KETAMINE - What's Old is New Again

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WHATS OLD…..

"Taming the Ketamine Tiger"

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

"DISSOCIATIVE ANESTHETIC"

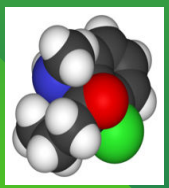
- Produces an atypical behavioral state.
  - State of sedation
  - Immobility
  - Amnesia
  - Marked analgesia
  - Feeling of dissociation from the environment
    - Without true unconsciousness

NEUROPHARMACOLOGY

- Ketamine, is primarily a non-competitive glutamate 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 opioid mu receptors and sigma receptors.

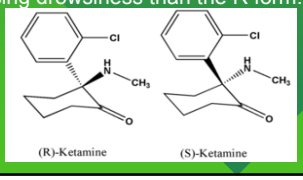
ORGANIC CHEMISTRY

- Phencyclidine derivative



- Has two steroisomers
  - R^- and S^+
    - Have different anesthetic potencies (1:3-4) but similar kinetics

- 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.



- 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

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)

- Cardiovascular system:
  - Direct myocardial depressant
    - Overridden by 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

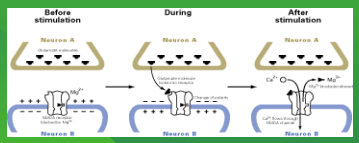
- Other:
  - Increases uterine tone without adverse effects on uterine blood flow
  - Does not release histamine

PHARMACKINETICS

- Onset of action:
  - IV <30 seconds
  - IM/ rectal 3 – 4 minutes
- Peak effects:
  - IV 1minute
  - IM/ rectal 5 – 20 minutes
  - PO 30 minutes
- Duration of action:
  - IV 5 - 15minute
  - IM/ rectal 12 – 25 minutes
  - Epidural 4 hours
- Metabolism:
  - 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.

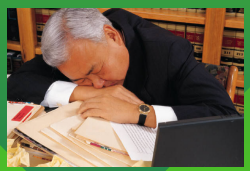


- Ketamine can prevent the induction of central sensitization caused by stimulation of peripheral nociception as well as blocking the wind-up phenomenon.

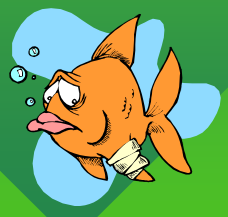
Multimodal Analgesia

- 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.

Joly V, Richebe P, Guignard B, Fletcher D, Maurette P, Sessler DI, Chauvin M. Remifentanil-induced postoperative hyperanalgesia and its prevention with small-dose ketamine. *Anesthesiology*. 2005; 103: 147-55

- 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:
  - Hyperanalgesia 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 hyperanalgesia
  - This hyperanalgesia is prevented by small-dose ketamine
    - NMDA pain-facilitator process

Adam F, Chauvin M, DaManoir B, Langlois M, Sessler DI, Fletcher D. Small-dose ketamine infusion improves postoperative analgesia and rehabilitation after total knee arthroplasty. *Analgesia & Anesthesia*. 2005;100: 475-80.

- 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

Heidari SM, Saghaei M, Hashemi SJ, Parvazinia P. Effects of oral ketamine on the postoperative pain and analgesic requirement following orthopedic surgery. *Acta Anaesthesiologica Taiwanica*. 2006;44(4):211-5

- 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, & linger time to first rescue
- Conclusion: Oral ketamine significantly reduces postoperative pain

Rakic, AM, Golembiewski, J. Low-dose ketamine infusion for postoperative pain management. Journal of Perianesthesia Nursing. 2009;24(4):254-7.

- 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.

Loftus, RW, Yeager, MP, Clark, JA, Brown, JR, Abdu, WA, Sengupta, DK, Beach, ML. Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic back pain undergoing back surgery. Anesthesiology. 2010;113(3): 639-46.

- 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 inductionand 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 Preemtive Analgesia

Kwok RFK, Lim J, Chan MTV, Gin T, Chiu KY. Preoperative ketamine improves postoperative analgesia after gynecologic laparoscopic surgery. *Anesthesia & Analgesia.* 2004; 98: 1044-9.

- 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

Aveline C, Hetet HL, Vautier P, Gautier JF, Bonnet F. Perioperative ketamine and morphine for postoperative pain control after lumbar disk surgery. *Journal of Pain.* 2006;10(7):653-8.

- 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.

Ketamine with Local Anesthetics

Gunduz M, Ozalevli M, Ozbek H, Ozcengiz 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.

Suzuki M, Haraguti S, Sugimoto K, Kikutani T, Shimuda Y, Sakamoto A. Low-dose intravenous ketamine potentiates epidural analgesia after thoracotomy. *Anesthesiology.* 2006; 105: 111-9.

- N = 50
- Methods:
  - Treatment groups:
    1) Continuous epidural infusion of ropivacaine & morphine with IV ketamine at 0.05 mg/kg/hr
    2) 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-ropivacine analgesia and reduced post-thoracotomy pain.

Ketamine for Chronic Pain

Webster LR, Walker MJ. Safety and efficacy of prolonged outpatient ketamine infusions for neuropathic pain. *American Journal of Therapeutics*. 2006; 13(4):300-5.

- 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

Himmelseher S, Durieux ME. Revising a dogma: Ketamine for patients with neurological injury? *Anesthesia & Analgesia*. 2005; 101:524-34.

- 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

Erb TO, Ryhult SE, Duitmann E, Hasler C, Luetschg J, Frei F. Improvement of motor-evoked potentials by ketamine and spatial facilitation during spinal surgery in a young child. *Anesthesia & Analgesia*. 2005; 100: 1634-6.

- 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.

Koerner IP, Brambrink AM. Brain protection by anesthetic agents. *Current Opinion in Anesthesiology*. 2006; 19(5):481-86.

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

Penney, R. Use of dexmedetomidine and ketamine infusions during scoliosis repair surgery with somatosensory and motor-evoked potential monitoring: A case report. AANA Journal. 2010;78(6):446-50.

- 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 properities of dexmedetomidine were balanced with the sympathomimetic properities of ketamine, and the patient required minimal vasoactive support.
- Provided satisfactory conditions for neurophysiologic monitoring.

Ketamine and the Pediatric Patient

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 adminnistered 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:
    - At end of procedure received:
    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)

Migita RT, Klein EJ, Garrison MM. Sedation and analgesia for pediatric fracture reduction in the emergency department: a systematic review. *Archives of Pediatric & Adolescent Medicine*. 2006; 160: 46-51.

- 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.

Conceicao MJ, Conceicao DB, Leao CC. Effects of a single dose of ketamine on postoperative pain in tonsillectomy patients. *Paediatric Anaesthesia*. 2006;16(9):962-7.

- 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 unwanted side effects noted
- Conclusion:
  - Small dose ketamine reduces postoperative pain.
  - Timing of administration makes no difference.

Ito H, Sobue k, Hirate MD, Sugiura T, So MH, Azami T, Sasano H, Katsaya H. Use of ketamine to facilitate opioid withdrawal in a child. *Anesthesiology*. 2006;104(5):1113.

- 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 mg/hr

- Sedation was weaned then discontinued on 58th postoperative day when patient was weaned from ventilator.
- Three hours post extubation received naloxone 60 mcg & flumazenil 130 mcg→ opioid withdrawal syndrome.
- Conventional withdrawal techniques failed.
- Ketamine was initiated at 10 mg/hr.
- Fentanyl was successfully weaned off, then ketamine.
- Patient was extubated

Luscri N, Tobias JD. Monitored anesthesia care with a combination of ketamine and dexmedetomidine during magnetic resonance imaging in three children with trisomy 21 and obstructive sleep apnea. *Paediatric Anaesthesia*. 2006;16(7):782-6.

- 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

Saricaoglu F, Dal D, Salman AE, Doral MN, Kilinc K, Aypar U. Ketamine sedation during spinal anesthesia for arthroscopic knee surgery reduced the ischemia-reperfusion injury markers. *Anesthesia & Analgesia*. 2005;101: 904-9.

- N = 30
- Arthroscopic knee surgery with tourniquet under spinal anesthesia with 12.5 mg bupivacaine
- Methods:
  - Treatment groups:
    1) Midazolam 0.01 mg/ kg
       Ketamine infusion at 0.5 mg/kg/hr to end of surgery
    2) Midazolam 0.01 mg/kg
- 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, Laguerta 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

Dal D, Honca KM, Akinci SB, Basgul E, Aypar U. Efficacy of prophylactic ketamine in preventing postoperative shivering. *British Journal of Anaesthesia*. 2005; 95: 189-92.

- 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

Poyhia R, Vainio A. Topically administered ketamine reduces capsaicin-evoked mechanical hyperalgesia. *Clinical Journal of Pain*. 2006; 22: 32-6.

- N = 9
- Assess the effect of topically applied ketamine

- Methods:
  - Treatment groups:
    1) Applied 1 mL of Ketamine gel (50 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

Koo SW, Cho SJ, Kim YK, Ham KD, Hwang JH. Small-dose ketamine reduces the pain of propofol injection. *Anesthesia & Analgesia*. 2006;103(6):1444-47.

- N = 245
- 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
    ---
    1) Ketamine 100 mcg/kg; 3 min before propofol
    2) Ketamine 100 mcg/kg; mixed with propofol
    3) 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

Kharasch, ED. Intraoperative methadone: rediscovery, reappraisal, and reinvigoration? Anesthesia & Analgesia. 2011;112(1):13-16.

IN CONCLUSION…