Emerging Roles for Ketamine in the ICU

Amy Green, PharmD, BCPS
Clinical Pharmacy Specialist, Neurocritical Care
Rush University Medical Center

No financial disclosures or conflicts of interest. Off-label uses of ketamine will be discussed.

Learning Objectives

• Define the mechanism of action of ketamine
• Discuss potential therapeutic uses of ketamine in the ICU
• Review ketamine dosing strategies for ICU patients
• Recognize ketamine associated adverse drug reactions.
History of Ketamine

- 1958 phencyclidine introduced into clinical practice by Parke-Davis
- 1962 ketamine synthesized by Parke-Davis
- 1960's ketamine used in Vietnam War as a battlefield anesthetic
- 1970 FDA approves for human and animal anesthetic use
- 1980's increased recreational use
- 1999 ketamine is changed to schedule III narcotic

Audience response system question

The anesthetic effects of ketamine are a result of activity at which of the following receptors?

A) GABA receptors
B) µ receptors
C) NMDA receptors
D) Acetylcholine receptors

Mechanism of action

- Non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptor Ca²⁺ channel pore (in CNS and spinal cord)
Central Nervous System Effects

• "Dissociative" anesthetic
  – Functionally dissociates the thalamus from the limbic cortex
  – Thalamus -relays sensory impulses from the reticular activating system to the cerebral cortex
  – Limbic cortex – involved with the awareness of sensation
• Patient appears conscious, but unable to respond to sensory input
  – Eyes open
  – Swallowing intact
  – Muscle contractures
• Complete anesthesia: induces analgesia, amnesia, and unconsciousness


Central Nervous System Effects

• Emergence reactions
  – hallucinations
  – floating sensations
  – vivid dreams
  – "near death experiences"
• Attenuated by premedication with benzodiazepines

Anrudder et al. CE in Anaesth, Crit Care & Pain. 2007

Central Nervous System Effects

• Reported to ↑ cerebral metabolism, cerebral blood flow, and intracranial pressure (ICP)
  – Traditionally avoided in traumatic brain injury (TBI) or space occupying intracranial lesions
• More recent literature suggests ketamine may ↓ ICP in TBI patients receiving propofol.

Albanese et al. Anesthesiology 1997;87:1329.
Audience response system question
Ketamine should be used with caution in patients with which of the following disease states?

A) epilepsy  
B) asthma  
C) severe burns  
D) myocardial infarction

Cardiac Effects
- Centrally mediated stimulation of the sympathetic nervous system
  - Tachycardia
  - ↑ arterial blood pressure
  - ↑ cardiac output
- Direct myocardial depressant (in large doses) usually only unmasked when autonomic control is absent
  - Spinal cord transection (loss of sympathetic output)
  - Severe end stage septic shock (depletion of catecholamine stores)

Respiratory Effects
- Minimal to no effect on respiratory drive
- Rare reports of transient ↓ ventilation after large IV bolus
- Increase salivation
  - Attenuated by premedication with anticholinergic (glycopyrrolate)
- Bronchodilation
  - Benefit in asthmatic patients

Aniruddha et al. CE in Anaesth, Crit Care & Pain. 2007
Other Effects

- Increased intraocular pressure
- Increase in muscle tone and rigidity
- Pupillary dilation
- Nystagmus
- Lacrimation

Pharmacokinetic Properties

- Bioavailability
  - IM 93%
  - Oral 20-25%
- IV onset 30 secs
- Protein Binding 20-50%
- Distribution \( t_{1/2} \) 10-15 min
- Highly lipophilic
- \( V_d \) 3 L/kg

- Hepatic metabolism
- Metabolites
  - Norketamine (active)
  - Dehydronorketamine
- Renal elimination of metabolites
- Elimination \( t_{1/2} \) 2-3 hrs

Potential ICU Roles for Ketamine

- Anesthesia/induction agent
- Analgesia
- Refractory status epilepticus
**Anesthesia/ Induction**

- FDA approved for use as an induction agent and as a maintenance anesthetic for diagnostic or surgical procedures
- Dosing:
  - Induction: 1 – 4.5 mg/kg bolus
  - Maintenance: 6 – 30 mg/hr
- As newer agents became available ketamine became less popular due to emergence reactions, psychological effects
- Etomidate gained popularity for induction in hemodynamically unstable patients
- Etomidate acutely inhibits cortisol synthesis = adrenal insufficiency

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**Etomidate v. Ketamine for RSI in Critically Ill Patients**

- Multicenter, randomized, controlled trial n = 649
- Etomidate 0.3mg/kg v. ketamine 2mg/kg for emergent intubation (excluded pts who did not reach hospital alive and those discharged from ICU before day 3)
- No significant difference
  - Mean maximum SOFA score
  - 28-day mortality
- % of pts with adrenal insufficiency: etomidate > ketamine
- No serious adverse reactions in either group

*RSI = rapid sequence intubation
SOFA = sequential organ failure assessment*


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**Analgesia**

- Ketamine shows evidence of analgesic properties at subanesthetic doses
- Ketamine analgesia ≠ opioid analgesia
- Proposed mechanism of analgesia:
  - Strong pain stimuli → activation of NMDA receptors → hyperexcitability of dorsal root neurons → central sensitization, pain memory
  - Ketamine blocks activation of the NMDA receptors.

Subramaniam et al. Anesth Analg 2004;99:482-95*
Ketamine as an Adjunct to Opioids

Potential Benefits

• May reverse opioid tolerance
• ↓ opioid requirements
  – ↓ vasopressor requirements
  – facilitates ventilator weaning
• Mechanism of action is unique/ alternate pain pathway compared to opioids
• May ↓ PONV incidence compared to opioids alone
• Low dose infusion (< 5 mcg/kg/min) rarely associated with adverse effects


Intravenous dosing strategies

Adjunct analgesia with opioid infusions:

0.06 mg/kg/hr – 2.7 mg/kg/hr =
1 mcg/kg/min – 45mcg/kg/min

Adjunct analgesia with opioids for pain associated with minor surgical procedures:

single bolus 0.15 – 1 mg/kg


Status Epilepticus (SE)

• Sustained seizure activity lasting more than 5 minutes or recurrent seizure activity without recovery between episodes.
• Response rates to 1st and 2nd line therapies are better if they are administered earlier

Refractory Status Epilepticus (RSE)

• Persistence of seizure activity despite appropriate treatment with at least 2 front-line anticonvulsant drugs

Audience response system question
What percentage of patients who receive treatment for status epilepticus progress to refractory status epilepticus?

A) 5%
B) 15%
C) 30%
D) 50%

• Why do first line agents lose their effect over time?
• Possible shift in mechanism between early SE and late RSE

- Early SE
  Inadequate GABAergic inhibitory receptor-mediated neurotransmission
- Late SE
  Excessive NMDA excitatory receptor-mediated neurotransmission


Ketamine for RSE Case Reports

<table>
<thead>
<tr>
<th></th>
<th>Sheth and Gidal 1998</th>
<th>Ubogu et al. 2002</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>13 y/o F unknown etiology</td>
<td>44 y/o M h/o neurosyphilis</td>
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<tr>
<td>Agents prior to ketamine</td>
<td>Diazepam, phenytoin, phenobarbital, lorazepam, midazolam, and lidocaine. for &gt; 4 weeks</td>
<td>Lorazepam, phenytoin, valproic acid, and propofol for ~ 4 days</td>
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<tr>
<td>Ketamine Dosing</td>
<td>2mg/kg bolus Infusion up to 7.5mg/kg/hr for 14 days</td>
<td>2mg/kg bolus Infusion 0.5-7.5mg/kg/hr</td>
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<tr>
<td>ADR</td>
<td>none</td>
<td>? Diffuse cerebellar and cerebral atrophy</td>
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</tbody>
</table>
Ketamine for RSE Case Reports

<table>
<thead>
<tr>
<th>Patient</th>
<th>Robakis &amp; Hirsch 2006</th>
<th>Pruss &amp; Hollkamp 2008</th>
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<tbody>
<tr>
<td>Age</td>
<td>30 y/o F etiology unknown</td>
<td>22 y/o F with mitochondrial disorder</td>
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<tr>
<td>Etiology</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Agents prior to ketamine**
- Fosphenytoin, gabapentin, phenobarbital, midazolam, propofol, pentobarbital, topiramate, levetiracetam, oxcarbazepine. For ~ 5 mo
- Lorazepam, phenytoin, thiopental, levetiracetam, propofol, midazolam

**Ketamine Dosing**
- Continuous infusion up to 7mg/kg/h
- 0.5 mg/kg bolus
  - Infusion 0.4 - 3.2 mg/kg/hr
  - For ~12 days

**ADR**
- none
- Acute inc in BP with bolus

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Hsieh et al.2010

**Patient**
- 23 y/o M with unknown SE etiology

**Agents prior to ketamine**
- Diazepam, valproic acid, midazolam, levetiracetam, phenytoin, topiramate, propofol, thiopental
  - Over 58 days

**Ketamine Dosing**
- 0.5 mg/kg bolus
  - Infusion 0.38 - 1.5 mg/kg/hr
  - For 8 days

**ADR**
- none

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Ketamine for RSE Case Reports

**Dosing strategy**
- Bolus 1-5 mg/kg
- Infusion 1 – 7.5 mg/kg/hr
  - (17 – 125 mcg/kg/min)
References


References

Post Test Questions

1. Which of the following adverse effects is not commonly associated with the use of ketamine?
   A. tachycardia
   B. bronchodilation
   C. hypotension
   D. vivid dreams

2. The mechanism responsible for ketamine’s ability to terminate refractory status epilepticus is:
   A. agonism of GABA receptors
   B. antagonism of GABA receptors
   C. agonism of NMDA receptors
   D. antagonism of NMDA receptors