Clinical Versatility:
Ketamine in the ICU

Christopher A. Droege, Pharm.D., BCCCP
Clinical Pharmacy Specialist, Critical Care
Program Director, PGY2 Critical Care Pharmacy Residency Program
UC Health – University of Cincinnati Medical Center
• I have no actual or potential conflicts of interest in relation to this activity.
OBJECTIVES

1. Explain the pharmacology and pharmacodynamics effects associated with ketamine in critically ill patients

2. Review considerations for ketamine storage, admixture preparation, and compatibility

3. Recognize potential indications for the use of ketamine in critically ill patients

4. List advantages and limitations to the use of ketamine in the ICU
Predisposing and Causative Conditions

Acute medical or surgical illness
Underlying medical conditions

Management of predisposing and causative conditions

Interventions

Invasive medical and nursing interventions
Mechanical ventilation

Medications
Sedative, analgesic, and antipsychotic medications

Hospital-acquired illness
ICU environmental influences

Pain
Anxiety
Delirium

Unresponsive
Deeply sedated
Lightly sedated
Calm and alert; Free of pain and anxiety
Pain; anxiety
Agitation; vent dyssynchrony
Dangerous agitation

Spectrum of Comfort and Sedation

Defining “Ideal” Sedative

Physical and Pharmacologic Sedative Properties

- Water-soluble, stable in solution, and long shelf-life
- Nonirritating following IV or IM administration
- No/minimal hypersensitivity reactions
- Rapid, smooth onset of action following IV or IM administration
- Minimal depression of cardiovascular and respiratory systems
- Rapid degradation to inactive, nontoxic metabolites
- Analgesia at subanesthetic levels
- Rapid, smooth emergence with minimal side effects
- Low cost

Ketamine Chemistry

- Arylcycloalkylamine structurally related to PCP
- Commercially available as a racemic mixture of the hydrochloride salt in the United States
  - S-(+)-ketamine and R-(-)-ketamine
- Each enantiomer with unique pharmacodynamic profiles

General Ketamine Pharmacology

• Nonbarbiturate anesthetic
• Analgosedative or sedatoanalgesic?
  • N-methyl-D-aspartate (NMDA) receptor antagonist
    • Sedative
  • Mu and kappa opioid receptor agonist
    • Analgesic
Receptor Pharmacology

• Binds to PCP-binding site of NMDA receptor complex

• NMDA normally excitatory; calcium-gated
  • Glutamate, aspartate, glycine act as agonists
  • Opening of channels and depolarization of neuron

• Block/interfere with sensory input to higher centers of CNS; memory processes

Channel Effects
- ↓ NMDA
- ↓ HCN1
- ↓ nACh
- ↓ L-type Ca²⁺

Neuromodulation Effects
- ↑ Glutamate
- ↑ Norepinephrine
- ↑ Dopamine
- ↑ Cortical ACh
- ↓ Pontine ACh
- ↓ Opioids & ERK1/2
- ↓ mGluR
- ↓ Neurosteroids
- ↓ NOX
- ↑ AMPAR insertion
- ↑ NMDAR1

Gene Expression
- ↑ GFAP
- ↑ BDNF
- ↑ mTOR

Hyponosis/Sedation
Psychomimetic
Analgesia
Antidepression

NMDA, N-methyl-D-aspartate; HCN1, hyperpolarization-activated cyclic nucleotide channel; ACh, acetylcholine; nACh, nicotinic acetylcholine receptors; ERK, extracellular signal-regulated kinases; mGluR, metabotropic glutamate receptors; AMPAR, α-amino-3-OH-5-methylisoxazole-4-propionic acid receptor; NOX, NADPH oxidase; GFAP, glial fibrillary acidic protein; BDNF, brain-derived neurotrophic factor; mTOR, mammalian target of rapamycin

“True” Analgosedative

- Produces mixture of antinociceptive actions at subdissociative doses
  - Modifies response to spectrum of opioid receptors, endogenous aminergic systems, and inhibition of nitric-oxide synthase
- Comparable to morphine for acute pain

Pharmacokinetic Properties

- Highly bioavailable after administration

<table>
<thead>
<tr>
<th>Route</th>
<th>Onset of Action</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>30 – 60 seconds</td>
<td>5 – 15 minutes</td>
</tr>
<tr>
<td>IM</td>
<td>180 – 240 seconds</td>
<td>12 – 25 minutes</td>
</tr>
</tbody>
</table>

- Undergoes hepatic biotransformation into multiple metabolites
  - Norketamine with 1/3 anesthetic potency

## Sedative Comparisons

<table>
<thead>
<tr>
<th>Agent</th>
<th>IV Dose</th>
<th>Onset of Action</th>
<th>Elimination Half-Life</th>
<th>Avoid</th>
<th>Consider</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>0.1 – 0.3 mg/kg</td>
<td>60 – 90 s</td>
<td>1 – 4 hours</td>
<td>Hemodynamically unstable, liver failure</td>
<td>Anxious; predicted difficult intubation</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>1 – 3 mcg/kg</td>
<td>&lt; 30 s</td>
<td>2 – 4 hours</td>
<td>Not tolerate decrease in minute ventilation</td>
<td>Blunt sympathetic response needed</td>
</tr>
<tr>
<td>Methohexital</td>
<td>1.5 mg/kg</td>
<td>&lt; 30 s</td>
<td>5 – 10 min</td>
<td>Septic shock, hypotension</td>
<td>Head injuries, elevated ICP, HS</td>
</tr>
<tr>
<td>Propofol</td>
<td>1 – 2 mg/kg</td>
<td>15 – 45 s</td>
<td>5 – 10 min</td>
<td>Hypotension, low ejection fraction</td>
<td>HS, head injuries, elevated ICP</td>
</tr>
<tr>
<td>Etomidate</td>
<td>0.3 mg/kg</td>
<td>15 – 45 s</td>
<td>3 – 12 min</td>
<td>Septic shock, seizure disorder</td>
<td>Hemodynamic instability</td>
</tr>
<tr>
<td>Ketamine</td>
<td>1 – 2 mg/kg</td>
<td>30 – 60 s</td>
<td>5 – 15 min</td>
<td>Hypertension, ↑ oral secretions</td>
<td>Hemodynamic instability, asthma</td>
</tr>
</tbody>
</table>

RSI, rapid sequence intubation; IV, intravenous; ICP, intracranial pressure; HS, hemodynamically stable

Cardiovascular Effects

• Produces a dose-related rise in rate-pressure product with transient cardiac index increase
• Exerts sympathomimetic effects by stimulating CNS outflow and decreasing catecholamine reuptake
• Net systemic vascular resistance change minimal

Pulmonary Effects

• Does not produce significant respiratory depression
• Rapid bolus dosing produces significant, maintained reductions in $P_aO_2$
• Demonstrates bronchial smooth muscle relaxation and antagonizes spasmodic potential of histamine

Miscellaneous Effects

• Increases skeletal muscle tone and occasionally muscle spasms
• Decreases serum free fatty acids
• Elevates plasma cortisol, renin, and prolactin
• Attenuates activity and production of nuclear factor-κB, tumor necrosis-α, and interleukin-6

Notable Adverse Effects

• Recovery reactions
  • Emergence reactions: “12%”
  • Recovery agitation: 0 – 30%
• Emesis: 5 – 15%
• Laryngospasm: 0.3%
• Respiratory depression with rapid IVP
• Increase in MAP, ICP, CO

ICP, intracranial pressure; CO, cardiac output

Ketamine Supplies and Storage

- Available in 10 mg/mL (20-mL), 50 mg/mL (10-mL), and 100 mg/mL (5-mL) multidose vials
  - 100 mg/mL concentration must be diluted prior to use
- Store between 68 – 77°F (20 – 25°C)
- Protect from light
- Vials can be colorless to slightly yellow
  - Darkens with prolonged exposure to light, but does not impact potency

Ketalar® (ketamine hydrochloride injection) [package insert]. Rochester, MI: JHP Pharmaceuticals, LLC; March 2012.
Admixture Preparation

• No “standard” concentration
• Can be added to 5% dextrose or 0.9% sodium chloride
• 10 mg/mL vials made isotonic with sodium chloride
  • 10 mg/mL: 300 mOsm/kg; 50 mg/mL: 387 mOsm/kg
• Variable stability at room temperature depending on concentration, but minimum is six days
Additional Considerations

- Compatible with many additives, drugs in syringes, and Y-site injections
- Can be administered via a central or peripheral line

**Dispensing Group: YELLOW** (Moderate Cost/High Frequency/ Moderate Risk)

<table>
<thead>
<tr>
<th>Actions required prior to dispensing:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacy Technician responsibilities:</td>
</tr>
<tr>
<td>1. First Dose: Prepare initial dose of product</td>
</tr>
<tr>
<td>2. Subsequent scheduled dose: prepare dose</td>
</tr>
<tr>
<td>3. Extra Dose requests (missing dose, next bag, etc.):</td>
</tr>
<tr>
<td>a. Call nurse and ask for a second search of tube stations, patient bins, and bedside</td>
</tr>
<tr>
<td>b. If workflow permits, send delivery technician directly to patient care area to help procure drug</td>
</tr>
<tr>
<td>c. If dose not found, reprint label and prepare for dispensing</td>
</tr>
</tbody>
</table>

| Pharmacist responsibilities: |
| 2. Verify product and see technician responsibilities for extra dose dispensing |

**Delivery method:**
- Can be tubed

**Storage:**
- See medication guidelines for further storage information.

---


*Ketalar® (ketamine hydrochloride injection) [package insert]. Rochester, MI: JHP Pharmaceuticals, LLC; March 2012.*
Administration Pearls

• No dose-related adverse effects (AE) within range of clinical doses
• Lower doses may be associated with faster recovery time
• Subdissociative IM ketamine displayed fewer airway and respiratory AE

Absolute Contraindications

• Age – airway complications identified in patients younger than three months
  • Differences in airway anatomy and likelihood of laryngeal excitability

• Mental state – known to exacerbate schizophrenia

• Caution in severe hepatic dysfunction (e.g., cirrhosis) and high-risk coronary artery disease with moderate- or high-dose infusions
Relative Contraindications

Major procedures stimulating the posterior pharynx (e.g., endoscopy)

History of airway instability, tracheal surgery, or tracheal stenosis

Active pulmonary infection or disease, including upper respiratory infections

Known or suspected cardiovascular disease (e.g., angina; heart failure; hypertension [blood pressures above 140/90]; coronary artery disease) due to concerns with sympathomimetic properties

Central nervous system masses, abnormalities, or hydrocephalus (potentially-increased intracranial pressure). *Minimal effect assuming normal ventilation and corresponding cerebral vasodilatory effect may improve overall perfusion.*

Glaucoma or acute globular injury given conflicting evidence of increased intraocular pressures

Thyroid disease or medications given potential for enhanced sympathomimetic response


Monitoring

• Supplemental oxygen while breathing room air
• Occasional head repositioning for optimal airway patency or suction of pharynx
• Pulse oximetry, vitals, and capnography
• For ICU use:
  • BPS, CPOT, RASS, SAS, CAM-ICU, ICDSC

BPS, Behavioral Pain Scale; CPOT, Critical-Care Observation Tool; RASS, Richmond Agitation Sedation Scale; SAS, Sedation-Agitation Scale; CAM-ICU, Confusion Assessment Method for the ICU; ICDSC, Intensive Care Delirium Screening Checklist

Being “Jack” – Potential Uses

• Acute pain management
• Adjunctive pain, agitation, and delirium treatment
• Alcohol withdrawal
• Status epilepticus (SE)
• Rapid sequence intubation (RSI)
Acute Pain: Patient Identification

• Several broad patient categories for subanesthetic ketamine
  • Expected post-operative pain to be severe
    • Abdominal, thoracic, orthopedic (e.g., limb; spine)
  • Opioid tolerant or dependent presenting for surgery or with exacerbation of chronic pain condition
  • Increased risk for opioid-mediated respiratory depression (e.g., obstructive sleep apnea)

Acute Pain: Dose Range

• Ketamine produced analgesia at plasma concentrations of 100 to 200 ng/mL
  • General anesthesia: 9000 to 25000 ng/mL

• Range includes a 0.3 to 0.5 mg/kg IV bolus, with or without an infusion started at 0.1 to 0.2 mg/kg/hr

• Data suggesting profound analgesic effect and decrease in opioid consumption for up to six weeks

Ketamine Versus Morphine

• Prospective, randomized, double-blind trial in adult patients in the ED experiencing moderate pain

• Randomized to ketamine 0.3 mg/kg or morphine 0.1 mg/kg IV push over 3 to 5 minutes

• Primary outcome: reduction in pain at 30 minutes

• Secondary outcome: incidence of rescue analgesia at 30 and 60 minutes

<table>
<thead>
<tr>
<th>Time Interval*</th>
<th>Group</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ketamine</td>
<td>Morphine</td>
</tr>
<tr>
<td>Baseline</td>
<td>8.6 (1.5)</td>
<td>8.5 (1.5)</td>
</tr>
<tr>
<td>15</td>
<td>3.2 (3.5)</td>
<td>4.2 (2.9)</td>
</tr>
<tr>
<td>30</td>
<td>4.1 (3.2)</td>
<td>3.9 (3.1)</td>
</tr>
<tr>
<td>60</td>
<td>4.8 (3.2)</td>
<td>3.4 (3.0)</td>
</tr>
<tr>
<td>90</td>
<td>4.8 (3.1)</td>
<td>3.9 (3.1)</td>
</tr>
<tr>
<td>Complete resolution of pain, N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>20 (44)</td>
<td>6 (13)</td>
</tr>
<tr>
<td>30</td>
<td>12 (27)</td>
<td>11 (24)</td>
</tr>
<tr>
<td>60</td>
<td>9 (21)</td>
<td>12 (27)</td>
</tr>
<tr>
<td>90</td>
<td>7 (16)</td>
<td>9 (21)</td>
</tr>
</tbody>
</table>

NRS, numeric rating scale; SD, standard deviation; CI, confidence interval
*Time in minutes from medication administration

Being “Jack” – Potential Uses

- Acute pain management
- **Adjunctive pain, agitation, and delirium treatment**
- Alcohol withdrawal
- Status epilepticus (SE)
- Rapid sequence intubation (RSI)
Adjunctive Analgosedation

• Retrospective study of 40 adult patients being mechanically ventilated patients in an SICU
• Impact of low-dose ketamine continuous infusions (i.e. 1-5 mcg/kg/min) as adjunctive analgesia
• Primary outcome: slope of change in morphine equivalents 12 hours pre- and post-ketamine infusion

## Adjunctive Analgosedation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>24 Hours Preketamine</th>
<th>24 Hours Postketamine</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ME (mg/hr)</td>
<td>6.66 (3.33 – 10)</td>
<td>0 (0 – 3.33)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vasopressor? (N)</td>
<td>16</td>
<td>18</td>
<td>0.651</td>
</tr>
<tr>
<td>PE equivalent (mg/hr)</td>
<td>70 (25 – 95)</td>
<td>50 (30 – 77.5)</td>
<td>0.236</td>
</tr>
<tr>
<td>Propofol (mg/hr)</td>
<td>150 (80 – 200)</td>
<td>32.5 (0 – 150)</td>
<td>0.002</td>
</tr>
<tr>
<td>RASS outside goal (N)</td>
<td>15</td>
<td>17</td>
<td>0.797</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>115 (100 – 134)</td>
<td>118.5 (102 – 136.5)</td>
<td>0.462</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>54 (47 – 61)</td>
<td>57.5 (53.5 – 64.5)</td>
<td>0.12</td>
</tr>
<tr>
<td>HR (BPM)</td>
<td>77 (72 – 89)</td>
<td>90 (80 – 98)</td>
<td>0.01</td>
</tr>
<tr>
<td>RR (BPM)</td>
<td>20 (15 – 25)</td>
<td>19.5 (15 – 26)</td>
<td>0.918</td>
</tr>
<tr>
<td>COMA Score</td>
<td>4 (1.5 – 10)</td>
<td>6 (4 – 12)</td>
<td>0.082</td>
</tr>
</tbody>
</table>

ME, morphine equivalents; PE, phenylephrine; RASS, Richmond Agitation Sedation Scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; RR, respiratory rate, COMA, Critical Care Observation of Motor Activity.

What About Trauma?

- Retrospective analysis of 36 patients

<table>
<thead>
<tr>
<th></th>
<th>Pre-ketamine</th>
<th>Post-ketamine</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids, mg IVME</td>
<td>431.3 (206.3 – 1012.4)</td>
<td>272.5 (52.5 – 772.5)</td>
<td>0.029</td>
</tr>
<tr>
<td>PRN opioids, mg IVME</td>
<td>51.3 (23.1 – 123.1)</td>
<td>62.5 (12.5 – 170)</td>
<td>0.681</td>
</tr>
<tr>
<td>Dexmedetomidine, mcg/kg/hr</td>
<td>0.7 (0.6 – 1.1)</td>
<td>0.9 (0.7 – 1.4)</td>
<td>0.002</td>
</tr>
<tr>
<td>Propofol, mcg/kg/min</td>
<td>35.4 (23.1 – 49.4)</td>
<td>22.8 (14 – 32.9)</td>
<td>0.002</td>
</tr>
<tr>
<td>Benzodiazepines*</td>
<td>14.3 (1.3 – 564.3)</td>
<td>17.2 (9.2 – 193.9)</td>
<td>0.7358</td>
</tr>
</tbody>
</table>

*, represented as milligrams of midazolam equivalents
IVME, intravenous morphine equivalents; PRN, as needed

# Impact on Delirium and Coma

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ketamine (N=39)</th>
<th>Non-Ketamine (N=40)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Analgesia and Sedation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Goal RASS (-2 to 0)</td>
<td>70 (47 – 87)</td>
<td>84 (68 – 93)</td>
<td>0.19</td>
</tr>
<tr>
<td>% Goal CPOT/BPS</td>
<td>99 (93 – 100)</td>
<td>91 (77 – 96)</td>
<td>0.044</td>
</tr>
<tr>
<td><strong>Delirium and Coma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delirium present, n (%)</td>
<td>29 (74)</td>
<td>34 (85)</td>
<td>0.274</td>
</tr>
<tr>
<td>Coma present, n (%)</td>
<td>16 (41)</td>
<td>6 (15)</td>
<td>0.013</td>
</tr>
<tr>
<td>Delirium- or coma-free days</td>
<td>6 (2 – 9)</td>
<td>4 (3 – 7)</td>
<td>0.351</td>
</tr>
<tr>
<td>ICU LOS, days</td>
<td>11 (7 – 24)</td>
<td>8 (5 – 13)</td>
<td>0.019</td>
</tr>
<tr>
<td>Hospital LOS, days</td>
<td>15 (11 – 28)</td>
<td>12 (7 – 20)</td>
<td>0.30</td>
</tr>
<tr>
<td>In-hospital mortality, n (%)</td>
<td>11 (28)</td>
<td>5 (13)</td>
<td>0.099</td>
</tr>
</tbody>
</table>

RASS, Richmond Agitation Sedation Scale; CPOT, Critical Care Pain Observation Tool; BPS, Behavioral Pain Scale; ICU, intensive care unit; LOS, length of stay
Caveats to Consider

- Higher proportion of ketamine patients on vasopressor and inotrope therapy
- Ketamine not started until 48 hours into admission
- 69% of ketamine patients also on propofol
  - Received over double total propofol (14.1 vs 5.6 gm) for a longer median duration
- Received more midazolam in a clinically significantly shorter duration of therapy

Being “Jack” – Potential Uses

• Acute pain management
• Adjunctive pain, agitation, and delirium treatment
• **Alcohol withdrawal**
• Status epilepticus (SE)
• Rapid sequence intubation (RSI)
Impact on Alcohol Withdrawal

• Retrospective observational cohort of 63 patients
  • 29 pre-guideline; 34 post-guideline
• Delirium tremens as defined by DSM V criteria
• Pre-guideline: benzodiazepines and phenobarbital
• Post-guideline: add IV ketamine infusion at 0.15-3 mg/kg/hr with or without 0.3 mg/kg IV bolus

# Ketamine Versus No Ketamine

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Ketamine (N=34)</th>
<th>No Ketamine (N=29)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ICU days</td>
<td>5.7</td>
<td>11.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean hospital days</td>
<td>12.5</td>
<td>16.6</td>
<td>0.03</td>
</tr>
<tr>
<td>Mean benzodiazepine dose, mg DE</td>
<td>1508.2</td>
<td>2525.1</td>
<td>0.02</td>
</tr>
<tr>
<td>Dexmedetomidine use, n (%)</td>
<td>9 (31)</td>
<td>3 (8.8)</td>
<td>0.10</td>
</tr>
<tr>
<td>Mean dexmedetomidine time, d</td>
<td>1.77</td>
<td>2.33</td>
<td>0.4</td>
</tr>
<tr>
<td>Intubations, n (%)</td>
<td>10 (29.4)</td>
<td>22 (75.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean benzodiazepine dose, mg DE</td>
<td>833.6</td>
<td>3016.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Propofol use, n (%)</td>
<td>9 (90)</td>
<td>20 (90.9)</td>
<td>0.9</td>
</tr>
<tr>
<td>Mean propofol time, d</td>
<td>2.4</td>
<td>4.57</td>
<td>0.03</td>
</tr>
</tbody>
</table>

DE, diazepam equivalents; d, days; ICU, intensive care unit

## Dosing Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ketamine (N=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketamine loading dose, n (%)</td>
<td>19 (55.9)</td>
</tr>
<tr>
<td>Initial infusion dose, mg/kg/hr*</td>
<td>0.24 (0.10)</td>
</tr>
<tr>
<td>Infusion dose during therapy, mg/kg/hr*</td>
<td>0.19 (0.10)</td>
</tr>
<tr>
<td>Duration of ketamine treatment, hr†</td>
<td>47 (35 – 71)</td>
</tr>
<tr>
<td>Total ketamine dose, mg†</td>
<td>825.4 (440 – 1456)</td>
</tr>
<tr>
<td>Benzodiazepine dose in DE, pre-ketamine, mg†</td>
<td>333.4 (106.6 – 626.6)</td>
</tr>
<tr>
<td>Benzodiazepine dose in DE, post-ketamine, mg†</td>
<td>450 (295 – 700)</td>
</tr>
<tr>
<td>Total benzodiazepine dose in DE, mg†</td>
<td>892.5 (453.3 – 1,646.6)</td>
</tr>
</tbody>
</table>

*, represented as mean (SD); †, represented as median (interquartile range)
DE, diazepam equivalents

Being “Jack” – Potential Uses

• Acute pain management
• Adjunctive pain, agitation, and delirium treatment
• Alcohol withdrawal
• Status epilepticus (SE)
• Rapid sequence intubation (RSI)
Impact on Status Epilepticus

• NMDA receptors upregulated and activity increased in late SE
  • Blocks cation exchange and reduces epileptiform burst discharges, inhibiting conduction of excitation

• Neuroprotective as it blocks Ca^{2+} influx, resulting in anti-inflammatory and antioxidant effects

• Change in intracranial pressure very small and may actually be associated with a net reduction

Evaluating Impact in Practice

- Multicenter, retrospective review to examine use, efficacy, and safety of ketamine in refractory SE
- Permanent control in 32% (19/60) of patients
  - Infusion doses higher than 0.9 mg/kg/hour
- Discontinued due to possible adverse events in 5 patients
- Mortality rate lower when SE controlled within 24 hours of ketamine infusion (16 vs 56%, \( p=0.0047 \))

Being “Jack” – Potential Uses

• Acute pain management
• Adjunctive pain, agitation, and delirium treatment
• Alcohol withdrawal
• Status epilepticus (SE)
• Rapid sequence intubation (RSI)
Impact on Rapid Sequence Intubation

• Multicenter, randomized, controlled, single-blind study

• Treatment groups
  – Etomidate 0.3 mg/kg versus ketamine 2 mg/kg

• Primary endpoint
  – Maximum SOFA score during first 72 hours in ICU

SOFA, Sequential Organ Failure Assessment

Consistency in Outcome

HR 1.2 (95% CI 0.9 – 1.6)

Adrenal Insufficiency: etomidate, 100/116 (86%) v. ketamine 56/116 (48%); p<0.0001

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etomidate</td>
<td>234</td>
</tr>
<tr>
<td></td>
<td>173</td>
</tr>
<tr>
<td></td>
<td>165</td>
</tr>
<tr>
<td></td>
<td>159</td>
</tr>
<tr>
<td></td>
<td>154</td>
</tr>
<tr>
<td></td>
<td>154</td>
</tr>
<tr>
<td></td>
<td>153</td>
</tr>
<tr>
<td>Ketamine</td>
<td>235</td>
</tr>
<tr>
<td></td>
<td>187</td>
</tr>
<tr>
<td></td>
<td>180</td>
</tr>
<tr>
<td></td>
<td>173</td>
</tr>
<tr>
<td></td>
<td>166</td>
</tr>
<tr>
<td></td>
<td>164</td>
</tr>
<tr>
<td></td>
<td>163</td>
</tr>
</tbody>
</table>
Shocking Hemodynamics?

- Rates of hypotension reported as high as 24%
- Shock index (pulse rate/systolic blood pressure) may indicate patients at risk if ≥0.9 preinduction

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HSI (N=31)</th>
<th>LSI (N=81)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension, n(%)</td>
<td>8 (25.8)</td>
<td>2 (2.5)</td>
<td>12 – 45%</td>
</tr>
<tr>
<td>Hypertension, n(%)</td>
<td>4 (12.9)</td>
<td>32 (39.5)</td>
<td>4 – 30%</td>
</tr>
</tbody>
</table>

HSI, high shock index (i.e., ≥0.9); LSI, low shock index (i.e., <0.9); CI, confidence interval
Hypotension defined as a systolic blood pressure >90 mmHg preinduction that decreased below 90 mmHg at any time measurement after induction
Hypertension defined as a systolic blood pressure <160 mmHg preinduction that increased above 160 mmHg at any time measurement after induction

Pharmacodynamic Advantages

- Produces a dose-related rise in rate-pressure product with transient cardiac index increase
  - Net systemic vascular resistance change minimal
- Does not produce significant respiratory depression
- Demonstrates bronchial smooth muscle relaxation

Pharmacodynamic Advantages

• Known to decrease serum free fatty acids
• Elevates plasma cortisol, prolactin, and renin
• Potential immunomodulatory benefit
  • Decreases activity and production of proinflammatory cytokines

Cost Comparison: IV Drips

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drip Concentration</th>
<th>Approximate Cost*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>2000 mcg/ 200 mL</td>
<td>$2.24</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>5 mg / 100 mL</td>
<td>$354</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>20 mg / 100 mL</td>
<td>$8.38</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>40 mg / 250 mL</td>
<td>$14.38</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>400 mcg / 100 mL</td>
<td>$45.82</td>
</tr>
<tr>
<td>Propofol</td>
<td>1000 mcg / 100 mL</td>
<td>$37.50</td>
</tr>
<tr>
<td>Ketamine</td>
<td>500 mg / 100 mL</td>
<td>$9.83</td>
</tr>
</tbody>
</table>

*Represented by average wholesale price

Potential Barriers

• NATIONAL SHORTAGE
• Fear of emergence reactions and agitation
• Unfamiliarity
• State board limitations/restrictions
• Institutional labeling (e.g., anesthesia only)
• Unclear controversy in certain populations
Fear of the Unknown?

• Sedative agents mentioned in SCCM Guidelines:
  • Dexmedetomidine: 59
  • Propofol: 54
  • Midazolam: 32
  • Lorazepam: 24
  • Ketamine: 4

“No studies have compared clinical outcomes in ICU patients sedated with either ketamine or other sedative agents.”

Post-Test 1: Which of the following statements most accurately describes the pharmacology of ketamine?

A. The primary effects are similar to barbiturates.
B. The analgesic property is solely due to an interaction with opioid receptors.
C. Associated with respiratory depression when used as a continuous infusion.
D. Changes in blood pressure are associated with increase in cardiac output.
Post-Test 2: Which statement best aligns with ketamine and one of its potential indications?

A. It should be considered in patients at risk for cardiac depression when used for acute pain.
B. It has been associated with hypotension in patients used for rapid sequence intubation.
C. It results in better control of agitation in mechanically ventilated, critically surgical patients.
D. It is associated with a substantial increase in intracranial pressure for patients in status epilepticus.
Post-test 3: Which of the following is a potential pharmacologic advantage of ketamine over conventional analgosedative agents for mechanically ventilated patients?

A. Ability to provide concurrent sedation and opioid-sparing analgesia

B. Emergence reactions leading to vivid dreams, hallucinations, irrational behavior, and frank delirium

C. Reduction of vasopressor requirements in patients with shock due to its impact on vascular resistance.

D. Demonstrates modest bronchoconstriction.
SUMMARY

• Ketamine provides dissociative sedation and a cataleptic state through NMDA antagonism
• Employs favorable cardiovascular and pulmonary pharmacodynamic properties
• Many potential and emerging roles in acute and critical care areas
• Potential barriers exist making its entry into routine analgosedative use difficult


Clinical Versatility: Ketamine in the ICU

Christopher A. Droege, Pharm.D., BCCCP
Clinical Pharmacy Specialist, Critical Care
Program Director, PGY2 Critical Care Pharmacy Residency Program
UC Health – University of Cincinnati Medical Center