Ketamine: Its Role in Acute Pain in the Opioid Tolerant

Kathleen Colfer MSN, RN-BC
Acute Pain Management Service
Thomas Jefferson University Hospital
Philadelphia, PA

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
deLeon-Casasola, O. Clinical Anaesthesiology. 16(4):521-5, 2002 Dec.

Cellular Mechanisms of Tolerance

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

Gintzler, A. et al. *Molecular Neurobiology* 21(1-2):21-33, 2000.
Smith, H.S., Drugs for Pain. 2003. pp. 153-155.
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

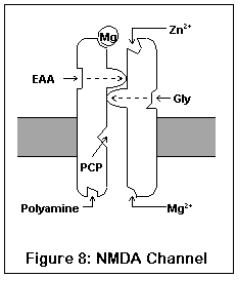
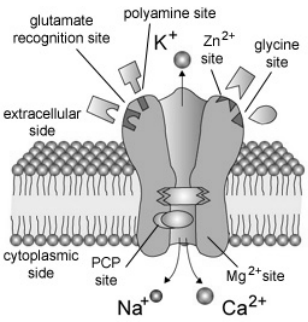


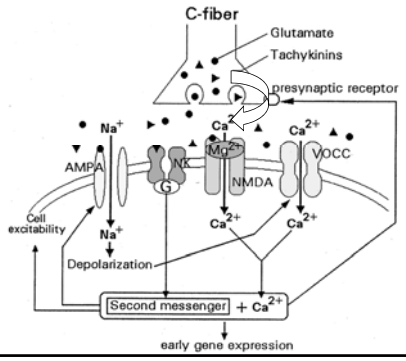
Figure 8: NMDA Channel

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

NMDA Receptor



Synaptic Activity



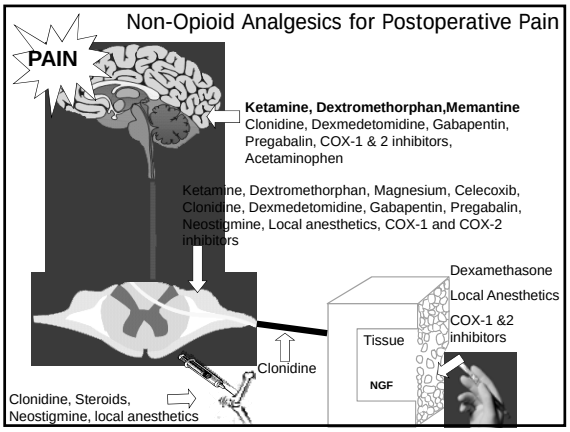
NMDA Receptor Antagonist

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

Santiago-Palma J, Smith H, Sang, C. *Drugs for Pain.* Haley & Belfus 2003: 241-53

NMDA Receptor Antagonists

- ketamine
- dextromethorphan
- amantidine/memantine
- magnesium



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. *Anaesthesia* 2001; 56 (7): 616-22[1]
Weinbroum A. *Anesthesia & Analgesia 2002* 94(6): 1547-52[2]

Dextromethorphan

- Less psychotomimetic effects[1]
- Anti-hyperalgesic effect[2]
- Safe to be an adjuvant[3]
- Study results inconsistent[3]
- Didn't recommend for post op pain[3]

[1]LePage, KT et al. Neuropharm. 2005; 49: 1-16.
[2]Duedahl, T. et al Pain 2005; 113 (3): 360-368.
[3]Duedahl, T. et al Acta Anaesth Scand. 2006; 50 (1): 1-13

Amantadine

- Low affinity NMDA channel blocker
- Anti-viral, Parkinson's
- Did not reduce pain scores in TAH pts.[1]
- Reduced IV PCA morphine consumption[2]
- Lower VAS scores around wound[2]

Gottschalk et al. Anesth & Analg. 2001; 93:192-6.[1]
Snijdelaar D. et al. Anesth 2004; 100 (1): 134-141.[2]

Magnesium

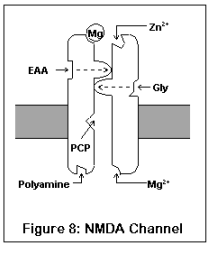


Figure 8: NMDA Channel

- Magnesium blocks ion channel
- Reduced opioid consumption[1]
- Intrathecal-prolonged analgesia[2]

Ozcan, P et al. *J Cardiothoracic & Vascular Anesthesia.*2007; 21(6): 827-31[1]
Buvanendran, A et al. *Anesth & Analg* 2002; 95(3): 661-6[2]

Ketamine

- Dissociative anesthetic, Schedule III
- Used in human and veterinary medicine
- Analgesic mechanisms centrally and peripherally[1]
- Reversal of opioid tolerance involve interaction between NMDA, nitric oxide pathway & μ-opioid receptors[2]

Kohrs R, Durieux ME. *Anesth Analg.* 1998; 87:1186-93
Mao J et al. *Pain* 1995; 62: 259-274

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

Thompson Micromedex® Healthcare Series: Drugdex® Drug Point

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 committies

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]

Bell, R.F. et al. *Acta Anaesthesiol Scand.* 2005; 49:1405-1428 (Cochrane review)[1]
Urban, M. et al. *HSSJ* (2008) 4: 62-65. Published online: 12/19/2007. Hospital for Special Surgery.[2]

Ketamine

- Attenuated tolerance[1]
- Reduced opioid consumption[1]
- Prevent central sensitization[2]
- Reduces wind up[2]

Kisson, I. et al. *Anesth Analg.* 2000; 91:1483-1488.[1]
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

Subramaniam, K. et al. *Anesth Analg. 2004; 99: 482-495*

Ketamine as Multimodal Agent

- In RCT, perioperative ketamine use:
  - Reduces opioid dose by 30%
  - Reduces chronic post surgical pain syndromes[1]
- 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[2]

[1]Lavand'homme P et al: *Anesthesiology 2005; 103: 813- 20*.
[2] 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

Hocking G, Cousins, M. *Anesth Analg.* 2003; 97: 1730-1739

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 O_2 saturation

http://www.javelinpharmaceuticals.com/pmi150.html. Accessed 3/21/2009.

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 & Pharmaco* 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

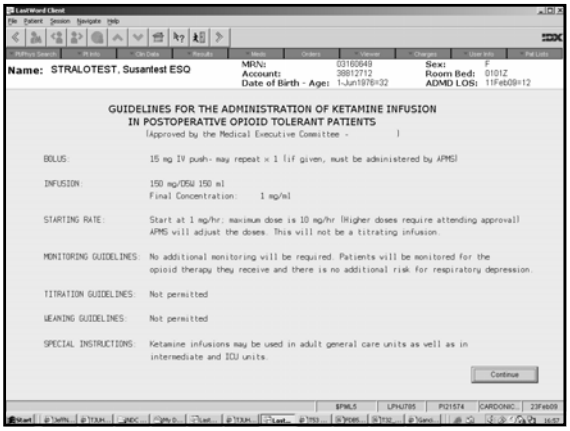
- General anesthesia; Adjunct: induction
  - 1 to 4.5mg/kg IV single dose
  - 1-2mg/kg IV infusion at 0.5mg/kg/min
- GA; Adjunct: maintenance
  - 0.1 to 0.5mg/min IV infusion, repeat as needed
  - 0.01 to 0.03mg/kg/min continuous IV infusion
- Procedural sedation:
  - 1-2mg/kg IV over 1-2min, then 0.25-0.5mg/kg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

Thompson Micromedex® Healthcare Series: Drugdex® Drug Point

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]

Carroll, I et al. *Reg Anesth &Pain Medicine,* 2004; 29(6): 576-591



Name: STRALOTEST, Susantest ESQ
MRN: 03160849 Sex: F
Account: 38812712 Room Bed: 0101Z
Date of Birth - Age: 1-Jun1976#32 ADMD LOS: 11Feb09#12

GUIDELINES FOR THE ADMINISTRATION OF KETAMINE INFUSION
IN POSTOPERATIVE OPIOID TOLERANT PATIENTS
(Approved by the Medical Executive Committee -)

BOLUS: 15 mg IV push- may repeat x 1 (if given, must be administered by APMS)

INFUSION: 150 mg/D5W 150 ml
Final Concentration: 1 mg/ml

STARTING RATE: Start at 1 mg/hr; maximum dose is 10 mg/hr (Higher doses require attending approval) APMS will adjust the doses. This will not be a titrating infusion.

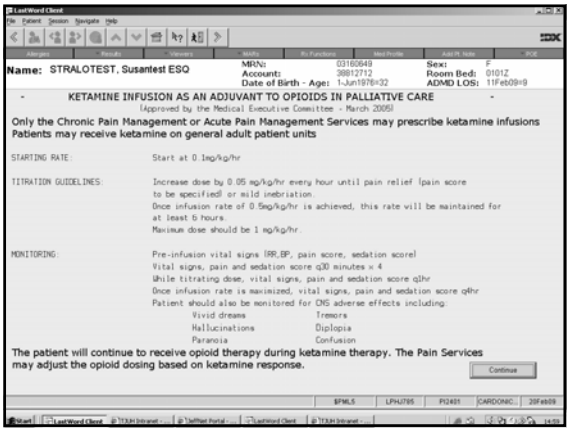
MONITORING GUIDELINES: No additional monitoring will be required. Patients will be monitored for the opioid therapy they receive and there is no additional risk for respiratory depression.

TITRATION GUIDELINES: Not permitted

WEANING GUIDELINES: Not permitted

SPECIAL INSTRUCTIONS: Ketamine infusions may be used in adult general care units as well as in intermediate and ICU units.

Continue



Name: STRALOTEST, Susantest ESQ
MRN: 03160849 Sex: F
Account: 38812712 Room Bed: 0101Z
Date of Birth - Age: 1-Jun1976#32 ADMD LOS: 11Feb09#9

KETAMINE INFUSION AS AN ADJUVANT TO OPIOIDS IN PALLIATIVE CARE
(Approved by the Medical Executive Committee - March 2005)

Only the Chronic Pain Management or Acute Pain Management Services may prescribe ketamine infusions
Patients may receive ketamine on general adult patient units

STARTING RATE: Start at 0.1mg/kg/hr

TITRATION GUIDELINES: Increase dose by 0.05 mg/kg/hr every hour until pain relief (pain score to be specified) or mild inebriation.
Once infusion rate of 0.5mg/kg/hr is achieved, this rate will be maintained for at least 6 hours.
Maximum dose should be 1 mg/kg/hr.

MONITORING: Pre-infusion vital signs (RR,BP, pain score, sedation score)
Vital signs, pain and sedation score q30 minutes x 4
While titrating dose, vital signs, pain and sedation score q1hr
Once infusion rate is maximized, vital signs, pain and sedation score q4hr
Patient should also be monitored for CNS adverse effects including:
Vivid dreams Tremors
Hallucinations Diplopia
Paranoia Confusion

The patient will continue to receive opioid therapy during ketamine therapy. The Pain Services may adjust the opioid dosing based on ketamine response.

Continue

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

Kathy Colfer MSN, RN-BC

kathcolfer@aol.com

215-955-2938