Are we any closer to taming the ketamine tiger?

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DISCLOSURES

• None
OBJECTIVES

• Discuss the pharmacology of ketamine when used in the ED or ICU
• Review the safety and efficacy of ketamine in the intensive care unit
• Select the ideal patient to receive ketamine
A BRIEF HISTORY OF KETAMINE

1956  Phencyclidine (PCP) first synthesized, found to be unsuitable for human anesthesia due to emergence delirium

1964  Ketamine, a short acting phencyclidine derivative, first studied in humans. Patients describe a feeling of “floating in outer space.” The term “Dissociative Anesthetic” is coined

1970’s  Wide use of ketamine as a drug of abuse

1980’s  Pharmacokinetics of ketamine studied to explain role of serum concentrations on efficacy and side effects

1990’s  Ketamine first studied for depression

2010’s  Ketamine explored for use in critically ill patients

Anesthesiology 2010; 113:678 – 86
KETAMINE PHARMACOLOGY

Normal NMDA receptor transmission

Presynaptic glutamate + postsynaptic depolarization $\rightarrow$ Mg$^{2+}$
block displaced, Ca$^{2+}$ enters cell

Inhibition of NMDA receptor by ketamine

Channel blocked by ketamine
Ca$^{2+}$ cannot enter cell

KETAMINE PHARMACOLOGY
MULTIPLE BINDING SITES

• Racemic mixture of S(+) and R(-) enantiomers
  – S(+) more potent
• N-methyl-D-aspartate (NMDA) receptor antagonist
  – PCP, d-methadone
• μ, κ, δ Opioid receptors
  – Naloxone will not reverse effect
• GABA agonist
• Sympathomimetic

Anesthesiology 1999;90:1539–45
KETAMINE PHARMACODYNAMICS

CEREBRAL

- Myoclonic activity due to increased subcortical electrical activity
- Increased cerebral blood flow
- Delirium/Emergence
  - Agitation, restlessness, dysphoria/euphoria, nightmares and hallucinations
  - Risks
    - Adults, females, >2mg/kg dose
- Neuroprotective vs neurotoxic
KETAMINE PHARMACOLOGY
DISSOCIATIVE ANESTHESIA WITH KETAMINE

• Fugue state or trance
  – Eyes may remain open, but the patient does not respond
• Normal or slightly enhanced muscle tone is maintained
• Occasional muscular clonus may be observed
• Analgesia is typically substantial or complete
• Total amnesia

Ann Emerg Med. 2011
Hypersalivation

- Sensory association cortex
- Limbic system
- Short and long term memory

KETAMINE PHARMACODYNAMICS
CARDIOVASCULAR AND RESPIRATORY

- Produces central sympathetic stimulation and norepinephrine reuptake inhibition
  - Contrast to other anesthetics
- Minimal affect on respiratory drive
  - Rapid administration or large boluses may produce apnea
- Increased salivation
  - Glycopyrrolate/atropine may not be effective
  - May affect airway patency
- Bronchodilator

Anaesthesist. 1991; 40: 238-244
Anesthesiology. 1982; 56(2): 119-136
KETAMINE PHARMACOKINETICS

- 16% bioavailability
- logP = 2.9
- Protein binding = 47%
- Rapid uptake into brain, rapid redistribution peripherally
  - Peak effect 1-5 minutes following IVP, 10-15 minutes after IM
- Elimination half life of 2 hours (hepatic)
  - Metabolite (nor-ketamine) much less potent
    - Nor-ketamine renal eliminated

Anaesthesist.1991;40:238-244
**EFFECT AND PLASMA CONCENTRATION**

- **Analgesic Dose (0.1-0.3mg/kg)**: Partial dissociated dose
- **Minimal psychiatric effects**
- **Partially dissociated dose (0.4-0.8mg/kg)**: Dissociated Dose
- **Procedures, intubation**
- **Recreational Dose (0.2-0.5mg/kg)**
- **Dissociated Dose (>0.7mg/kg)**
- **Procedures, intubation**

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**Ketamine Concentration**

- **Recreational Dose (0.2-0.5mg/kg)**
- **Analgesic Dose (0.1-0.3mg/kg)**: Minimal psychiatric effects
- **Partially dissociated dose (0.4-0.8mg/kg)**
- **Dissociated Dose (>0.7mg/kg)**: Procedures, intubation
**EFFECT AND PLASMA CONCENTRATION**

- **Dissociated Dose (>0.7mg/kg)**
- **Partially dissociated dose (0.4-0.8mg/kg)**
- **DANGER ZONE**
- **Analgesic Dose (0.1-0.3mg/kg)**

*Graph showing the relationship between ketamine concentration and emergence reactions.*
STRATEGIES TO AVOID EMERGENCE

• Benzodiazepines traditionally used
  – No data for benefit
  – ? Worsen symptoms

• Counseling
  – Providing pre-sedation counseling or allowing for emergence in sensory controlled setting
KETAMINE IN THE ICU

Analgesic properties
- Does not decrease respiratory drive
- Does not cause hemodynamic instability

Emergence phenomenon
- Seizure-like activity
- Adverse effects in decompensated heart failure
- Ambiguous dosing

References:
<table>
<thead>
<tr>
<th>Ketamine?</th>
<th>Fentanyl</th>
<th>Morphine</th>
<th>Hydromorphone</th>
<th>Dex</th>
<th>Propofol</th>
<th>Midazolam</th>
<th>Lorazepam</th>
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<td>Unaffected by renal/hepatic dysfunction</td>
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Dex = dexmedetomidine

# Evaluations of Ketamine in Critically Ill Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Regimen</th>
<th>Results</th>
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<tbody>
<tr>
<td>Anesth Analg. 2003</td>
<td>93 SICU</td>
<td>0.5mg/kg bolus + 0.06-0.12mg/kg/hr</td>
<td>↓ Morphine consumption ↔ Pain/Sedation scores</td>
</tr>
<tr>
<td>Crit Care Med. 2003</td>
<td>25 TBI</td>
<td>5mg/kg/hr</td>
<td>↔ ICP, CPP</td>
</tr>
<tr>
<td>Crit Care Med. 2005</td>
<td>30 TBI</td>
<td>5.7mg/kg/hr</td>
<td>↔ ICP, CPP</td>
</tr>
<tr>
<td>Anaesth Int Care. 1997</td>
<td>25 HF</td>
<td>2.5mg/kg/hr</td>
<td>↓ Cardiac index ↑ MAP, PCWP, SVR</td>
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<tr>
<td>Acta Neurochir (Wien). 1996</td>
<td>24 TBI</td>
<td>6.2 mg/kg/hr</td>
<td>↑ ICP, CPP, TF tolerance ↓ Dopamine use</td>
</tr>
<tr>
<td>J Neurosurg Anesthesiol. 2007</td>
<td>24 TBI or SAH</td>
<td>Max 2mg/kg/hr</td>
<td>↔ ICP, CPP, GI motility ↓ Norepinephrine use</td>
</tr>
</tbody>
</table>

SICU – surgical intensive care unit; TBI – traumatic brain injury; ICP – intracranial pressure; CPP – cerebral perfusion pressure; HF – heart failure; MAP – mean arterial pressure; PCWP – pulmonary capillary wedge pressure; SVR – systemic vascular resistance; TF – tube feeding
WHEN SHOULD WE AVOID KETAMINE?

WHEN SHOULD WE THINK OF USING KETAMINE?
WHO SHOULD NOT RECEIVE KETAMINE?

PATIENTS WITH ADHF

- Increases sympathetic activation
- Increases
  - Blood pressure
  - Heart rate
  - Pulmonary pressures
  - Cardiac workload
KETAMINE IN HEART FAILURE
25 MECHANICALLY VENTILATED PATIENTS WITH HF

Ketamine  Sufentanil

Cardiac Index

Mean Arterial Pressure

Anaesthesist.1991;40:238-244
KETAMINE IN HEART FAILURE
25 MECHANICALLY VENTILATED PATIENTS WITH HF

Ketamine administered at 2.5mg/kg/hr

Anaesthesist.1991;40:238-244
KETAMINE AND BISPECTRAL INDEX
22 WOMEN UNDERGOING ROUTINE GYNECOLOGIC SURGERY TREATED WITH 0.5MG/KG OF KETAMINE VS SALINE

WHO SHOULD RECEIVE KETAMINE?

OPIOID TOLERANT PATIENTS

• Opioid tolerance due to desensitization and internalization of opioid receptors
  – NMDA receptor inhibition at low ketamine doses may inhibit opioid receptor internalization
• Central sensitization (wind-up) in patients with chronic and neuropathic pain
  – May be due to enhanced neurotransmission via the NMDA receptor
• Higher doses of ketamine effect μ, κ, and Δ opioid receptors

WHO SHOULD RECEIVE KETAMINE?

REDUCE OPIOID REQUIREMENTS

93 PATIENTS ADMITTED TO SICU AFTER ABDOMINAL SURGERY

- Ketamine & Morphine
- Morphine only

Anesth Analg 2003;97:843–7
WHO SHOULD RECEIVE KETAMINE?

PATIENTS WITH A HISTORY OF DEPRESSION

Ketamine 0.5mg/kg vs placebo

Arch Gen Psychiatry. 2006;63(8):856-864
WHO SHOULD RECEIVE KETAMINE?

PATIENTS WITH HYPO TENSION

• Patients receiving norepinephrine or epinephrine to maintain MAP >65mmHg (n=20)
  – Randomized to fentanyl/midazolam or ketamine/midazolam
  – Significant decrease in vasopressor requirements in ketamine group (-13% vs +33%, p=0.003)

• Head injury patients receiving fentanyl/midazolam or ketamine/midazolam (n=35)
  – Significantly less catecholamine usage in ketamine group (p <0.05)

Anaesthesist.1991;40:238-244
WHO SHOULD RECEIVE KETAMINE?

PATIENTS ON EXTRACORPOREAL MEMBRANE OXYGENATION

- Patients on ECMO require more sedation due to their disease and sequestration of drug by the circuit
- Sequestration is proportional to lipophilicity (logP >2.3) and protein binding (>80%)
  - Ketamine
    - LogP 2.9
    - 47% protein bound
- Addition of ketamine to patients on ECMO decreased sedative and vasopressor requirements

Critical Care (2015) 19:164
F1000Res. 2015 Jan 16;4:16
Pharmacotherapy. 2016 Jun;36(6):607-16
WHO SHOULD RECEIVE KETAMINE
PATIENTS WITH REFRACTORY STATUS EPILEPTICUS (RSE)

• In RSE potency/efficacy of GABA-ergic drugs decreases
  – At the same time NMDA receptors increase
• Retrospective studies and case reports
  – Multiple failed AEDs prior to ketamine (5-6)
  – Prolonged status (~9 days)
• No reported side effects
• Dosage
  – 7.5-10 mg/kg/hr

Epilepsia. 2013: 1498-1503
Epilepsy research 2000: 117-122
Neurology. 1998: 1765-1766
PRACTICAL CONSIDERATIONS

METHODS OF DELIVERY IN INTENSIVE CARE

• Low dose continuous infusion (5-20mg/hr, 0.1-0.5mg/kg/hr)
• Added to IV PCA (1mg/mL)
• Added to epidural / epidural PCA (0.4-0.5mg/mL)
  – Use with caution, unclear toxicity
• Single IV dose (0.15-1mg/kg)
  – Usually during/prior to painful procedures
• Also IM, IT, intranasal described
PRACTICAL CONSIDERATIONS
KETAMINE AND BISPECTRAL INDEX

• Ketamine will falsely increase BIS readings
  – Does not reflect increase in level of consciousness
• Important in operating room and during NMB (if BIS relied upon)
• Mechanism
  – Dissociation causes feedback loop (elevated θ activity)
<table>
<thead>
<tr>
<th>Drug</th>
<th>AWP ($)</th>
<th>Approximate Cost for 24 hours* ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketamine (500mg/50mL)</td>
<td>11.86</td>
<td>5.69</td>
</tr>
<tr>
<td>Dexmedetomidine (200 mcg/2mL)</td>
<td>38.40</td>
<td>319.20</td>
</tr>
<tr>
<td>Dexmedetomidine Premix (200 mcg/50mL)</td>
<td>66.66</td>
<td>559.94</td>
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<tr>
<td>Fentanyl (2.5mg/50mL)</td>
<td>21.00</td>
<td>35.28</td>
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<tr>
<td>Propofol (1000mg/100mL)</td>
<td>14.40</td>
<td>36.29</td>
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<tr>
<td>Midazolam (100mg/20mL)</td>
<td>16.56</td>
<td>19.87</td>
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<tr>
<td>Lorazepam (60mg/20mL)</td>
<td>26.87</td>
<td>53.74</td>
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<tr>
<td>Water (1L/1L)</td>
<td>1.99</td>
<td>5.97</td>
</tr>
</tbody>
</table>

*Estimated using my best guess of average hourly doses and in no way scientific

Lexicomp AWP. Accessed 9/15/16
Quicktrip. Drive to Young Harris, GA 10/21/16
CONCLUSIONS

• Use of ketamine will rise in the next years
• Hospitals and health systems should be working on protocols for safe and effective ketamine administration
  – Bolus vs continuous infusion
  – Intubated vs extubated patients
  – PCAs
• Ketamine is a reasonable addition to the analog-sedation armamentarium of the modern ICU
POST TEST QUESTIONS

True or False:

Ketamine causes more respiratory depression than opioids.

False
Ketamine artificially increases bispectral index (BIS) values

True
POST TEST QUESTIONS

Which of the following ketamine regimens would be appropriate for a 57 year old male with chronic pain who was admitted to your unit following abdominal surgery and is requiring a lot of narcotics?

A. Ketamine 0.5mg/kg IV Once
B. Ketamine 7.5mg/kg/hr continuous infusion
C. Ketamine 0.01mg/kg/hr continuous infusion
D. Ketamine 1mg/mL PCA with 1mg dose, 6 minute lockout, 10mg hourly maximum
Are we any closer to taming the ketamine tiger?

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