Michigan Medicine

Ketamine IV Continuous Infusion Guidelines for Mechanically Ventilated Adult ICU Patients

Background

Ketamine is a N-methyl-D-aspartate receptor (NMDA) antagonist that creates a state of dissociative amnesia in patients. It is used frequently used for as an anesthetic for procedural sedation and in the operating room, as well as an induction agent rapid sequence intubation. Recent literature has suggested that ketamine may be an effective sedative agent in mechanically ventilated patients. It has also has been studied in patients suffering from alcohol withdrawal, status asthmaticus, and status epilepticus.

Pharmacokinetics

Absorption: 100% IV absorption

Distribution: 5-16 L/kg (increased in critically ill patients)

Onset: Less than one minute

Metabolism/Excretion: CYP3A4 and CYP2D6 mediated metabolism via N-demethylation and hydroxylation to norketamine and dehydronorketamine. Norketamine is an active metabolite with ~33% potency of ketamine; dehydronorketamine is an inactive metabolite.

Half-Life: Ketamine = 5-17 minutes, norketamine = 180-300 minutes

Pharmacodynamics

Ketamine primarily acts as an antagonist to the NMDA receptor, although it also has some antagonistic effects of delta, kappa, and mu receptors as well. Ketamine also inhibits re-uptake of catecholamines, which can yield an increase in blood pressure.

Considerations

ICU attending approval required for continuous infusion ketamine use

Ketamine should be used cautiously in patients with:

- Uncontrolled hypertension
- Pulmonary hypertension
- Moderate-severe hepatic dysfunction (Child-Pugh Class B and C)
- History of coronary artery disease
- Atrial arrhythmias
- Concomitant use of strong CYP3A4 and CYP2D6 inhibiting medications
- Patients with pre-existing history of schizophrenia or bipolar disorder

Contraindications

- Allergy to ketamine
- Active coronary ischemia

Adverse Effects

- Hypertension
- Hyper salivation
- Transient respiratory depression
- Agitation
- Ketamine emergence reactions

Management: Hyper salivation may be managed via the administration of glycopyrrolate 0.4 mg IV Q6H as needed. Emergence reactions may be managed with the administration of a benzodiazepine, either lorazepam 1-2 mg IV or midazolam 2-4 mg IV as needed. Hypertension is best managed by decreasing rate or stopping ketamine infusion; no studies to date have described management of ketamine-induced hypertension with antihypertensive agents.

Indications and Dosing

Sedation in adults who cannot tolerate other agents: Continuous infusion of 0.2 – 1.2 mg/kg/hr. Recommended initial rate is 0.2 mg/kg/hr. Titrate by 0.1 mg/kg/hr every 15 minutes to goal RASS.

Status Asthmaticus**:** Optional bolus dose of 0.5 mg/kg (max 50 mg) followed by continuous infusion of 0.5 – 2.5 mg/kg/hr. Recommended initial rate is 0.5 mg/kg/hr. Titrate by 0.1 mg/kg/hr every 15 minutes to clinical response.

Alcohol Withdrawal: Optional bolus dose of 0.3 mg/kg (max 30 mg) followed by continuous infusion of 0.15.-0.30 mg/kg/hr. Recommended initial rate is 0.15 mg/kg/hr. Titrate by 0.05 mg/kg/hr every 15 minutes to clinical response.

Status Epilepticus**:** Optional 1.5 mg/kg loading dose (150 mg max) followed by 1-10 mg/kg/hr continuous infusion. Starting rate and titration are at the discretion of ICU team only.

Pain: Consult acute pain service for approval to use ketamine for pain. https://michmed-clinical.policystat.com/policy/6412949/latest/

Ketamine dose may titrated down to off quickly over the period of 60 minutes if necessary due to adverse events or for an awakening trial

Dose Adjustments

*Renal Dysfunction**:** Due to the primarily hepatic metabolism of ketamine, dose does not need to be adjusted for renal dysfunction. Ketamine has been administered to patients with ESRD without effects of dose accumulation noted.

Hepatic Dysfunction:** To date, no studies have been conducted demonstrating that ketamine can be used safely in patients with moderate-severe hepatic dysfunction. However, given that ketamine is

predominantly hepatically metabolized, use in this population certainly puts patients at risk for accumulation of ketamine and the drug should be used with caution in these patients.

Monitoring Parameters

Check blood pressure, respiratory rate, sedation level, and pain score prior to and once 15-30 minutes following bolus dose, initiation of infusion, or infusion dose change. While on continuous infusion, check blood pressure, respiratory rate, sedation level, pain score, and SpO_2 once every 4 hours.

Ketamine cause vivid dreams, hallucinations, and anxiety. These adverse effects may be managed with as needed benzodiazepines. However, discontinuation or avoidance of ketamine may also be necessary in patients experiencing these adverse effects. Ketamine may contribute to development of ICU delirium, although incidence is not well-described. Ketamine should be used cautiously in patients with a pre-existing history of psychiatric illness.

Administration

Continuous infusion intravenous ketamine may be administered through either a peripheral or central line.

Orderable

Ketamine 10 mg/mL 50 mL infusion bag

References:

1. Ketelar [package insert]. Rochester, MI: JHP Pharmaceuticals LLC, 2012
2. Wang X, Ding X, Tong Y, Zong J, Zhao X, Ren H, Li Q. Ketamine does not increase intracranial pressure compared with opioids: meta-analysis of randomized controlled trials. J Anesth. 2014 Dec;28(6):821–827
3. Erstad BL, Patanwala AE. Ketamine for analagosedation in the critically ill. J Crit Care. 2016 May 25;35:145-149.
4. Patanwala AE, Martin JR, Erstad BL. Ketamine for analagosedation in the intensive care unit: a systematic review. J Intensive Care Med. 2015 Dec 8.
5. Jabbour HJ, Naccache NM, Jawish RJ , et al. Ketamine and magnesium association reduces morphine consumption after scoliosis surgery prospective randomised double-blind study. Acta Anaesthesiol Scand. 2014;58(5):572–9
6. Kang JG, Lee CJ, Kim TH, et al. Analgesic effects of ketamine infusion therapy in korean patients with neuropathic pain: A 2-week, open-label, uncontrolled study. Curr Ther Res Clin Exp. 2010 Apr;71(2):93-104.
7. Kator S, Correll DJ, Ou JY, et al. Assessment of low-dose i.v. ketamine infusions for adjunctive analgesia. Am J Health Syst Pharm. 2016 Mar 1;73(5 Suppl 1):S22-9.
8. Zakine J., Samarcq D., Lorne E., et al. Postoperative ketamine administration decreases morphine consumption in major abdominal surgery: a prospective, randomized, double-blind, controlled study. Anesthesia & Analgesia. 2008;106(6):1856–1861.
9. Umunna BP, Tekwani K, Barounis D, Kettaneh N, Kulstad E. Ketamine for continuous sedation of mechanically ventilated patients. J Emerg Trauma Shock. 2015 Jan-Mar;8(1):11–15. doi: 10.4103/0974-2700.145414.
10. Miller AC, Jamin CT, Elamin EM. Continous intravenous infusion of ketamine for maintenance sedation. Minerva Anestesiol. 2011;77(8):812–20.

11. Howton JC, Rose J, Duffy S, Zoltanski T, Levitt MA. Randomized, double-blind, placebo-controlled trial of intravenous ketamine in acute asthma. Ann Emerg Med. 1996;27:170–175.
12. Petrillo TM, Fortenberry JD, Linzer JF, Simon HK. Emergency department use of ketamine in pediatric status asthmaticus. J Asthma. 2001;38:657–64.
13. Heshmati F, Zeinali MB, Noroozinia H, Abbacivash R, Mahoori A. Use of ketamine in severe status asthmaticus in intensive care unit. Iran J Allergy Asthma Immunol. 2003;2:175–80.
14. Sabharwal V, Ramsay E, Martinez R, et al. Propofol-ketamine combination therapy for effective control of super-refractory status epilepticus. Epilepsy Behav. 2015 Nov;52(Pt A):264-6.
15. Hôfler J, Rohracher A, Kalss G, et al. (S)-Ketamine in refractory and super-refractory status epilpeticus: a retrospective study. CNS Drugs. 2016 Jul 27.
16. Gaspard N, Foreman BP, Alvarez V, Cabrera Kang C, Probasco JC, Jongeling AC, Meyers E, Espinera A, Haas KF, Schmitt SE, Gerard EE, Gofton T, Kaplan PW, Lee JW, Legros B, Szaflarski JP, Westover BM, LaRoche SM, Hirsch LJ, Critical Care EEG Monitoring Research Consortium (CCEMRC) New-onset refractory status epilepticus. Neurology. 2015;85:1604–1613.
17. Aroni F, Iacovidou N, Dontas I, Pourzitaki C, Xanthos T. Pharmacological aspects and potential new clinical applications of ketamine: Reevaluation of an old drug. J Clin Pharmacol. 2009;49:957–64.
18. Capel MM, Jenkins R, Jefferson M, Thomas DM. Use of ketamine for ischemic pain in end-stage renal failure. J Pain Symptom Manage. 2008;35:232–4.
19. Tawfic QA, Bellingham G. Postoperative Pain Management in Patients with Chronic Kidney Disease. J Anaesthesiol Clin Pharmacol. 2015 Jan-Mar; 31(1): 6–13.
20. Pizon AF, Lynch MJ, Benedict NJ, Yanta JH, Frisch A, Menke NB, Swartzentruber GS, King AM, Abesamis MG, Kane-Gill SL. Adjuct Ketamine Use in Management of Severe Ethanol Withhdrawal. Crit Care Med. 2018 Aug;46(8):e768-e771
21. Garber PM, Droege CA, Carter KE, Harger NJ, Mueller EW. Continuous Infusion Ketamine for Adjunctive Analgosedation in Mechanically Ventilated, Critically Ill Patients. Pharmacotherapy. 2019 Mar;39(3):288-296.
22. Groetzinger LM, Rivosecchi RM, Bain W, et al. Ketamine Infusion for Adjunct Sedation in Mechanically Ventilated Adults. Pharmacotherapy. 2018; 38(2): 181-188.
23. Shurtleff V, Radosevich JJ, Patanwala AE. Comparison of Ketamine-Versus Nonketamine-Based Sedation on Delirium and Coma in the Intensive Care Unit. Journal of Int Care Med. 2018; epub ahead of print.
24. Walters MK, Farhat J, Bischoff J, et al. Ketamine as an Analgesic Adjuvant in Adult Trauma Intensive Care Unit Patients With Rib Fracture. Ann Pharmacother. 2018; 52(9): 849-854.
25. Pruskowski KA, Harbourt K, Pajoumand M, et al. Impact of Ketamine Use on Adjunctive Analgesic and Sedative Medications in Critically Ill Trauma Patients. Pharmacotherapy. 2017; 37(12): 1537-1544.

Authors: Nick Farina, PharmD

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