - Sleep disturbances
  - Oncogenesis

- Chronic pain may indefinitely develop into a disease of itself
So where do we go from here?
An ounce of prevention...

- Preventive analgesia (Wall, 1988)
  - Early opioids
  - NSAIDS / COX2 Inhibitors
  - Local anesthetic- before incision
  - Regional anesthesia
  - NMDA antagonists
    - Magnesium
    - Ketamine
    - Dextromethorphan
    - Methadone
  - Adjuncts: Memantine (Namenda), Tricyclic antidepressants, Nicotine agonists
Magnesium and Ketamine

With these two super heroes...

Wind up is
Washed up !!
Magnesium and Ketamine

- Ability to act alone as NMDA receptor antagonists but, synergistic together.
Magnesium

The “drug” that don’t get no respect...
Magnesium Deficiency

- Magnesium deficiency is endemic in:
  - 7-11% of hospitalized patients
  - 40% of patients with concurrent electrolyte abnormalities

Magnesium levels in surgery

- Abdominal surgery is associated with hypomagnesemia
  - 5 studies revealed postop decreases in control group of 10-30% in serum Mg^{++}
  - 6 of 7 trials of bolus pretreatments of IV Mg^{++} yielded serum increases of 31-84%

- ?? Do lower serum levels of Mg^{++} affect pain levels postop.

Magnesium & analgesia

- Magnesium supplementation alone may decrease postop pain.
- 8 trials (57% of all reviewed) reported significant decrease in postop analgesic use after intraop infusions of Mg++. 
  - Morphine use decreased 12-47% (1-2 days)
  - Fentanyl decreased 53-80% (2-4 hrs)

Magnesium-How to

- Initial Bolus of 30-50 mg/kg. (2 - 3.5 grams in 70kg patient)
- Infusion in surgery of 8-10 mg/kg/hr. (600 – 700 mg/hr).


Magnesium: Clinical tidbits

- Even if only improves analgesia 57% of studies reveal there are other benefits.
  - Decreased Postop shivering
  - Improved postop sleep quality
  - Decreased airway irritability
  - Prevents succinylcholine myalgias
  - Decreased sympathetic responses
  - Improved skeletal muscle relaxation
  - Bronchodilatation

CAUTION

- Reduce Non depolarizer NMB drug induction and maintenance doses 25% when Mg++ is bolused 40mg/kg.

- Mg++ WILL recurarize patients if loading dose is given at end of anesthetic.

What do Magnesium and Ketamine have in common with The Sanford Health-Meritcare Merger?
Sanford & MeritCare
Health
Stronger Together
Ketamine and Magnesium

- Combinations of ketamine and magnesium potentiate each other.
- Combinations are more effective analgesics than either alone; thus,
- Superadditive (>90%) effect of coadministration allows for reduced doses of each; thus, less side effects.

**Ketamine Infusion Dosing**

**THINK SMALL**

- Ketamine exerts NMDA effects at subanesthetic levels.

- **Analgesic level:** 30-120 ng/ml serum
  - 6 mg/hr/70 kg patient = 50 ng/ml
  - 15 mg/hr/70 kg patient = 125 ng/ml

- **Side effects at:** >200 ng/ml serum
  - 25 mg/hr/70 kg patient = 200 ng/ml

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Of 24 studies reviewed using ketamine, 14 (58%) demonstrated preventive analgesia effects.

Usual study boluses: 0.15 – 1 mg/kg 10 – 70 mg / 70kg patient

Ketamine and Magnesium
My recipe

- Infuse between induction and incision by combining:
  - 20-30 mg/kg magnesium
  - 0.25mg/kg ketamine
  - Reduce NMB dosing by 25%
  - Repeat if surgery > 2 to 3 hours length.
  - Careful NOT to give magnesium near end of surgery.
Postop PCA Ketamine

- Often given PCA as 1:1 with Morphine with synergistic effects.
- 60% of studies demonstrate a morphine sparing effect of 45-60%.
- Combination provides a significant decrease in Morphine side effects yet found no increase in psychotomimetic effects in 9 of 11 studies.

Dextromethorphan

- Dextromethorphan is a low affinity noncompetitive NMDA antagonist.
- Dextrorphan (its metabolite) has 8x the NMDA affinity.
- Dextrorphan is a phencyclidine like (PCP) compound.

Yueh-Ching, C et al. Binding of dimemorfan to sigma-1 receptor and its anticonvulsant and locomotor effects in mice, compared with dextromethorphan and dextorphan. Brain Research. 1999; 821:516-519
Dextromethorphan

- Preventive analgesia benefit in 67% of studies.
- Dosed parenterally at 1 mg/kg (IV or IM) preoperatively (NOT PO)


- Effective as premed adjunct for tonsillectomy and mastectomy

Dextromethorphan has analgesic effect beyond its pharmacologically active period

Table 3. (excerpts) Visual Analogue Scale and Retrospective Verbal Pain Scores

<table>
<thead>
<tr>
<th>Score Variable</th>
<th>Preincisional Dextromethorphan</th>
<th>Postincisional Dextromethorphan</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-h VAS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td><strong>13</strong> (0–30)*</td>
<td><strong>31</strong> (22–50)</td>
<td><strong>37</strong> (24–42)</td>
</tr>
<tr>
<td>Movement</td>
<td><strong>30</strong> (22–43)*</td>
<td><strong>53</strong> (32–61)</td>
<td><strong>55</strong> (26–63)</td>
</tr>
<tr>
<td>24-h VAS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td><strong>27</strong> (10–31)</td>
<td><strong>35</strong> (17–53)</td>
<td><strong>38</strong> (16–45)</td>
</tr>
<tr>
<td>Movement</td>
<td><strong>32</strong> (11–42)</td>
<td><strong>46</strong> (27–58)</td>
<td><strong>44</strong> (27–56)</td>
</tr>
</tbody>
</table>

Helmy treated upper abdominal surgery patients with 120 mg IM DM 30 minutes preincision versus postincision versus placebo.

- Preincision Tx grp had significantly decreased pain and analgesia requirements postop.
- Preincision Tx grp also had less hypoxemic events

Methadone

- Mixed isomers
  - S-isomer: a potent MNDA antagonist
  - R-isomer: Potent Mu agonist
- 10-20 minute onset parenterally so it is easy to titrate.
- 24 hour half-life: Caution for toxicity
- Load dose 10-20 mg IV
- Excellent drug for patients with opioid abuse, addiction, overuse issues.
Nicotine agonists

- Nicotine is investigational analgesic
  - Activates preganglionic inhibitory pathways in descending spinal pathways.
  - Less Substance P, Neurokinins and glutamate/glycine released at nerve endings.
  - Thus, less NMDA stimulation.
  - RESULT: Significantly, less post-operative pain and less opioid usage with nicotine agonists.
Nicotine agonists (Flood-2004)

Nicotine nasal spray dose of 3 mg versus NS nasal spray placebo during closure.

- VAS scores Nicotine grp: 4-5
- VAS scores Placebo grp: 7-8
- Analgesic effects last 24 hours despite 45 minute kinetics lifespan of nasal nicotine.

Nicotine agonists (cont)

- No side-effect of increased sympathetic activity as hypothesized (rather, decreased HR & BP)
- Does not work on smokers as they seem to be desensitized to nicotine from chronic use
- Nicotine patch is even more effective than nasal spray with VAS scores in PACU of 1-2. (not dose dependent)
- Nicotine agonist drugs currently in development.
Propofol Vs. Inhal agents: Hyperalgesia

Miscellaneous NMDA antagonists/adjuncts

- Memantine (Namenda) for phantom limb pain
- Antidepressants (esp. TCAs)
Overview

- NMDA activation BAD...
- NMDA antagonism GOOD !!
You’ve arrived... or survived

Questions?
You’ve arrived... or survived

Questions?