The Role of NMDA Receptor Antagonist Drugs in the Acute Care Setting
Debra Drew MS, ACNS-BC, RN-BC
Christine Peltier BSN, RN-BC

Why should I care about NMDA receptor drugs?

Objectives

• Describe wind-up phenomenon, central sensitization and pain memory.
• List two NMDA receptor antagonist drugs that can be used in the acute care setting to manage pain
• State two indications for use of NMDA receptor antagonist drugs in the acute care setting.
• List two potential side effects of low dose ketamine
Introduction: Role of NMDA (N-methyl-D-aspartate) receptors

- Opioid-sparing in opioid tolerance
- Neuropathic pain
- Opioid-induced hyperalgesia
- Wind-up phenomenon
- Neuroplasticity

Wind-up

- Discovered in 1965 by Mendell and Wall.
- Defined as the progressive increase in response of central neurons that may be induced by high-intensity activity in the peripheral nociceptors that synapse on these neurons (Pasero & McCaffery 2011).
- Differs from central sensitization and hyperalgesia in that wind-up can be short lasting (St. Marie 2010).

Neuroplasticity

- An intricate group of processes that allows neurons in the brain to compensate for injury and adjust their responses to changes in their environment. (St. Marie 2010)
- Following noxious stimuli, when pain is persistent there are changes to the chemical, structure and functional plasticity of neurons in the spinal segment of the nervous system. Can contribute to adaptive and maladaptive mechanisms.
Central Sensitization

- CNS changes which distort or amplify pain, increasing its degree, duration and spatial extent in a way that no longer directly reflects the specific qualities of peripheral noxious stimuli.
- Central sensitization represents an uncoupling of the clear stimulus response relationship that defines nociceptive pain. Woolf (2011)
- Plays a crucial role in the pathogenesis of chronic pain.
- Brief intervals of acute pain can induce long-term neuronal remodeling.
Central Sensitization-4


Opioid-Induced Hyperalgesia

• Broadly defined is a state of nociceptive sensitization caused by exposure to opioids.

• State characterized by a paradoxical response: patients actually are more sensitive to certain painful stimuli and increases in opioid doses.

• The NMDA receptor antagonists ketamine and dextromethorphan have shown promise in treating OIH.
**NMDA receptor**

- Glutamate
- Na⁺
- Ca²⁺
- Glutamate recognition site
- Cell membrane
- Mg²⁺
- K⁺
- Na⁺
- Ca²⁺
- Ion channel

**NMDA receptor antagonist drugs**

**Clinical implication of drug pharmacology**

- Glutamate is the principal excitatory neurotransmitter throughout the central nervous system closely involved in nociceptive processing. It is involved in the development of central sensitization.
- Glutamate stimulates the NMDA receptor
- NMDAR antagonists block the excitatory action of glutamate

**Ketamine**

- IM: 2-4 mg/kg, IV 0.2-0.75mg/kg, Continuous IV infusion: 1-6mcg/kg/min.
- Some institutions limit dosing to approximately 70 kg adult dose: eg. 5-50mg IV bolus, 1-20mg/hr infusion
- Adverse reactions: hallucinations, confusion, dream-like state, irrational behavior
- Precautions: dose-related increase in heart rate and blood pressure
- Considerations: produces anesthesia at high dose.
Methadone

- Dosing: Opioid naïve: 2.5-5mg po q 8 hrs.

- Adverse effects: CNS depression, respiratory depression, QTc prolongation, constipation, nausea and vomiting, disorientation

- Precautions: Potential drug-drug interactions with other QTc prolonging agents, as well as CYP3A4 and CYP2D6 inhibitors.

- Special considerations: drug has long and variable half-life of 8-59 hrs. With higher doses, monitor ECG for possible QTc prolongation. No single ratio for equianalgesic dosing between morphine and methadone.

Post-Surgical Hyperalgesia

Amantadine

- Has been used in treatment of Parkinson’s disease and spasticity in humans.

- Mixed results in clinical trials.

- Shown more promise in veterinary medicine for the treatment of hyperalgesia: eg. Post declawing

- Dosing: 200mg infused over 3 hrs or 100-200mg/day

- Adverse effects: orthostatic hypotension, dry mouth, dizziness, agitation, confusion, hallucinations, dyskinesia (Jamer, 2011) Experienced in 52.6% of patients in one study.
Memantine

- Little efficacy in clinical trials
- Dosing: 10-30mg/day po
- Adverse effects: Hypertension, dizziness, drowsiness, confusion, anxiety, hallucinations, cataract

Dextromethorphan

- Has shown some efficacy in neuropathic pain.
- Dosing: 45-400mg/day po
- Adverse effects: light-headedness, drowsiness, confusion, nervousness, visual disturbances, serotonin syndrome
- Special considerations: extensive metabolizers of dextromethorphan experienced better analgesia than poor metabolizers.
- Precautions: Dextromethorphan inhibits cytochrome P450 2D6 isoenzyme. Could lead to drug-drug interactions. Eg. increased TCA levels (Pasero & McCaffery 2010)

Meperidine

- 75mg IV dose approximately equivalent to 10mg IV morphine
- Adverse effects: constipation, respiratory depression, hypotension, nausea, vomiting, sedation, urinary retention
- Precautions: active metabolite, normeperidine, is neurotoxic. Can cause tremors, myoclonus and seizures when accumulates in presence of renal or hepatic insufficiency and with use > 3 days.
- Considerations: drug-drug interaction with MAO inhibitors
Magnesium

- Hypothetical/theoretical implications
- Disappointing or mixed results in randomized trials.
- Dose: 4 gram IV bolus, 500-1000mg IV bolus, 4 hour IV infusion of 70mg/kg.
- Adverse effects: infusion site pain, flushing, burning eyes, and fatigue.

Multi-modal analgesia

- Clinical implications
  - Opioid-sparing in opioid tolerance
  - Neuropathic pain
  - Opioid-induced hyperalgesia
  - Wind-up phenomenon
  - Neuroplasticity

Don’t get frazzled with tough pain management situations: remember the advantages of the NMDA receptor antagonist drugs in multi-modal analgesia.
## Role of NMDA Receptor Antagonists in the Acute Care Setting

**Debra Drew & Christine Peltier**

**ASPMN National Conference, Tucson, 2011**

### Drug Interactions with Methadone*

<table>
<thead>
<tr>
<th><strong>May Increase</strong> serum Levels of Methadone</th>
<th><strong>May decrease</strong> serum levels of Methadone</th>
<th>May cause an unpredictable interaction (↑ or ↓ methadone levels)</th>
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</thead>
<tbody>
<tr>
<td>Alcohol (acute ingestion)</td>
<td>Alcohol (chronic ingestion)</td>
<td>MAOIs</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Abacavir</td>
<td>Stavudine</td>
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<td>Ciprofloxacin</td>
<td>Barbiturates</td>
<td>Tricyclic antidepressants</td>
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<tr>
<td>Diazepam</td>
<td>Carbamazepine</td>
<td>Tramadol (withdrawal symptoms)</td>
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<tr>
<td>Fluconazole</td>
<td>Cocaine</td>
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<tr>
<td>Fluoxetine</td>
<td>Ritonavir</td>
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<td>Grapefruit juice</td>
<td>Phenytoin</td>
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<td>Omeprazole</td>
<td>Ribavirin</td>
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<td>Paroxetine</td>
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<td>Sertraline</td>
<td>St. John’s Wort</td>
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<td>Sodium bicarbonate</td>
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</tbody>
</table>

*List is not complete: only drugs that have scientific documentation: case series, animal or laboratory studies are included in this table.*
References

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