Is Ketamine Getting On Your Nerves?

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I have no disclosures or financial relationships to announce.
The Search for Ideal Anesthetic

- No respiratory suppression
- No reduction in blood pressure
Ketamine is developed by professor Dr. Calvin Stevens working with Parke Davis as a consultant.
The Search for Ideal Anesthetic

✓ No respiratory suppression
✓ No reduction in blood pressure
• May actually stimulate circulatory system
• Uniquely appropriate for:
  o Children
  o Asthmatics
  o Emergency surgery
  o Induction agent or supplemental anesthetic
1970

First used in Vietnam War soldiers

Properties of Ketamine

- Anesthesia
- Amnesia
- Dissociative agent
- Hallucinogenic properties
- Analgesia
World Health Organization (WHO)

Lists ketamine as an essential medication for any basic health system

(19th WHO Essential Medication List, 2015)
What the WHO Wasn’t Thinking of... Pain

(http://www.medicinenet.com)
World of Increasing Refractory Chronic Pain

• Opioids may fail to completely relieve pain
  o Increased dosing to control symptoms
  o Increased adverse events
• Inability to adequately control neuropathic pain
• Tolerance
• Increased abuse
• Increased deaths
Why Ketamine, Why Now?

• Pain medication in a world with decreasing options
• Increased understanding of chronic pain pathways and opioid tolerance
• Increased “difficult to treat” pain
• Pain medication with decreased respiratory and circulatory compromise
• Unique and multiple analgesic actions
• Reduced opioid consumption
Ovid Medline Search 1946-July 2015

- 37 Studies
- Intranasal ketamine (1 mg/kg)
  - effective in emergencies, ED
  - break-through pain
  - Pediatric orthopedic procedure
  - Scene of accident
- Topical preparations
  - Tonsillectomy patients, post-operatively (gargle, throat swab, peritonsillar injections)
  - CRPS
- IV ketamine
  - Pediatric orthopedic injuries/procedures

(Sawynok, 2014)^2
Spinal Windup

- Increased excitability of pain signaling via dorsal horn neurons
- Trigger for hyperalgesia
- Mediated by unmyelinated afferent C fibers
- Dependent on glutamate and Substance P
- NMDA receptor dependent
- Can be blocked by ketamine and other NMDAR antagonists

(Herrero, Laird, Lopez-Garcia, 2000)³
Central Sensitization

- Change in pain signaling within the CNS
- Recruitment of non-nociceptive neurons, Aβ-fiber mediated pain
- Not coupled to true pain-receptor input
- Result of the plasticity of the CNS
- Cause of chronic pain states, i.e. CRPS

(Latremoliere, Woolf, 2008)⁴
But What About the Risks?

• Vivid dreams
• Dissociative properties
• Diversion
• Narrow therapeutic window between analgesia and sedation, psychomimetic effects
• Antinociceptive actions of nor-ketamine
• Lack of clarity of effect for specific pain syndromes
• Difficulty initiating in hospitalized patients
• Difficulty finding compounding pharmacies
What About the Risks?

- Low dosing concentrations
- Rapid onset of action
- Topical routes effective
- Causes analgesia in doses of $1/10^{th}$ to $1/100^{th}$ that of anesthesia dosing
- May be particularly effective in intradermal and transdermal application
- Cost effective
- May be the last and best option in cancer patients at the end-of-life
WHO’s Pain Relief Ladder

1. Pain persisting or increasing
   - Non-opioid
   +/− Adjuvant

2. Pain persisting or increasing
   - Opioid for mild to moderate pain
   +/− Non-Opioid
   +/− Adjuvant

3. Freedom from Cancer Pain
   - Opioid for moderate to severe pain
   +/− Non-Opioid
   +/− Adjuvant

(World Health Organization Treatment for Cancer Pain 2016)
What Makes Ketamine a Choice for Patients with Difficult-to-Control pain?

Four specific modes of action
1. Mu Receptor Agonist

- Bind mu receptors in the midbrain (periaqueductal gray) and medulla (raphe nuclei), disinhibiting the nerves which increases release of endogenous endorphins from neurons
- Directly inhibit afferent nerve transmission pre- and post-synaptically in the dorsal horn of the spinal cord reducing pain transmission to the brain

(Sleigh, Harvey, Voss, Denny, 2014)\(^6\) (Busti, 2015)\(^8\)
2. Cholinergic Receptor Antagonist

- Analgesia
  - Alters cholinergic neurotransmission, increasing levels of serotonin and norepinephrine
  - Augments antinociceptive pathways

- Has been looked at as an anti-depressant
  - Rapid onset
  - Effect long-lasting, about 1 week

(Sleigh, Harvey, Voss, Denny, 2014)
3. Anti-Inflammatory Action

- Analgesia
  - Reduces production of inflammatory cells implicated in propagation of nociceptive stimuli
  - Decreases inflammatory cell recruitment
  - Positive effect on cytokine production and inflammatory mediators
  - Limits exacerbation of inflammation without causing a negative effect on the healing process.

(Loix, DeKock, Henin, 2011)
4. NMDA Receptor (NMDAR) Antagonist*

- Key Points about ketamine in subanesthetic doses:
  - Prevents spinal windup
  - Inhibits central sensitization
  - Inhibits NMDA receptors on sensory afferent nerve endings
  - Topical and peripheral applications engage lower affinity mechanisms than systemic doses
  - When given orally following surgery, ketamine causes a significant reduction in pain

(Sawynok, 2015)²
NMDA Receptor (NMDAR) Antagonist

• Analgesia
  o Inhibition of nitric oxide synthase
  o Lowers production of nitric oxide
  o Blocks calcium and sodium channels, which attenuates hyperalgesia
  o Possible prevention of opioid tolerance
Traditional Pain Therapy: Opioids, Mu-Receptor Agonists

- Traditional pain treatment
- Follows the WHO Treatment Stepladder
Nervous System Action of Opioids

• Act on mu-receptors in spinal cord, brain and, to a lesser degree, peripheral nerves
• Agonist for release of endorphin-like substances
• Often have buildup of byproducts that can cause renal, liver damage
  o Morphine-3-glucuronide
  o Hydromorphone-3-glucuronide
• Known to cause tolerance

(Busti, 2015)
Opioid Action on NMDA Receptor

- The effects of exogenous opioids on NMDARs
  - Increases excitability
  - Increases glutamate availability =>
  - NMDAR activation
  - Leads to neuronal apoptosis =>
  - Increased pain
  - Opioid Tolerance

(Mao, Sung, Ji, Lim, 2002)
Intravenous Ketamine for Rapid Opioid Dose Reduction, Reversal of Opioid-Induced Neurotoxicity, and Pain Control in Terminal Care: Case Report and Literature Review

Pain Medicine 2015; 0: 1–6 doi: 10.1111/pme.12865
Case Report

(Winegarden, Carr, Bradshaw, 2015)
Objective. We report a case of opioid-induced neurotoxicity (OIN) in an actively dying hospice patient, its reversal and improved analgesia that followed opioid dosage reduction made possible after addition of IV ketamine. We briefly review the diagnosis and treatment of OIN.
Case Report

- 42 y.o. male
- Stage IV pleomorphic sarcoma, rt inguinal region
- Dx: 26 months previously
- Initial tx: surgery, chemotherapy
- Remission: 5 mos
- Tx following recurrence: chemotherapy, radiation
Case Report

- Metastasis to spine, B/L lungs, liver and lymphatic system
- Seen at four oncology centers in the U.S.
- Treatment at two pain clinics
Case Report

- 80# wt loss in 6 mos
- Karnofsky Performance Scale 50%
- Site of sarcoma open wound 12 x 6 cm
- Multiple cauliflower-shaped malignancies of rt LE
  - Largest 5 x 5 x 2.5
  - Escalating pain, neuropathic and musculoskeletal quality
Case Report

Medications:

- IV hydromorphone 40 mg/hr basal, 60 mg/hr PCA via ACW port
- Intrathecal (IT) morphine 0.2 mg/hr
- Oral methadone 80 mg TID
- Total morphine equivalent dose...?

- Adjuvants: Alprazolam 4 mg q 4 hrs PRN, Sertraline 150 mg/day
Pain Exacerbation: Bone Pain

- Known bone metastasis
- Not on NSAID
- Started dexamethasone 8 mg daily
- Pain relief within 2 hours, increased as bone-related pain increased with good results, to total of 12 mg daily
Pain Exacerbation: Tumor Lesions

• Open cancerous lesion right inguinal region, satellite lesions of right lower extremity
• Painful dressing changes
• Continual burning, aching quality
• Initiation of tetracaine 7 mg, clonidine .2 mg, gabapentin 6 mg and ketoprofen 120 mg made to spray TID and prior to dressing changes
• Topical pain controlled throughout hospice course
Pain Exacerbation: Generalized Pain

- Wife (RN) had privately increased IV hydromorphone by 15 mg/hr with negative effect.
- Concern for opioid-induced hyperalgesia.
- Reduce hydromorphone by 10%, continue gradual reduction until able to discontinue - significant education to patient and family.
- Increase methadone to 100 mg TID.
- Continue IT morphine at .2 mg q hour.
Sudden Deterioration: “All-Over” Pain

- Pain rated “10/10”
- Myoclonus
- Agitation
- Visual Hallucinations
- Tachycardia, tachypnea
- Diaphoresis
- Aggressive Behaviors
- Pinpoint pupils
Diagnosis?

Opioid-induced neurotoxicity

- Risk of seizure, death
- Limited treatment options
Treatment

- IV ketamine, 10 mg bolus and 10 mg/hr continuous infusion
- Decrease of IV hydromorphone by 30% q 24 hrs
- D/C of methadone despite favorable neurotoxicity risk factor
- Continuation of IT morphine due to decreased risks of systemic side-effects
Outcome

- Pain reduced from “10/10” to “7/10” within 12 hours with reduction of neurotoxic symptoms, patient peaceful
- Pain < 3/10 at 24 hours
- Patient died peacefully in wife’s arms at 36 hours, goal of death at home fulfilled
**Conclusion.** OIN should be considered as an etiology of CNS dysfunction occurring with prolonged, high-dose opioid therapy. This case highlights the opioid-sparing and analgesic properties of low-dose ketamine, allowing reversal of OIN in the home hospice setting.
Is Ketamine Getting On Your Nerves?

- Topical combination:
  - Ketamine 10%, clonidine .2 mg and gabapentin 6 mg
- Compounded to cream or spray
- Apply 1 ml TID and w/ dressing changes
  - Cancer-related pain
  - CRPS
  - Herpetic Neuralgia
  - ? Trigeminal Neuralgia
  - Chronic pain (back pain, DJD, joint pain)
The Future of Ketamine:

“Topical approaches to analgesia have the potential to produce pain relief with minimal adverse systemic effects due to low plasma levels, and, as mechanisms involved in peripheral pain signally have come to be better understood, there has been considerable interest in exploration of novel topical agents as analgesics.”

(Sawynok, 2015)²
References: