Guideline

Guidelines for the Use of Ketamine Continuous Infusion for Refractory Status Asthmaticus in Adults

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BACKGROUND[1-16]

Ketamine is a dissociative anesthetic with analgesic, bronchodilating, and immunomodulatory properties. Several mechanisms of action have been proposed to explain the activity of ketamine. Ketamine is a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist (anesthetic and bronchodilatory effects), inhibits cerebral uptake of catecholamines (cardiovascular stimulation and beta-2 receptor mediated bronchodilation), and has anticholinergic and calcium channel blocking properties (bronchiolar smooth muscle relaxation). Advantageous properties of ketamine include maintenance of normal pharyngeal-laryngeal reflexes, no impact on airway patency, and no effect on respiratory drive (ketamine may depress ventilation but does not reduce the respiratory response to rising levels of carbon dioxide).

Most of the literature surrounding ketamine use in refractory status asthmaticus is in the form of case reports or case series, with very limited data available from well-designed, prospective, randomized, blinded clinical trials. There is also a high likelihood of publication bias, where studies demonstrating no benefit likely go unpublished. The available literature shows that ketamine may increase peak expiratory flow rate and PaO_2 and decrease mean peak airway pressure and $PaCO_2$. Continuous infusions of ketamine have been studied as an adjunctive agent for refractory pain and sedation management in postoperative intensive care, refractory status asthmaticus and traumatic brain injury in doses ranging from 1-150 mcg/kg/minute (0.06-9mg/kg/hr).

The purpose of this document is to provide guidance on the use of ketamine in refractory status asthmaticus in adult patients in a critical care setting.

Status asthmaticus is considered refractory when patients are persistently hypoxic (PaO2 <88%) after receipt of conventional treatments for status asthmaticus (e.g. inhaled beta agonists, inhaled muscarinic antagonists, systemic glucocorticoids, magnesium sulfate, oxygen).

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PRESCRIBING/ORDERING[3]

- Continuous infusion concentration: 10 mg/mL (1000 mg/100 mL)
- Titration is provider-only, based on clinical response

CRITERIA FOR USE[1,7]

- Adjunct agent for bronchodilation in adults with refractory status asthmaticus not responding to standard therapy

CONTRAINDICATIONS

- Patients in whom a significant elevation in blood pressure would be hazardous (e.g., abdominal aortic aneurysm, intracranial hemorrhage, subarachnoid hemorrhage, hypertensive emergencies)
- Known allergy or hypersensitivity to ketamine
- ***Relative*** contraindications:
    - Patients in whom an elevation in intracranial pressure would be hazardous (e.g., intracranial hemorrhage, traumatic brain injury, intracranial mass)
        - Despite historical reports of increased intracranial pressure (ICP), more recent studies show only a minimal increase in ICP. Increased ICP is no longer considered an absolute contraindication to the use of ketamine.
    - Known or suspected schizophrenia (even if stable or controlled with medications)
        - While historical data suggests that sub-dissociative doses of ketamine may cause transient cognitive and behavioral disturbances that are more pronounced in patients with a history of schizophrenia, evidence is lacking for this reaction in patients receiving full dissociative doses. Furthermore, as these responses are typically transient, a risk-benefit discussion for use in a patient with severe agitation is warranted.

DOSING[1,2,7-16]

Evidence

- Evidence for using ketamine in adults with refractory status asthmaticus is limited and has varying results

AU Health

- Loading Dose: 0.5mg/kg
- Continuous infusion: 0.5mg/kg/hr or 1mg/kg/hr (provider to select dose upon ordering)
- Use ideal body weight
    - An adjusted body weight may be used based on patient-specific clinical response
- See Guideline for Non-Procedural Ketamine Use in the Non-Intubated Patient in the Pediatric Emergency Department and Pediatric Intensive Care Unit for information on pediatric use of ketamine for status asthmaticus.
- Consider using glycopyrrolate 0.2 mg IV every 6 hours to prevent hypersalivation/bronchorrhea

EMERGENCE REACTIONS[1,17,18]

- Ketamine has been associated with emergence reactions characterized by hallucinations, confusion, combativeness, nightmares, delirium, dysphoria, visual changes, irrational behavior and excitement and most commonly occur with downward titration of ketamine.
- The incidence of emergence reactions is approximately 12% in adults, though the range varies from 0 to 50%.
    - Risk factors: Adult, female gender, higher dose
- Benzodiazepines are considered the first line treatment for emergence reactions.
    - Treatment: midazolam or lorazepam 2 mg IV every 10 minutes until adequate sedation is reached

NOTABLE ADVERSE DRUG REACTIONS[1,2,17-21]

- Increased blood pressure and/or heart rate
- Increased tracheobronchial secretions
- Increased muscle tone and purposeless movements (dyskinesia/dystonia/hypertonia)
- Tachyarrhythmias
- Emergence reactions
- Apnea (with rapid administration of very high doses)
- Vomiting

NOTABLE DRUG INTERACTIONS[1]

- Cisatracurium: reports of prolonged paralysis
- Barbiturates and opioids: prolonged recovery time

DRUG COMPATIBILITY AND STABILITY[1,2]

- Ketamine is not compatible with: Lactated ringers or potassium chloride containing solutions (this list is not all inclusive and a compatibility assessment should be performed before concurrent administration of ketamine with other continuous infusions through the same access point)
- Ketamine bags should be discarded 24 hours after preparation per USP 797 Guidelines.

DRUG MONITORING[1,2,15,17-18]

- With a bolus dose and with each dose increase, the patient's blood pressure, heart rate and respiratory rate should be monitored (every 5 minutes for 15 minutes).
- If an intracranial pressure monitor is in place, consider increased monitoring with bolus doses and dose increases.
- Tracheobronchial secretions

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APPENDIX 1. PHARMACOKINETIC PARAMETERS:[1-3]

Bioavailability:

- Intranasal: 35-50%
- IM: 93%

Onset of action: 30 seconds (peak effect within 60 seconds)

Duration of action: 5-10 minutes

Distribution (V_{dss}): 2.4 L/kg

Elimination:

- Urine: 91%
- Feces: 3%

Half-life: 10-15 minutes for anesthetic action and 2.5 hours for complete metabolism

There are no dosage adjustment recommendations for renal or hepatic dysfunction.