Ketamine: Past, Present, Future

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The Speaker has Nothing to Disclose

No relationships financial or otherwise that would bias the information being presented

Objectives

• Discuss the pharmacological considerations of ketamine
• Explore the role ketamine plays in the anesthesthetic plan
• Identify uses of ketamine outside of the anesthesia plan
• Review the evidence regarding the use of ketamine for the treatment of pain
What the Patient Saw and Heard

“A big paisley shaped blob making a horrible noise”
The “Shape” was his nurse

In the beginning...

• Initial thought: sole anesthetic agent

• Criteria of ideal anesthetic:
  – Blockade of sensory, motor, autonomic and cognitive functions


Pharmacokinetics of Ketamine

• Water and lipid soluble:
  – Absorbable by
    • Intravenous
    • Intra-muscular
    • Subcutaneous
    • Epidural
    • Oral, rectal, trans nasal - topical
Pharmacokinetics of Ketamine

- Rapid uptake brain uptake and redistribution
- Peak effect:
  - 1 – 5 minutes I.V.
  - 10 – 15 minutes I.M.
  - 15 – 30 minutes oral

Induction dose GA: 1 - 2 mg/kg I.V. or 3 – 5 mg I.M.
Procedural sedation: 0.5 – 1 mg/kg I.V.

Pharmacodynamics – Central Nervous System

- Anesthesia, analgesia, amnesia
- Depression of:
  - Sensory association areas of the cortex, components of the limbic system and thalamus

Limbic system: processing center

- Integrates information with sensory association cortex
- Thalamus and brainstem
- Information has meaning
- Sensory input from body
Depression of the Limbic System

• CNS unable to receive or process sensory information
• Unable to assess emotional significance of information
• Cataleptic state: eyes open, nystagmus, seems awake – completely unaware of environment

CNS Effects

• Analgesic Effects
  – Centrally
  – Peripherally

Emergence

• Floating sensation
• Vivid dreams
• Blurred visions
• Hallucinations, delirium
  – Frequency: between 5 - 30%
  – Most common: age > 16, female, shorter procedures
Recommendations

• Midazolam 3.75 – 7.5 mg
  – When ketamine is used during anesthesia
  – Decrease incidence and severity of hallucinations

Pharmacodynamics – Cardiovascular

Other Cardiac Effects

• Inhibits neuronal reuptake of catecholamine's
  - elevates circulating concentrations -
  – Further stimulation of the sympathetic nervous system
  – Centrally acting depressants – benzodiazepines, alpha and beta blocking agents - verapamil
Pharmacodynamics - Respiratory

- Functional Residual Capacity
- Minute Volume
- Tidal Volume
- Response to hypercarbic drive

Pharmacodynamics - Respiratory

- Spontaneous respiration
- Muscular tone - tongue, pharynx
- Protective Airway Reflexes

Pharmacodynamics - Respiratory

- Transient Apnea
- Aspiration
  - Salivary and tracheal-bronchial mucus gland secretion increased (antisialogue)

  Bronchodilator – decrease in airway resistance
Ketamine and Anesthesia

- Enhances effects of muscle relaxants
- Ideal - induction and maintenance:
  - Hypovolemia
  - Pericardial tamponade
  - Constrictive pericarditis
  - Cardiogenic shock
  - Critically ill, trauma, battlefield, cardiac surgery

Ketamine and Peds

- Induction – I.M.
- Cyanotic conditions – increases SVR and cardiac output
- Neuromuscular disorders - Risk for MH – avoid volatile anesthetics and muscle relaxants
- Positive RCT evidence – use in asthma

Outpatient Anesthesia

- Effective analgesia and sedation
- Predictable pharmacokinetics and cardiopulmonary stability
- Low cost
- Significant HYPOXIC events
- “Ketafall” – propofol mixed with, non specific dose
Ketamine and Pain

Transmission of Pain

Types of Pain

- Nociceptive – tissue damage
- Neuropathic – nerve damage
- Visceral – deep, organ
- Acute pain -25 million Americans experience
- Chronic Pain - 50 million Americans live with
- Cancer Pain

**Types of Pain**

- Central Pain – damage to CNS
- Complex Regional Pain
- Allodynia - pain from normal stimulus
- Hyperalgesia - perception of pain out of proportion

**N-methyl-D-Aspartate Receptor**

NMDA-glutamate receptor – calcium channel

Normal Physiology:
- Involved in development of central sensitization of dorsal horn neurons (transmits pain signals)
  - Normal Resting Membrane Potential - channel blocked by magnesium – inactive

**Abnormal Transmission**

- Prolonged excitement – NMDA channel unblocks, calcium moves into cell
  - Neuronal “hyperexcitability” - reduction in opioid responsiveness, hyperalgesia and allodynia
Abnormal Pain Transmission

- Chronic activation of receptor – plastic changes in neural circuitry of spinal cord
  - More efficient transmission of pain
  - Normal stimuli interpreted as pain – secondary hyperalgesia

Dosing

Induction dose GA: 1 - 2 mg/kg I.V. or 3 – 5 mg I.M.

Procedural sedation: 0.5 – 1 mg/kg I.V.

Analgesic or antihyperalgesic: 0.15 – 0.25 mg/kg/hour


Ketamine

Ketamine - NMDA receptor channel blocker

Stops ‘wind up’
Ketamine and Pain

• Acts on dorsal horn – central pain
  – fibromyalgia
• “Opioid resistant” patient
• Ketamine + Opioid – may reduce by 30%, decreased PONV

What’s the Evidence?

• Cochrane Database
  – Ketamine + opioid PCA – reduction in post op pain intensity or opioid requirement 27 out of 37 trials – mild or absent SE
  – Results are mixed: low dose + morphine PCA?
  – Ketamine PCA – chronic pain, extreme opioid tolerance

What’s the Evidence?

• Chronic non cancer pain (neuropathic or ischemic)
  – Sub anesthetic dose - 29 RCTs
    • Provides relief
    • Undesirable effects limit use
    • Long term use should be restricted
What’s the Evidence?

• Cancer pain – 2 studies, insufficient evidence
  – “Burst” treatment – 4 hour infusion 600 mcg/kg – lasts one week
  – 100mg/24 hour – I.V., repeated one month, reduced opioid need 70%

Burn Patients

Long Term Effects

• Cognition and memory
  • Diminished attention span
  • Impairs episodic memory acquisition – memory retrieval unaffected
  • Semantic memory (general knowledge) mixed
  • Irreversible cell death?

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Ketamine and Depression

- Major Depressive Disorder (MDD)
  - 2002, RCT – single I.V. Sub anesthetic may relieve depressive symptoms
  - Second RCT – Treatment Resistant (TRD) – ECT and meds – rapid but transient antidepressant effect
    Effects peaked 24 hours/ lasted several weeks


Reviewing the Evidence

- Variables:
  - major depressive disorder (MDD)
  - Treatment resistant (TRD) – definition?
  - Depressed patients with bipolar disorder
  - Comorbidities: anxiety, polypharmacy
  - Assessment: 4, 24, 72 hours
  - Dose: 0.5mg/kg I.V. over 40 – 60 minutes

Ketamine Dose Reported in Studies

- Typical Dose: 0.5mg/kg I.V. Infusion over 40 – 60 minutes
- Other doses reported:
  - 2 cases: 0.27 to 0.3 mg/kg/hour for 5 days
  - 2 cases: 0.5 – 1.0 mg/kg I.M.
  - Number of doses – 1 to 3 or 6
Antidepressant Response

• 20 studies/ 163 patients
• Acute response: 50% or greater, reduction of at least one symptom of depression
• 72 hours post infusion: response 14 – 70%

Implications

• Ketamine may:
  – Enhance antidepressants
  – Enhance ECT – single treatment, decrease seizure threshold, increase seizure duration
  – Actively suicidal – rapid onset

Recreational Use

• Illegal
• “Out of body”, “near death”, to “K hole”
• Internationally -
  – China 2009, 8.5 million tons, precursor
  – U.K. - £ 20 per gram
  – U.S. – 2009 est. 1 – 2% of 10th and 12th graders
Recreational Use

• Highest mortality risk: Death by ‘accident”
  – Drowning
  – Hypothermia
  – Third degree burns
  – MVA – 2 studies, Hong Kong, 45% of injured drivers in nonfatal MVAs, 3% of fatalities (Cohen, Liao, Gupta, 2011)


SE of Long Term Use

• Ulcerative Cystitis
  • Frequency, urgency, dysuria, urge incontinence, occasional painful hematuria
  • CT: thickened bladder wall, smaller capacity, severe inflammation
  • Cystoscopy: severe cystitis
  • Could increase risk of cancer
  • UTI
  • Prognosis: 1/3, 1/3, 1/3

Patient Care Priorities

• Assessment: Monitoring, BP, pulse oximetry
• Neuro assessment
• Safety assessment and monitoring
• Drug administration
• Consistent patient/family teaching
References