Ketamine: Its Role in Acute Pain in the Opioid Tolerant

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Objectives

1. Identify the role of NMDA receptor antagonists
2. Recognize how ketamine can be used safely and effectively in acute pain management

Off-Label Use

Use outside FDA approved indication
FDA allows off label prescribing
Professional judgment safe and effective
**Off-Label**

- Pharma cannot promote off label use
- FDA does not restrict other parties from discussing or distributing written materials
- Can anyone request a label change?
- Extremely costly and time consuming

**Opioid Tolerance**

- Develops with repeated use of opioids
- Need to increase dose to maintain equipotent analgesic effects
- Expected physiologic occurrence
- Does not imply or cause addiction

Ballantyne, J. NEJM 2003; 349:1943-1963


**Cellular Mechanisms of Tolerance**

- Uncoupling of G-proteins from opioid receptors
- Down regulation of opioid receptors
- Activation of N-methyl-D-aspartate (NMDA) receptor


Ballantyne, J., NEJM. 2003;349: 1943-53
Opioid Induced Hyperalgesia

- Abnormally intense or prolonged pain
- Likely up-regulation of compensatory pro-nociceptive pathways
- May aggravate pre-existing pain
- Does develop in humans

Angst M, Clark D. Anesthesiology. 2006; 104: 570-587.

Glutamate

- Major excitatory amino acid
- Interaction with receptors essential for CNS function
- Activates the NMDA receptor

N-methyl-D-aspartate Receptor

- Glutamate receptor
- Involve ion channel
- Distinct binding sites
- Ketamine binds to PCP

Figure 2: NMDA Channel
NMDA Receptor Antagonist

- Inhibit the normal function of the receptor
- Interrupts flow through ion channel
- Decreased transmission of nociceptive information

NMDA Receptor Antagonists

- ketamine
- dextromethorphan
- amantidine/memantine
- magnesium

Non-Opioid Analgesics for Postoperative Pain

Ketamine, Dextromethorphan, Memantine, Clonidine, Dexmedetomidine, Gabapentin, Pregabalin, COX-1 & 2 inhibitors, Acetaminophen

Ketamine, Dextromethorphan, Magnesium, Celecoxib, Clonidine, Dexamethasone, Gabapentin, Pregabalin, Neostigmine, Local anesthetics, COX-1 and COX-2 inhibitors

Clonidine, Steroids, Neostigmine, local anesthetics

Dextromethorphan

- Most readily available NMDA receptor antagonist
- Antitussive approved in 1958
- Reduced pain intensity\(^1,2\)
- Reduced analgesic requirements\(^1,2\)

Weinbroum A. et al. Anesthesia 2001; 56 (7): 616-21
Weinbroum A. Anesthesia & Analgesia 2002 94(6): 1547-52
Dextromethorphan

- Less psychotomimetic effects¹
- Anti-hyperalgesic effect²
- Safe to be an adjuvant³
- Study results inconsistent³
- Didn’t recommend for post op pain³


Amantadine

- Low affinity NMDA channel blocker
- Anti-viral, Parkinson’s
- Did not reduce pain scores in TAH pts.¹
- Reduced IV PCA morphine consumption²
- Lower VAS scores around wound²


Magnesium

- Magnesium blocks ion channel
- Reduced opioid consumption¹
- Intrathecal-prolonged analgesia²

Ketamine

- Dissociative anesthetic, Schedule III
- Used in human and veterinary medicine
- Analgesic mechanisms centrally and peripherally\(^1\)
- Reversal of opioid tolerance involves interaction between NMDA, nitric oxide pathway & µ-opioid receptors\(^2\)

Kohrs R, Durieux ME. Anesth Analg. 1998; 87:1186-93

Ketamine

- FDA label
  - General anesthesia; Adjunct
  - Procedural sedation
- Crosses placenta
- WHO-compatible with breastfeeding
- Thompson-can’t rule out infant risk
- Metabolized by liver- half life 2.5hr.
- Pharyngeal & laryngeal tone maintained

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Levels of Evidence

- Level I- systematic review of randomized controlled trials-meta analysis
- Level II- one or more well designed randomized controlled trials
- Level III-non randomized or cohort or case controlled analytical studies (multi-center)
- Level IV-opinions of respected authorities based on clinical experience, descriptive studies, or expert committees
Ketamine

- Reduces morphine requirements\(^1\)
- Adverse effects mild or absent\(^1\)
- Reduced post op nausea and vomiting\(^1\)
- Reduced post op pain in opioid tolerant spinal fusion patient\(^2\)


Ketamine

- Attenuated tolerance\(^1\)
- Reduced opioid consumption\(^1\)
- Prevent central sensitization\(^2\)
- Reduces wind up\(^2\)

Woolf, CJ, Thompson, SWN. Pain. 1991; 44: 293-299.\(^2\)

Ketamine

- Low dose useful and safe in 54% studies
- Consider as additive in post op opioid tolerant
- Best used as continuous infusion
- Adding to PCA morphine not useful
- No reduction in opioid side effects
- Low dose not associated with CNS side effects

Ketamine as Multimodal Agent

- In RCT, perioperative ketamine use:
  - Reduces opioid dose by 30%
  - Reduces chronic post surgical pain syndromes

- Dose:
  - 0.1 - 0.5 mg/ kg bolus ± 0.1 - 0.5 mg/kg/hr infusion

- Side effects:
  - < 10% of patients had complaints of psycho-cognitive effects

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Visser E et al: Biomedicine & Pharmacology 2006; 60: 341

Ketamine in Chronic Pain Management

- Not enough evidence to advocate routine use of ketamine in chronic pain
- Lack of enough good quality studies
- Reasonable third line option
- Severe acute on chronic episodes of neuropathic pain use continuous infusions


Ketamine Routes of Administration

- Oral
- Nasal
- Rectal
- Topical
- Epidural, Intrathecal
- Intramuscular
- Intravenous
Intranasal Ketamine

- Phase III trials
- Placebo controlled phase II trials
- Moderate – Severe post op pain
- Breakthrough pain
- 10-50mg doses
- No changes in vital signs or O2 saturation


Considerations

- No dose adjustment for renal failure
- Insufficient data to direct use in liver failure
- Contraindicated in acute porphyria
- No good data for dosing in elderly
- Lack of safety data in pregnancy and breastfeeding
- No data for pts with resp. disease, OSA or cardiac disease

Visser, E et al. Biomedicine & Pharmacology 2006; 60: 341-8

Considerations

- Ketamine is opioid sparing
- May need to administer a benzodiazepine
- Use controlled administration device
- Administer boluses over 60 seconds
**Precautions**

- Psychosis and schizophrenia
- Post Traumatic Stress Disorder
- Neurological issues (Cranial)- Recent head injury, increased ICP

**Dosing**

- General anesthesia; Adjunct: induction
  - 1 to 4.5mg/kg IV single dose
  - 1-2mg/kg IV infusion at 0.5mg/kg/min
- GA; Adjunct: maintenance
  - 0.1 to 0.5mg/min IV infusion, repeat as needed
  - 0.01 to 0.03mg/kg/min continuous IV infusion
- Procedural sedation:
  - 1-2mg/kg IV over 1-2min, then 0.25-0.5mg/kg q5-10min as needed

**Sub-anesthetic Ketamine Dosing**

- Only to be ordered by those familiar with ketamine
- Literature favors intra-op initiation
  - 0.25-0.5mg/kg single bolus
  - 1 to 6 mcg/kg/min infusion (may continue for a few days)\(^1\)

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Potential Side Effects

- Tremors
- Dizziness
- Nausea
- Hallucinations
- Vivid dreams
- May require benzodiazepine
Monitoring
- Pre and post bolus pain score, HR, BP, sedation scale
- At least same as opioid monitoring
- Monitor for adverse effects
- Notify physician if psychomimetic effects intolerable

Documentation
- Initiation of therapy
- Boluses and rate changes
- Document any side effects

Discontinuation of ketamine
- No formal weaning necessary
- Can just stop infusion
- If patient experiencing adverse CNS effects, may continue for several hours
Conclusion

- Subanesthetic ketamine safe & effective
- Protocols and dosing vary
- Use will most likely increase
- We have had no adverse events

Case Study

- 33 y.o. Iraq war veteran; s/p fall
- Mult. Fractures all four extremities
- Vertebral fx’s- back surg. 6 days pre-call
- B/L wrist fusions day of pain consult
- External fixator- R tib/fib fx
- MSContin 30mg q6hr, hydromorphone pca

Questions