Ketamine: One Drug to Rule Them All…

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Learning Outcomes:

1. Describe the pharmacodynamics/ pharmacokinetics of ketamine
2. Discuss new and novel uses of ketamine
3. Explore common indications, dosing, and key nursing considerations for ketamine in emergent patients

EXPLORE YOUR BIAS!!! (Pro or Con)

Psychedelic Beginnings

Li & Vlisides, 2016

- The story of ketamine starts, as so many amazing stories do, with angel dust, or phencyclidine (PCP for short).
- First synthesized in 1956 by Parke Davis Co. chemists, phencyclidine was capable of causing the appearance of:
    - DRUNKENESS in rodents,
    - DELERIUM in dogs,
    - CATALEPTOID STATES in pigeons,
    - ANESTHESIA in monkeys,
- **In sum:** a safe and reliable anesthetic in humans!
- Unfortunately, it also caused an intense, prolonged emergence delirium that made it undesirable for human use.
- In 1962 organic chemist Calvin Stevens synthesized ketamine, then known as CI-581.
- With the first dose administered 3 August, 1964 by Drs. Edward Domino and Guenter Corssen of U Michigan.
- Ketamine rapidly produced anesthesia, with minimal side effects compared to phencyclidine.
- FDA approved in 1970 for human use as Ketalar/ketamine.

Chen & Malek, 2015

- Ketamine saw some of its first applications "in Vietnam as a wartime anesthetic, analgesic, and amnesic agent."

Pharmacodynamics/Pharmacokinetics

Lexicomp

Noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist that blocks glutamate "Produces cataleptic-like state" of dissociation "by direct action on the cortex and limbic system"

- Onset IV: 30sec

- Onset IM: 3-4 minutes
- Duration IV: 5-10 minutes
- Duration IM: 12-25 minutes
- Metabolism: Hepatic, excreted in urine
- Half-life: Alpha 10-15 min Beta: 2.5 hours

Li & Vlisides, 2016

- **Ketamine REDUCES NEURONAL EXCITATION by NMDA** producing dissociative anesthesia/amnesia
- ACTIVATES AMPA receptors producing antidepressant effects
- ACTIVATES GABA-A receptors producing anesthetic properties
- AMPA: alpha-amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid
- GABA: gamma-aminobutyric acid
- Ketamine is soluble in water and lipids, and can be administered via multiple routes, with different bioavailabilities:
    - **IV = 100% Tmax 3 min**
    - **IM = 93% Tmax 5-10 min**
    - **IN = 8-45% Tmax 10-20 min**
    - **PO = 17-29% Tmax 30 min**
    - **PR = 11-25% Tmax 30-45 min**

Cardiovascular Effects

Li & Vlisides, 2016

- At both subanesthetic and anesthetic doses, ketamine is predominantly a **sympathomimetic**
- **INCREASED ARTERIAL PRESSURES**
- **INCREASED HEART RATE**

Pulmonary Effects

Li & Vlisides, 2016

- **Preserves upper airway reflexes**
- **Increases genioglossus muscle activity-** elevating and pushing tongue forward, increasing upper airway diameter
- **Bronchodilation**
- BEWARE: **hypersalivation and Laryngospasm**

Neurological Effects

Li & Vlisides, 2016

- Safely used in patients with elevated ICP while helping to maintain optimal hemodynamic profiles
- MAY be neuroprotective and potentially beneficial in brain trauma

- (possibly related to inhibition of spreading cortical depolarizations after TBI, possibly attenuating extension of ischemic damage)
- Side effects: dizziness, nausea, hyperreflexia and transient clonus

The Ketamine-Brain Continuum

Analgesic Dose: 0.1-0.3 mg/kg
Recreational Dose: 0.2-0.5 mg/kg
Partially Dissociated Dose: 0.4-0.8 mg/kg
Dissociative Dose: >0.7 mg/kg
(Strayer, 2013)

Indications

Austere Environments

- E.g. military applications, the Thai cave rescue!

Chemotherapy/Hematopoietic Cell Transplant (HCT)

Shillingburg et al., 2017

- 40% of patients receiving standard dose chemo, 80% of pt receiving radiation to head and neck, and 100% of pt undergoing hematopoietic cell transplant suffer from oral mucositis.
- Mucositis is a dose-limiting toxicity which results in reduction/cessation of treatment in 35% of pt receiving chemotherapy.
- Pt received 20mg/5ml swish (30s) and spit QID, with PRN doses Q4-hour.
- Onset of action was within 15min and reported to last 1-3 hours.
- Pt reported decreased pain, better sleep, less use of "magic mouthwash", and reduction in narcotic analgesia requirements.

Ketamine: A Remarkable Antidepressant

Lener et al., 2017

- "…our group and others have consistently demonstrated that **a single IV infusion of 0.5mg/kg of ketamine** produces an antidepressant response in individuals with treatment resistant Major Depressive Disorder (MDD)." ""The time course of antidepressant response to ketamine is characterized by an initial reduction in depressive symptoms within two hours, a maximal reduction in depressive symptoms within 24 hours, and a sustained response for up to one week."

Kishimoto et al., 2016

- A single infusion of ketamine has **ultra-rapid (40 min) efficacy** for Major Depressive Disorder and Bipolar Disorder, **lasting up to 1 week**.
- Ketamine was associated with **greater remission starting at 80min and lasting until days 3-5.**
- "Development of easy-to-administer, repeatedly given NMDA receptor antagonists without risk of brain toxicity is of critical importance."

- Compared to standard antidepressant therapy with onset of efficacy of 2 weeks and non-significant reduction in remission.

Lapidus et al., 2014

- A randomized, double- blind, crossover, placebo-controlled study found that **50mg intranasal racemic ketamine** improved depressive symptoms within 24 hours compared to placebo in 20 patients with MDD.
- This dose is approximately equivalent to 0.15-0.34 mg/kg IV (based on bioavailability of IN route)
- Although there may be considerable variability associated with intranasal ketamine administration in terms of bioavailability, this means of administration was well tolerated with minimal psychotomimetic or dissociative effects and no significant hemodynamic changes.

Suicidality

Lener et al., 2017

- In an emergency department setting, Larkin and Beautrais found that suicidal ideation resolved in 14 actively suicidal patients following an IV **bolus of ketamine (0.2 mg/kg) administered over one to two minutes**. In that study, antidepressant effects were seen at 40 minutes post-administration, and sustained improvements in suicidality scores lasted for over 10 days [58].
- Cites a meta-analysis of 7 clinical trials with similar findings.
- **"Interestingly, the reduction in suicidality associated with ketamine administration may occur independently of its antidepressant effects."**

Ballard et al., 2014

- As measured by the SSI (Scale for Suicide Ideation), "ketamine infusion [0.5mg/kg over 40 min] was associated with increased with to live, … and decreased wish to die."

Wilkinson et al., 2018

- "**ketamine was associated with a significantly greater proportion of patients being free from suicidal ideation compared with control treatments**, as assessed by clinician-administered ratings, at postinfusion days 1, 2, 3, and 7; **over half of the participants reported no suicidal ideation across all postinfusion time points.**
- **The number needed to treat for ketamine** (compared with control treatment) **for being free of suicidal ideation was in the range of 3.1–4.0** for all time points 1 to 7 days after ketamine infusion."
- Comparator: Aspirin to prevent MI 5-year NNT = 44, 77 net important bleeding complication (Sanmuganathan, et al., 2001).

Alcohol Withdrawal

Guirguis et al., 2017

- "As a result of chronic alcohol use, there is a downregulation of [inhibitory] γ-aminobutyric acid (GABA) receptors, and an increase in [excitatory] N-methyl-d-aspartate (NMDA) receptors."

- ”Up to 20% of hospitalized patients abuse alcohol, and approximately 8% experience alcohol withdrawal symptoms during hospitalization.”
- “On discontinuation or reduction of consumption of alcohol, there is increased central nervous system (CNS) excitation as a result of NMDA receptors no longer being inhibited by alcohol. This results in autonomic hyperactivity, psycho- motor agitation, anxiety, and seizures.”

Pizon et al., 2018

- Adjunctive **ketamine infusions 0.15-0.3 mg/kg/hr** in severe etoh withdrawal/delirium, **+/- 0.3mg/kg bolus**.
- A ketamine infusion in patients with delirium tremens was associated with **reduced gamma-aminobutyric acid agonist requirements, shorter ICU length of stay, lower likelihood of intubation, and a trend toward a shorter hospitalization**.
- **Reduced ICU stay 2.83 days** (0.043), decreased hospital stay of 3.66 days (p=0.13)

Shah et al., 2018

- Used a higher starting dose infusion (0.75mg/kg/hr)
- Found initial symptom control within 1hr
- Found decreases in lorazepam requirements.

Interesting to me:

- **Mean time to start of [ketamine] infusion was 41.4 hours**

  [*Would earlier initiation produce greater benefits?]*
- ”While there is no standard definition of BZD resistance, one criteria suggested is the **requirement of greater than 40 mg of diazepam (or equivalent) within 1 h, which may necessitate adjunctive treatment options”**

Pizon et al., 2018

- “a short acting, continuously infused NMDA antagonist, like ketamine, may safely attenuate the demonstrated neuroexcitatory contribution of NMDA stimulation in severe ethanol withdrawal, reduce the need for excessive GABA agonist–mediated sedation, and limit associated morbidity.”

The Agitated Patient

Cole et al., 2018

- Administered **500mg ketamine IM** for Altered Mental Status Scale **(AMSS) score of +4**
- **Median time to adequate sedation= 4.2 minutes**
- Profound agitation may be a precursor to ExDS and its significant metabolic disturbances.
- Though the final common pathway for death in ExDS is not known, expert consensus suggests it involves a combination of acidosis, hyperthermia, and sympathomimetic surge.
- Therefore, if ketamine can rapidly sedate these patients it may curb or prevent the complications of ExDS.

This study caught my attention, good and bad:

- Looked at PROFOUND agitation +4 on the Altered Mental Status Scale (AMSS) [Range -4 to +4, most agitated]
- 56 patients presented to study hospital, 7 excluded [1 <18, 6 *they didn't start the stopwatch!!!]*
- INTERESTING: 57% were intubated (!!!), but ***36% were intubated by a single physician!!!***
- **This goes back to our biases- and perhaps too much focus on GCS=8, intubate???**

Gottlieb et al., 2018

- "Agitation can encompass a wide variety of findings, and a patient's agitation may be secondary to a dangerous medical condition rather than primary psychosis"
- Table 1. Dangerous Causes of Agitation (p.448)

  [THIS is why we (the ED) are involved: To rule out underlying organic causes!!!]

Riddel et al., 2017

- "Ketamine appears to be faster at controlling agitation than standard ED medications."
- Ketamine is unlikely to resolve the underlying processes causing agitation and in this context
- it is used to gain rapid control of violent patients so that safe medical evaluation can proceed and treatment of the underlying cause can commence.

Agitation/Ability to Control Graphic:
Reuben Strayer
Image: https://twitter.com/emupdates/status/850746456923402240

Hopper et al., 2015

- The rapid onset of ketamine, **under 5 min**, compares favorably to haloperidol and droperidol, in which peak sedation can take **more than 20 min**.
- **"**Two…patients received a ''B-52'' consisting of haloperidol, lorazepam, and diphenhydramine, traditionally thought to be extremely effective in sedating agitated patients, yet still required ketamine to resolve agitation. This may highlight ketamine's usefulness with severely agitated patients, as well as introducing ketamine as a potential alternate medication for patients nonresponsive to traditional pharmacological interventions."
- a high proportion **(62.5%)** of patients required additional pharmacologic treatment for their agitation, implying that ketamine itself is not an ideal treatment for the underlying cause of agitation, but rather a means of initial management of severe agitation.

Procedural Sedation and Analgesia

Bellolio et al., 2016

- Ketamine and ketamine/propofol had the highest rate of agitation. Among the studies that used ketamine, the incidence of agitation was 164.1 per 1,000 sedations
- Laryngospasm occurred in one patient (4.2 per 1,000 sedations, 95% CI = 0 to 8.5) who received ketamine and who was managed conservatively per authors' report.38

- The use of ketamine (170.0 per 1,000 sedations) had the highest incidence of vomiting
- ACEP has established their evidence in adult PSA as a Level A recommendation for the use of propofol, Level B for etomidate and the combination of propofol and ketamine, and Level C for the use of ketamine alone.

Pain

Karlow et al., 2018

- Ketamine is a **safe, effective alternative to opioids** in the treatment of acute pain in the ED, with **few clinically significant adverse events**.
- For patients with **opioid use disorders or substance use disorders** that require a potent analgesic in the ED such as a narcotic, ketamine may be a favorable option compared to an opioid.
- In the elderly or patients with chronic pulmonary disease, the treating physician may be hesitant to administer opioids due to concerns for respiratory depression.
- Some opioids can "stack" in patients with renal failure causing delayed respiratory depression and failure. Ketamine may be preferable in such patients to reduce respiratory complications.
- **Adverse effects include: laryngospasm, nausea and vomiting, and emergence reactions**.
- New research indicates that **a short infusion of LDK compared to a push dose** is associated with fewer psychiatric adverse effects and less sedation.
- Another less well-known associated adverse event from ketamine is the development of **lower urinary tract symptoms (LUTS)** such as frequency, urgency, and dysuria as well as the possibility of renal failure.

Mahshidfar et al., 2017

Low Dose Ketamine (LDK) 0.2mg/kg

- Low dose ketamine… leads to significant reduction of pain when compared to that of intravenous morphine. It also created fewer complications than morphine.

Sickle Cell Pain

Palm et al., 2018.

- Low-dose ketamine infusion as an adjunct to opioid and other nonopioid therapies may reduce pain in patients requiring high-dose opioid analgesics during VOEs. There were no serious complications associated with ketamine infusion. Further study is needed to explore optimal treatment of patients with painful VOEs as well as the role of ketamine therapy in these patients.
- Case studies included one patient requiring 6300mg of morphine equivalents/day, experiencing desaturations and somnolence attributed to high-dose opioids. Pt was started on ketamine at 5/mcg/kg/min (0.3mg/kg/hr). Pain score fell to 0, RASS score remained 0 to -1, and somnolence/desaturation episodes resolved while on ketamine.

Palliative Care

McNulty & Han, 2012

- "this case report, which describes our experience in treating a 44-year-old male hospice patient with severe constant anxiety, fear, and depression in addition to multiple near-terminal comorbid physical conditions that produce chronic pain. Prior treatments prescribed to resolve this patient's pain, anxiety, and depression had proven ineffective**.**
- **However, a single low-dose (0.5 mg/kg) subcutaneous test injection of ketamine provided dramatic relief from those symptoms for 80 hours**, although the anesthetic effects of that drug are not of long duration. This good outcome has been **sustained to date by daily treatment with a compounded flavored oral ketamine solution (40 mg/5 mL)**

Rapid Sequence Intubation

Rocketamine Image: https://twitter.com/srrezaie/status/925419537947856897

Lyon et al., 2015

The "3-2-1":

- **3mcg/kg fentanyl**
- **2mg/kg ketamine**
- **"1" 1.2-1.5mg/kg rocuronium**
- "The combination of fentanyl and ketamine effectively attenuated the hypertensive response to tracheal intubation."
- Using full dose (3:2:1) or reduced dose (1:1:1) regimens appeared to produce superior laryngoscopy views and more favourable physiology during tracheal intubation when compared to a traditional protocol [0.3mg/kg etomidate and 1.5mg/kg succinylcholine].

[BE MINDFUL THE KETAMINE WILL WEAR OFF BEFORE THE ROCC]

Ketamine Infusions

Benken et al., 2017

- Use in neurosurgical ICU pt, high-dose sedatives and analgesia led to hypotension.
- Ketamine eliminated other agents and allowed weaning/extubation.

Groetzinger et al., 2018

- Continuous ketamine infusion for adjunct light sedation was well tolerated in a cohort of critically ill adults, with an acceptable safety profile.

Miller et al., 2011

- In addition to its efficacy in relieving bronchospasm via bolus administration, continuous infusion of ketamine has also been shown to safely improve pulmonary function.
- Numerous studies have demonstrated that ketamine infusion in- creases PaO_2 and decreases $PaCO_2$.
- Despite general anesthesia, patients treated with keta- mine exhibit preservation of functional residual capacity, minute ventilation and tidal volume.

Miller et al., 2011

CAUTIONS:

- Ketamine should be avoided in decompensated heart failure or cardiogenic shock, ketamine's negative inotropic effects may be unmasked, resulting in deterioration in cardiac performance and cardiovascular instability
- Ketamine may raise pulmonary artery pressures, thus it should be used with caution in patients with pulmonary hypertension.

ICU sedation:

- **1mg/kg bolus followed with 1mgkg/hr, titrated by 0.5mg/kg/hr Q5-20 min** to reach target sedation (Ramsay Sedation Scale of 4) or max dose 4.5mg/kg/hr
- For ventilated pt with **refractory bronchospasm**:
- **1-2mg/kg bolus then 1-2mg/kg/hr fpr 2-3 hours**

Groetzinger et al., 2018

Light sedation strategy:

- **0.1-0.5mg/kg bolus then 0.05-1mg/kg/hr** (max dose 2.5mg/kg/hr)

Questions are welcome!!!

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