Emerging Roles for Ketamine in the ICU

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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

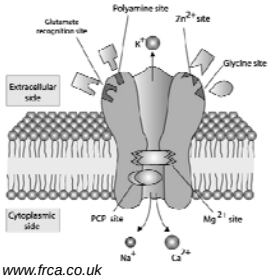
Audience response system question

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 Ca^{+2} channel pore (in CNS and spinal cord)



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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

Evers Alex S et al. Chapter 13. General Anesthetics. Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11e.

Central Nervous System Effects

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

Anirudda 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)

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

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?

Evers Alex S et al. Chapter 13. General Anesthetics. Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11e

Other Effects

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

Evers Alex S et al. Chapter 13. General Anesthetics. Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11e

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
- Vd 3 L/kg

- Hepatic metabolism
- Metabolites
  - Norketamine (active)
  - Dehydronorketamine

- Renal elimination of metabolites
- Elimination $t_{1/2}$ 2-3 hrs

Evers Alex S et al. Chapter 13. General Anesthetics. Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11e

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 insufficieny

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

Jabre et al. *Lancet* 2009;374:293-300.

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.

Owen H, Reekie RM, et al. *Anaesthesia* 1987;42:1051-6.
Subramaniam et al. *Anesth Analog* 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

Subramaniam et al. *Anesth Analog* 2004;99:482-95.

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

Subramaniam et al. *Anesth Analog* 2004;99:482-95.
De Pinto et al. *Journal of Opioid Management* 2008;4(1):54-6.
Edrich et al. *Anesth Analog* 2004; 99:893-5.

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

Lowenstein et al. *Epilepsia* 1999; 40:120-2.
Aldredge et al. *NEJM* 2001;345:631-7.
Mayer et al. *Arch Neurol* 2002;59:205-10.

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 loose their effect over time?
- Possible shift in mechanism between early SE and late RSE

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

Bleck TP *Arch Neurol*. 2001;59:188-9.
Borris DJ et al. *Epilepsy Research* 2000;42:117-22.

Ketamine for RSE Case Reports

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

Ketamine for RSE Case Reports

	Robakis & Hirsch 2006	Pruss & Holtkamp 2008
Patient	30 y/o F etiology unknown	22 y/o F with mitochondrial disorder
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

Ketamine for RSE Case Reports

	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

Ketamine for RSE

<u>Dosing strategy</u>

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

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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