Co-analgesics: Ketamine and Lidocaine

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Ketamine Overview

- Class: General dissociative anesthetic
- Physiological effects are dose related: anesthesia, analgesia, mood elevation
- Uses: Anesthesia, procedural sedation, acute pain, chronic pain, depression, post-traumatic stress disorder
- Racemic mixture in US (S-entantiomer not available)

History

- Derivative of phencyclidine (PCP)
- 1st used in 1964 in humans for dissociative anesthesia
- Found to be relatively safe.
- Sxs: "floating in outer space", "no feeling in arms or legs"
- FDA approval in 1970 as an anesthetic.
- Widely used in surgical theaters in Viet Nam war due to its minimal effect on hemodynamics

Neuropharmacology

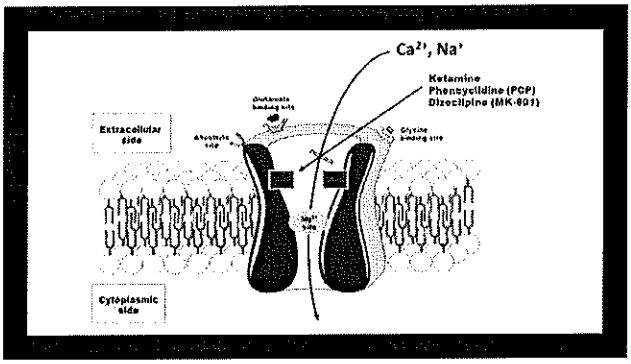
- Ketamine is a non-competitive antagonist of NMDA receptor at PCP binding sites.
- Decreases opening of the NMDA channel in response to binding of excitatory neurotransmitter glutamate (the primary agonist).
- Results in decreased neuronal activity.
- Water & lipid soluble; crosses blood-brain barrier rapidly
- At high doses, binds to mu > kappa > sigma receptor
- Effects not reversed with naloxone

Cohen et al., 2018; Schwenk et al., 2018

Neuropharmacology

- Ketamine antagonizes the NMDA receptors in the CNS.
- The NMDA receptors, when activated, plays a role in cognition, pain, opioid tolerance, mood regulation, and are the primary receptors involved in central sensitization and windup.
- Central Sensitization: repeated or sustained noxious stimuli leads to increased neuronal responsiveness in dorsal horn of the spinal cord. As a result, the dorsal horn is "sensitized" or "hyperexcitable" leading to allodynia, hyperalgesia, referred pain.
- Windup: Progressive increase of pain sensations with repeated stimuli due to central pain amplification of spinal cord.
- Ketamine also acts on other pathways (antagonist at nicotinic, & muscarinic receptors, activates D2, facilitates GABA-A signaling) that may account for non-neuropathic and peripheral effects.

Cohen et al., 2018; Schwenk et al., 2018



Non-anesthesia Uses

- Acute postop pain
- Severe opioid resistant pain, neuropathic pain, phantom limb pain or chronic pain
- Opioid adjunct in refractory cancer pain
- Treatment resistant major depression (NMDA antagonism)
- PTSD (NMDA antagonism)
- Refractory seizures (NMDA and GABA-A, GABA-B receptor effects)

Cohen et al., 2018; Schwenk et al., 2018

Routes

- Intravenous
- Intramuscular
- Intranasal
- Intrathecal
- Inhalational
- Oral (elixir or compounded)
- Topical
- Rectal

Cohen et al., 2018; Schwenk et al., 2018

Metabolism

CYP 450 (2B6 and 2C9 possible polymorphisms)

Half-life 2.3 +/- 0.5 hrs.

Norketamine is major metabolite

Excretion in urine

Cohen et al., 2018; Schwenk et al., 2018

Clinical Effects

- Subanesthetic (low doses): analgesia, sedation.
- High doses: general anesthesia.
- Increases: HR, B/P, salivary and tracheobronchial secretions, and bronchodilation d/t SNS effects (treat with benzodiazepines and alpha-2 agonists).
- Minimal effect on RR and airway reflexes
- Less tolerance and tachyphylaxis than opioids

Cohen et al., 2018; Schwenket al., 2018

Special Properties

Airway, respiratory rate is remarkably preserved

No hypotension

Few such agents exist for anxiolysis, analgesia, & amnesia

Analgesia is "double" that of morphine

Amnesia induced is similar to that induced by midazolam

Safest anesthetic for inexperienced anesthesia providers

Cohen et al., 2018; Schwenket al., 2018

Effects on the Neuro System-Anesthetic doses

Trancelike state from electrophysiologic dissociation between limbic and higher cortical systems=dissociative anesthesia

Brainstem activity remains normal

Pt's sedated but appear to be awake, cortical awareness is blocked from external stimuli i.e. auditory, visual, or pain-related input=dreamlike state

Awareness of time blunted

Cohen et al., 2018; Schwenket al., 2018

Psychological Effects-Anesthetic Doses

- Changes perception of distances
- Speech sound unintelligible
- Vivid auditory and visual hallucinations (often avoidable by co-administration of a benzodiazepine)

Cohen et al., 2018; Schwenk et al., 2018

Effects on Respiratory System

Causes bronchodilation

Ketamine stimulates CNS causing an increase in circulating catecholamines having a direct relaxant effect on airway smooth muscle

Useful for those with asthma

Cohen et al., 2018; Schwenk et al., 2018

Effects on Cardiac System

Increases blood pressure, heart rate, stroke volume, coronary artery blood flow and cardiac output (MAP usually increased by 25mm HG)

Used in patients with hypotension & hypovolemia such as trauma pt undergoing rapid sequence intubation, pts undergoing emergency cardioversion, amputation, or chest tube placement

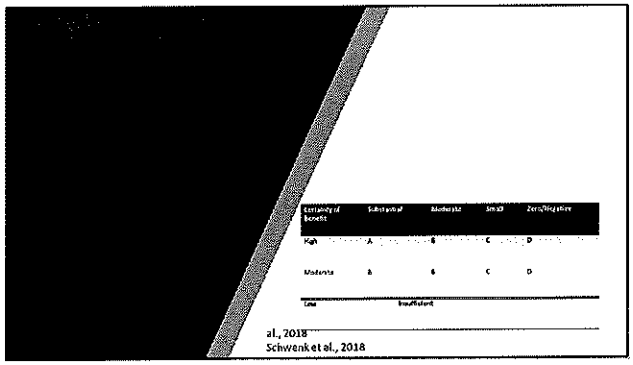
Dose dependent negative inotropic effect on cardiac muscle in catecholamine depleted states.

Cohen et al., 2018; Schwenk et al., 2018

Subanesthetic use- Adverse Events

- Nausea/vomiting
- Hallucinations which may be pleasant or unpleasant
- Hypertension, tachycardia, arrhythmias
- Hepatotoxicity (elevated enzymes)
- Lower urinary tract issues-bladder pain syndrome and interstitial cystitis with chronic and repetitive use.
- Tonic-clonic movements

Cohen et al., 2018; Schwenk et al., 2018



al., 2018
Schwenk et al., 2018

Indications:

- Surgeries Associated with Severe Pain (Grade B recommendation)
  - Upper abdominal
  - Thoracic surgery
  - Lower abdominal
  - Orthopedic (limb and spine)
- Opioid Tolerant and Dependent Patients with Acute Pain
  - Surgical: Spine surgeries (Grade B recommendation)
  - Acute Exacerbation of chronic pain condition: Sickle Cell Pain (Grade C recommendation), Cancer Pain
  - Other: ERCP pancreatitis, renal colic
- Those with increased risks for opioid related ADEs
  - OSA but high-level evidence is lacking (Grade C recommendation)

Schwenk et al., 2018

Acute Pain-Evidence

- Periop ketamine: reduced opioid consumption, rest pain and pain with movement at 24h and 48h postop.
  - Brink et al (2018) systematic review of 130 studies with 8341 participants
- Periop ketamine: major ortho surgeries (TJR, spine, arthroscopic) reduced opioid use, pain scores, time to first opioid at 24h and 48h postop. Joint arthroplasty most significant effects.
  - Riddell et al (2019) systematic review and meta-analysis 20 studies with 1271 participants
- Lap cholecystectomy: postop ketamine associated with significant difference in pain scores and opioid use compared to placebo
  - Ye, Wu, & Zhou (2017) meta-analysis
- Periop ketamine in opioid tolerant patients: At 24h postop, sl reduction in movement pain, no reduction in rest pain; 97.3mg MEDD reduction
  - Meyer-Frießem (2022) systematic review and meta-analysis

Sub-anesthetic Dosing for Acute Pain

Cooney & Quinlan-Colwell, 2021, Schwenk et al. 2018

Dosage for Procedural Sedation

Schwenk et al., 2018

Relative Contraindications

- Severe cardiovascular disease (angina, heart family, malignant HTN) (Grade C evidence)
- Pregnancy (Grade B evidence)
- Psychosis (Grade B evidence)
- Catecholamine depleted states
- Severe liver disease (Grade C evidence)
- CSF obstructive states (severe head injury, masses) (Grade C evidence)
- Intra-ocular pressure pathology (glaucoma, acute globe injury) (Grade C evidence)
- Active cocaine use

Cohen et al., 2018; Schwenk et al., 2018

Ketamine Use in those with SUD

- Acute pain, Short course of IV ketamine:
  - no evidence to show increase risk of ketamine Use Disorder
- Chronic pain, higher doses may pose increased risks.
- Recommended to assess risk on an individual basis and exercise precautions in monitoring for use disorder.

Nurses' Role in Subanesthetic Dosing: NYS Board of Nursing

"Within the first 24 hours of initiation of low-dose ketamine administration, RNs, with demonstrated competence, can administer and monitor patients on this regimen only to patients in recovery rooms, critical care, hospice, step-down or palliative care areas, that is, in patient care units with low patient to nurse ratios. Following this time period, and with no evidence of untoward side effects, such patients can be cared for by RNs, with demonstrated competence, on general patient units".

- *NYS Board of Nursing, updated April, 2021*

NYS BON and Low-dose Ketamine Infusion

- Requires an Acute Pain Service or Anesthesiology patient assessment for appropriateness before initiation of therapy and a patient-specific order for a low-dose ketamine infusion
- Must be prepared only by the pharmacy.
- Should be infused through its own dedicated IV line (when possible) or via the most proximal port of a carrier solution through painless IV tubing to avoid inadvertent infusing.
- Should NOT be poloused as a treatment for pain except by an anesthesia provider.
- Infuse using an IV infusion control device with a locked control panel.
- Monitor Vital signs, alertness, orientation, evidence of nystagmus, bad dreams and unpleasant hallucinations.
- Notify prescriber for HR >100/min, systolic B/P < 90 mmHg, RR <10/min, oxygen saturation <93% and symptoms of emergence reactions such as bad dreams, hallucinations and nystagmus.
- The facility must provide a written policy and procedure that documents an RN's role in the administration of low-dose ketamine.

Ketamine and Chronic Pain: Indications

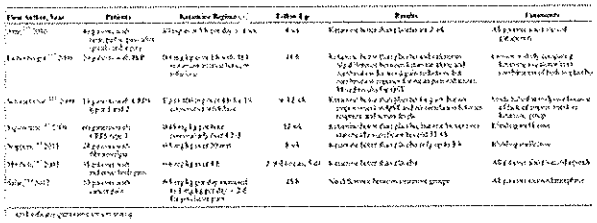
- Small studies, not well controlled, variable dosing protocols
- 2018 Guideline recommendations
  - Spinal cord injury pain (weak evidence supports short term improvement)
  - CRPS (moderate evidence supports improvement up to 12 weeks)
  - Mixed neuropathic pain, fibromyalgia, cancer pain, ischemic pain, headache, spinal pain (weak evidence for immediate improvement)

Cohen et al., 2018

Ketamine and Chronic Pain: Variable Treatment Protocols

- Intravenous
  - IV Bolus up to 0.35mg/kg
  - IV Infusion rate: 0.5 to 2mg/kg/h
  - IV infusion rates up to 7mg/kg/h for refractory pain in ICU setting
  - Some chronic pain conditions, IV infusion of 80mg over 2 hours
- Oral (limited data)
  - 0.25-0.5mg/kg tid
  - 0.8mg/kg/d
  - 10-25mg/d or 0.5 mg/kg at HS
- Intranasal (variable uses/dosing)
  - [FYI: Spravato (eskatamine) 28 mg/dose for treatment resistant depression]. T

Randomized Placebo-Controlled Trials Evaluating IV Ketamine for Chronic Pain



Cohen et al., 2018

Nursing Implications

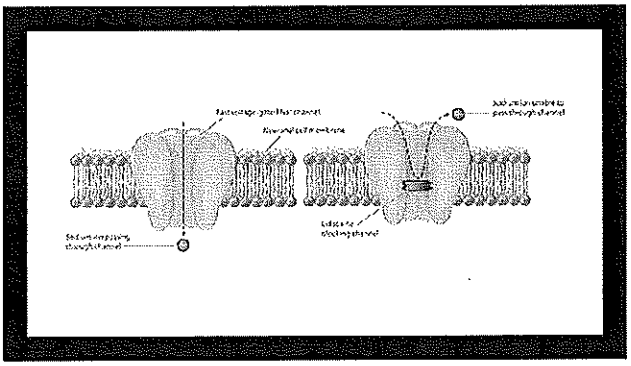
- Patient education
- Patient assessment and reassessment
  - Pain
  - Sedation especially if concurrent opioid/benzodiazepine use
  - Function
  - Adverse effects: CNS and C/V
  - Chronic Use: monitor liver and kidney function

Cooney & QuinlanCotwell, 2021

Sodium Channel Blocker: Lidocaine

- Classified as anesthetic and class 1b antiarrhythmic
- Nonselectivelyinhibits voltage gated sodium channelsleading to decreased neuronal pain transmission
- Sodium channelsare upregulatedin neuropathic pain states
- Other proposed MoA: NMDA receptor antagonism, blockade of capsaicin-sensitive afferents, substance P and bradykinin blockade, interacting with glycine in spinal cord, altering levelsof neurotransmitters.
- Steady state in 4-8 hrs without a bolus
- Context-sensitive half life after a 3 day infusion-40 min.
- Hepatic metabolism via CYP 450
- Renal excretion

Elpa et al., 2016



Acute Pain Indications

- Intra-abdominal surgery: facilitates return of gut function, prevent ileus, reduce LOS, reduce n/v, counter opioid-induced hyperalgesia.
- Sever pain refractory to other multimodal analgesics, unable to tolerate opioids, open abdominal surgery if unable or decline epidural or other intervention.
- Renal colic.
- Critical limb ischemia.
- Neuropathic pain

Elpe et al., 2016; Masic et al., 2018.

Postoperative Pain Studies

- Reductions in postoperative pain, opioid requirements, opioid related ADEs, opioid related ADEs and hospital stay.
  - Hutson & Abd-Elsayed, 2019; Kintzel, Knol, & Roe, 2018
- Lap cholecystectomy: significant reductions in pain and opioid consumption at 12h and 24h postoperatively
  - Zhao et al., 2018: meta-analysis 6 RCTs with 176 patients
- Postoperative pain: inconclusive re: pain or opioid use reduction d/t poor quality studies and inconsistencies
  - Weibel et al, 2018: Cochrane review of 68 trials. n= 4,525

Chronic Pain Indications

- Neuropathic pain:
  - Diabetic neuropathy
  - Postherpetic neuralgia
  - Central pain
  - Spinal cord injury
  - Fibromyalgia
  - Multiple sclerosis
  - CRPS
  - Chronic migraines and medication overuse headaches
  - Opioid refractory cancer pain

Hutson & Abd-Elsayed, 2019; Kintæl, Knol, & Roe, 2018

IV Lidocaine and Acute Pain

Masic et al., 2018: Systematic Review, 13 studies, 512 patients
Studies involved bolus 1-2 mg/kg; bolus 50-100mg; infusion 1mg/kg/h

- IV lidocaine superior to IV morphine for renal colic and critical limb ischemia
- IV lidocaine superior to IV dihydroergotamine (DHE) for acute migraine
- IV lidocaine equivalent to IV ketorolac for acute radicular low back pain.
- IV lidocaine less effective than IV chlorpromazine for acute migraine.
- Neuro s/e most common: slurred speech, altered MS
- No routine monitoring of lidocaine levels

IV Lidocaine Consensus Statement

Foo et al., 2020

- IBW for dose calculations. Avoid if < 40kg; do not exceed 120mg/h.
- Do not use along with other LA interventions, including nerve blocks.
- Loading dose not to exceed 1.5mg/kg over 10 min.
- Infusion not to exceed 1.5mg/kg/h; reassess after 24h.
- Use a separate IV line for infusion.
- Recommend placement in a unit providing frequent monitoring.
- Monitor for toxicity; have ready access to 20% lipid emulsion.

Contraindications

- Hepatic or renal impairment
- Low plasma protein levels
- Sedated patients (unable to perform neuro assessment)
- Cardiac arrhythmia disorders
- Seizure disorders
- Recent administration of LA (within 4 h)

Nursing Implications

- Assess for s/sx LAST.
  - Risk increased with liver and renal dysfunction and low plasma protein
  - Therapeutic level 1.5-5 mcg/ml
  - Neurologic toxicity s/sxs at lidocaine level > 5mcg/ml
  - C-V toxicity s/sxs at lidocaine level > 10mcg/ml
- Initial toxicity with neuro sxs: perioral numbness, tinnitus, metallic taste, mild dizziness, visual changes to sever sxs n/v, tremors, confusion, seizures, LOC
- Later CV sxs: changes in HR, B/P, arrhythmias, CV collapse

Hunter et al., 2021

Nursing Implications: Practices May Vary

- Initial IV bolus by anesthesia providers in a monitored setting.
- Bolus usually requires close monitoring for LAST.
- IV infusions safely managed on med/surg and peds floors.
- Every 4 hr neuro assessment and v/s.
- Routine lidocaine levels often not required.
- Lidocaine levels if liver or renal dysfunction
- Turn infusion off if any s/sxs toxicity
- Independent double checks with initiation and setting changes
- Availability of benzos, 20% intralipids, LAST treatment algorithm,

Hunter et al., 2021

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