**KETAMINE - What’s Old is New Again**

Mary Wojnakowski, CRNA, PhD  
Associate Professor  
Midwestern University  
Nurse Anesthesia Program

**WHATS OLD…..**

“Taming the Ketamine Tiger”

Domino, EF. Taming the ketamine tiger. Anesthesiology. 2010;113(3):678-84.

**“DISSOCIATIVE ANESTHETIC”**

- Produces an atypical behavioral state.
  - State of sedation
  - Immobility
  - Amnesia
  - Marked analgesia
  - Feeling of dissociation from the environment
    - Without true unconsciousness

**NEUROPHARMACOLOGY**

- Ketamine is primarily a non-competitive 
  _NMDA_ receptor antagonist.
  - Studies also seem to indicate that ketamine is
    'use dependent' meaning it only initiates its 
    blocking action once a glutamate binds to the 
    _NMDA_ receptor.

- At high doses, ketamine has also been 
  found to bind to _opiates_ mu receptors and 
  sigma receptors.

**ORGANIC CHEMISTRY**

- Phencyclidine derivative
• Has two stereoisomers
  – R⁺ and S⁺
  • Have different anesthetic potencies (1:3-4) but similar kinetics

• Soluble in aqueous solutions
  – Does not require a lipid solvent like propofol or etomidate
  – Produces profound analgesia at subanesthetic doses.

• pH is 3.5 to 5.5 (pKa 7.5)

• Highly lipid soluble
  – 12-35% plasma protein bound
  – 44% nonionized at physiologic pH

• Cardiovascular system:
  – Direct myocardial depressant
    • Overcomes the central sympathetic stimulation, neuronal release of catecholamines, & inhibition of neuronal uptake of catecholamines.
    • Increase in systemic arterial pressure
    • Increase in heart rate
    • Increase in cardiac output

• Pulmonary system:
  – Bronchial smooth muscle relaxant
    • As effective as inhalational agents in preventing bronchospasm
    • Increase in pulmonary arterial pressure
    • Increases salivary & tracheobronchial secretions

• Neurological system:
  – Seizure threshold is not altered
  – Increase in cerebral metabolism, blood flow, & ICP

• Other:
  – Increases uterine tone without adverse effects on uterine blood flow
  – Does not release histamine

• Its R⁺ and S⁺ stereoisomer have different binding affinities.
  – (S)-Ketamine has about four times greater affinity for the PCP site of the NDMA receptor than (R)-Ketamine (in guinea pig brain).
  – The S form also seems to be better at inducing drowsiness than the R form.

PHARMACODYNAMICS
• Dosing:
  – Sedation/Analgesia
    ▪ IV: 0.5 – 1.0 mg/kg
    ▪ IM/rectal: 2.5 – 5.0 mg/kg
    ▪ PO: 5 – 6 mg/kg
  – Induction
    ▪ IV: 1.0 – 2.5 mg/kg
    ▪ IM/rectal: 5 – 10 mg/kg
  – Infusion
    ▪ 15-80 mcg/kg/min
      • Augment with diazepam IV 2 -5 mg or midazolam IV 1 -2 mg
  – Epidural/ Caudal
    ▪ 0.5 mg/kg
      • Dilute in saline or local anesthetic (1 mL/kg)
PHARMACKINETICS

- Onset of action:
  - IV <30 seconds
  - IM/rectal 3 – 4 minutes
- Peak effects:
  - IV 1 minute
  - IM/rectal 5 – 20 minutes
  - PO 30 minutes
- Duration of action:
  - IV 5 - 15 minutes
  - IM/rectal 12 – 25 minutes
  - Epidural 4 hours
- Demethylation & hydroxylation by hepatic CYP
  - One of the produced metabolites is active
    - Norketamine (Metabolite I)
      - Has a potency of 30% of the parent drug & longer half-life

WHATS NEW...

- Strong pain stimuli activate NMDA receptors and produce hyperexcitability of dorsal root neurons. This induces central sensitization, wind-up phenomenon, and pain memory.
- Ketamine can prevent the induction of central sensitization caused by stimulation of peripheral nociception as well as blocking the wind-up phenomenon.

Multimodal Analgesia

- Simultaneous use of multiple analgesic methods or drugs.

Review of the Current Literature...

Ketamine as an Adjunct Analgesic
Bell RF, Dahl JB, Moore RA, Kalso E. Perioperative ketamine for acute postoperative pain. The Cochrane Database of Systematic Reviews. 2006; 3; 1-61.

- **N = 37 trials (2240 participants)**
- **Methods:**
  - Search from 1966-2004
  - Randomized, controlled trials being treated with perioperative ketamine or placebo
- **Results & Conclusion:**
  - Subanesthetic doses of ketamine reduce rescue analgesia requirements, pain intensity, PCA morphine consumption, PONV.
  - Adverse effects were mild or absent.


- **Methods:**
  - **N = 75**
  - Major upper abdominal surgery
  - Treatment groups:
    1) Intraoperative remifentanil at 0.05 mcg/kg/min
    2) Intraoperative remifentanil at 0.40 mcg/kg/min
    3) Intraoperative remifentanil at 0.40 mcg/kg/min Ketamine 0.5 mg/kg just after incision followed by infusion at 5 mcg/kg/min until skin closure then 2 mcg/kg/min for 48 hours
- **Results:**
  - Hyperalgesia in group 2 was greater compared to the other two groups
  - No difference between group 1 and 3
- **Conclusion:**
  - Large doses of intraoperative remifentanil triggers postoperative hyperalgesia
  - This hyperalgesia is prevented by small-dose ketamine
  - NMDA pain-facilitator process


- **N = 40**
- Elective total knee arthroplasty with general anesthesia & continuous femoral nerve block
- **Methods:**
  - Treatment groups
    1) Ketamine 0.5 mg/kg bolus before skin incision followed by infusion at 3 mcg/kg/min until emergence from anesthesia followed by infusion at 1.5 mcg/kg/min for 48 hours
    2) Placebo
- **Results & Conclusions:**
  - Group 1 required less morphine, reached 90° flexion more rapidly.
  - No difference in side effects


- **N = 72**
- Traumatic patients undergoing orthopedic operations
- **Methods:**
  1) Ketamine group
    - 5 mg/kg po every 8 hours for 24 hours
  2) Control group
- **Results:**
  - Ketamine group had lower pain scores, morphine use, & longer time to first rescue
- **Conclusion:** Oral ketamine significantly reduces postoperative pain


- Low-dose ketamine (0.2-1 mg/kg) has a 1-2.5% incidence of hallucination or dysphoria while maintaining adequate pain relief.
- Patients have less PONV.
- Patients have decreased pain on long-term follow-up.


- **N = 101**
- Opiate-dependent patients undergoing major lumbar spine surgery
- **Methods:**
  - Treatment group
    - 0.5 mg/kg IV ketamine on induction of anesthesia, and a continuous infusion at 10 mcg/kg/min begun on induction and terminated on wound closure
  - Placebo group
- **Results:**
  - Total morphine consumption was significantly reduced in treatment group at 24 hrs, 48 hrs, 6 weeks.
  - No difference between groups regarding side effects.
**Ketamine for Preemptive Analgesia**


- **N = 135**
- **Methods**
  - Treatment groups
    - 1) Preincision group
      - Ketamine IV 0.15 mg/kg immediately before induction of anesthesia
    - 2) Postoperative group
      - Ketamine IV 0.15 mg/kg after wound closure
    - 3) Placebo group

- **Results & Conclusions:**
  - Group 1 had lower pain scores, longer time to first request for analgesia, & lower morphine consumption
  - No difference r/t hemodynamic variables or side effects


- **N = 69**
- **Methods:**
  - Treatment groups (started before incision)
    - 1) Morphine 0.1 mg/kg
    - 2) Ketamine 0.15 mg/kg
    - 3) Morphine 0.1 mg/kg and Ketamine 0.15 mg/kg

- **Results:**
  - KM group had less pain at rest & on mobilization
  - KM group had decreased morphine consumption
  - KM group had lower incidence of PONV
- **Conclusion:** Ketamine small dose combined with morphine improves postoperative analgesia & reduces opioid-related side effects.

**Gunduz M, Ozakvli M, Ozbek H, Ozogenc D. Comparison of caudal ketamine with lidocaine or tramadol administration for postoperative analgesia of hypospadias surgery in children. *Paediatric Anaesthesia*. 2006;16(2):158-63.**

- **N = 62 (ASA I or II; 1-10 years)**
- **Methods:**
  - Treatment groups
    - 1) Caudal ketamine 0.25 mg/kg plus 2% Lidocaine 2mg/kg
    - 2) Caudal ketamine 0.25 mg/kg plus Tramadol 1mg/kg

- **Results:**
  - Sevoflurane concentrations were lower in lidocaine group
  - Postoperative pain scores were lower in lidocaine group
- **Conclusion:** Caudal ketamine & lidocaine reduce anesthetic requirements and provide superior pain control.


- **N = 50**
- **Methods:**
  - Treatment groups:
    - Continuous epidural infusion of ropivacaine & morphine with IV ketamine at 0.05 mg/kg/hr
    - Placebo
    - Epidural in place for 2 POD; ketamine infusion for 3 POD

- **Results:**
  - Ketamine group has lower pain scores
  - Ketamine group had lower baseline pain scores at 1 & 3 months
    - Placebo group was still taking pain medications.
- **Conclusions:**
  - Very-low-dose ketamine potentiated morphine-ropivacaine analgesia and reduced post-thoracotomy pain.
Ketamine for Chronic Pain


- N = 13
- Outpatients with neuropathic pain (noncancer) uncontrolled with opioids, anticonvulsants, and/or antidepressants
- Methods:
  - Continuous IV or sub-q infusion
    - 0.12-0.25 mg/kg/hr
    - Duration was 5-28 days
- Results:
  - 85% reported a decrease in pain
  - No side effects
- Conclusion: Ketamine reasonable alternative treatment for nonresponsive neurogenic pain.

Ketamine and Brain Injury


- N = 79 trials (> 500 participants)
- Methods:
  - Search from 1994-2004
  - Randomized controlled trials
  - Nonrandomized controlled or cohort trials
- Results & Conclusions:
  - Ketamine does not increase ICP when used with controlled ventilation, co-administration of a GABA receptor agonist, and without nitrous oxide.
  - Hemodynamic stimulation induced by ketamine improved cerebral perfusion.
  - In the lab:
    - Ketamine has neuroprotective effects
    - S(+)-ketamine has neuroregenerative effects
  - NOTE:
    - Improved outcomes were only reported with brief recovery observation intervals
    - Neurotoxic effects noted after large doses


- Case study
  - Child serves as own control
- Methods:
  - First attempt (No MEP's could be recorded)
    - Propofol 50-100 mcg/kg/min
    - Remifentanil 2 mcg/kg/min
  - Second attempt (MEP's could be obtained)
    - Ketamine 20 mg bolus followed by infusion of 4 mg/kg/hr
    - Remifentanil 2 mcg/kg/min
- Results & Conclusions:
  - Ketamine-based anesthesia improves the signal quality of MEP's.


- Review paper
- Proposed change of paradigm in anesthetic neuroprotection.
- Recent research indicates antagonism of NMDA receptors provide superior protection.

- 15-year-old girl
- Intraoperative wake-up test
- Dexmedetomidine 0.9-1.2 mcg/kg/hr
- Ketamine 0.4-0.6 mg/kg/hr
- Maintenance: 60% nitrous and fentanyl infusion 1-2 mcg/kg/hr

The sympatholytic properties of dexmedetomidine were balanced with the sympathomimetic properties of ketamine, and the patient required minimal vasoactive support.

 Provided satisfactory conditions for neurophysiologic monitoring.

Dalens BJ, Pinard AM, Letourneau DR, Albert NT, Truchon RJY. Prevention of emergence agitation after sevoflurane anesthesia for pediatric cerebral magnetic resonance imaging by small doses of ketamine or nalbuphine administered just before discontinuing anesthesia. Anesthesia & Analgesia. 2006; 102: 1056-61.

- N = 90
- 6 mo to 8 years scheduled for cerebral MRI under general anesthesia
- Methods:
  - Treatment groups:
    1) Ketamine 0.25 mg/kg
    2) Nalbuphine 0.1 mg/kg
    3) Placebo
- Results & Conclusions:
  - Group 3 was most agitated at all times
  - Group 1 & 2 more obtunded at 5 and 10 minutes BUT all groups met discharge criteria at 30 minutes
  - Group 1 & 2 were more awake and quiet (Most in group 1; all in group 2)


- N = 8 studies (1086 participants)
- Assess safety & efficacy of various forms of analgesia and sedation
- Results:
  - Ketamine-midazolam was more effective & had fewer side effects than fentanyl-midazolam or propofol-fentanyl.


- N = 90
- Methods:
  - Treatment groups
    1) Control
    2) 0.5 mg/kg before surgical start
    3) 0.5 mg/kg after operation ended
- Results:
  - Significantly less pain in group 2 & 3
  - Less to no need for rescue morphine in group 2 & 3 respectively
  - No unexpected side effects noted
- Conclusion:
  - Small dose ketamine reduces postoperative pain.
  - Timing of administration makes no difference.


- Case report
- 2-year-old (9.5 kg)
- Transposition of great vessels scheduled for a Rastelli operation
- Required ECMO postoperatively
  - Fentanyl 50 mcg/hr
  - Midazolam 10 mcg/hr
- Sedation was weaned then discontinued on 58th postoperative day when patient was weaned from ventilator.
- Three hours post extubation received naloxone 80 mcg & flumazenil 130 mcg—opioid withdrawal syndrome
- Conventional withdrawal techniques failed.
- Ketamine was initiated at 10 mg/hr
- Fentanyl was successfully washed off, then ketamine.
- Patient was extubated

- Goal: effective sedation with limited effects on cardiovascular & ventilatory function.
- Bolus:
  - Ketamine 1mg/kg
  - Dexmedetomidine 1 mcg/kg
- Maintenance infusion:
  - Dexmedetomidine 1 mcg/kg/hr
- One patient required a repeat of the bolus doses & an increase in infusion to 2 mcg/kg/hr.
- No hemodynamic or respiratory effects.
- No central apnea.

Other Studied Uses of Ketamine


- N = 30
- Arthroscopic knee surgery with tourniquet under spinal anesthesia with 12.5 mg bupivacaine
- Methods:
  - Treatment groups:
    1) Midazolam 0.01 mg/kg
    2) Ketamine infusion at 0.5 mg/kg/hr to end of surgery
- Results & Conclusions:
  - Group 1 had lower MDA & HPX levels after reperfusion
  - Ketamine attenuates lipid peroxidation which results in tissue injury

McDaniel WW, Sahota AK, Vyas BV, Laguna N, Hategan L, Oswald J. Ketamine appears associated with better word recall than etomidate after a course of six electroconvulsive therapies. J ECT. 2006; 22: 103-6.

- N = 10
- ECT for severe depression
- Methods:
  - Patients served as their own controls
  - Treatment groups:
    1) Etomidate 0.3 mg/kg
    2) Ketamine 1.0 mg/kg
- Results:
  - Group 2 had less impairment of short-term memory loss
- Conclusion:
  - The effect of ECT on memory is mediated by glutamate at NMDA receptors
  - NMDA receptor antagonists may offer protection from memory dysfunction


- N = 90
- Undergoing general anesthesia for an anticipated duration of 60-180 minutes
- Methods:
  - Treatment groups (administered 20 min before end of surgery):
    1) Pethidine 20 mg
    2) Ketamine 0.5 mg/kg
    3) Placebo
- Results:
  - Fewer patients in group 1 & 2 were shivering on arrival in the recovery room
  - Time to first analgesic requirement was less in group 1 & 2
- Conclusions:
  - Low dose ketamine is effective in preventing postoperative shivering


- N = 9
- Assess the effect of topically applied ketamine
- Methods:
  - Treatment groups:
    1) Applied 1 mL of Ketamine gel (30 mg/mL)
    2) Placebo
    - Applied to bilateral forearms 10 minutes before intradermal injection of capsaicin (250 mcg)
- Results:
  - Intensity & unpleasantness of mechanical hyperalgesia was less with ketamine
  - No side effects were noted
- Conclusion:
  - Preemptive topical ketamine reduces central sensitization secondary to its absorption into circulation

- **Methods:**
  - Treatment groups (immediately followed by propofol 2.5 mg/kg):
    1) saline
    2) lidocaine
    3) Ketamine 10 mcg/kg
    4) Ketamine 50 mcg/kg
    5) Ketamine 100 mcg/kg
  - Ketamine 100 mcg/kg; 3 min before propofol
  - Ketamine 100 mcg/kg; mixed with propofol
  - Oral Midazolam 7.5 mg; 90 min before arrival in OR

- **Results:**
  - Pain lowest in K100 group
  - Pain lowest in pre-administration group
  - No side effects
  - Conclusion: Administration of ketamine 100 mcg/kg immediately before propofol injection provided optimal dose & timing.

Batta S. Low-dose ketamine analgesia for use in under-developed countries. *Anesthesia & Analgesia*. 2007;104(1);232

- Postoperative analgesia
- Face lack of drugs, lack of money, and risk of diversion.
- Plastic reconstructive surgery in children
- Start ketamine before induction of anesthesia
  - Give an IV bolus of 10 mg
  - Followed by infusion of 0.1-0.15 mg/min for first 3 postoperative days
- Reported no significant pain, nightmares, or hemodynamic instability.

More… What’s Old is New Again


IN CONCLUSION…

THANK YOU