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Drug Shortage Alert
Parenteral Ketamine
Date of last update: November 2023

Recommendations and information provided in this Drug Shortage Alert are compiled by experts in the field. Practitioners are advised to consult with their institution's staff to ensure that response to any drug shortage is in line with internal policies and procedures.

INTRODUCTION

- Parenteral ketamine is on shortage due to increased demand, shortages of the active ingredient, and manufacturing delays.[1]
- Parenteral ketamine may be used for endotracheal intubation, sedation of mechanically ventilated patients, analgesia, alcohol withdrawal, asthma exacerbations, procedural sedation, refractory status epilepticus (SE), and agitated delirium.
- This summary provides information in the event of a shortage and its impact on adult patients, by providing potential management strategies, pharmacotherapeutic considerations, and safety implications.
- The recommendations provided within this document are pertinent to adult patients. They are based on both current evidence, including a review of available literature by the SCCM Drug Shortages and Medication Safety Committee, and the need for conservation during this shortage.

MANAGEMENT STRATEGIES

- Depending on your institution's supply, consider reserving ketamine for the following scenarios:
    - Endotracheal intubation: Intubation in critically ill patients is fraught with complications, and the most common complication, according to the literature, is post-intubation hypotension. Ketamine and etomidate are commonly chosen sedatives as both may mitigate the hemodynamic derangement that can occur during endotracheal intubation in critically ill patients. Ketamine may be chosen over etomidate in patients with shock as etomidate invariably lead to adrenal suppression, further adding to multiorgan failure with some reports of harm.[2-6]
    - Pain control: Studies have documented improved pain scores and reduced opioid use when ketamine is added to the pain management plan, with some evidence demonstrating reduced opioid consumption after hospital discharge.[7-8] Ketamine may also be beneficial in patients with history of polysubstance abuse and opioid use disorder.
    - Refractory SE and super-refractory SE: Ketamine may decrease seizure burden in patients with continued seizures despite first- and second-line therapies (refractory SE) and in patients with continued seizures despite more than 24 hours after addition of a third-line drug (super-refractory SE).[9-10]

- Agitated delirium unrelated to uncontrolled pain: Agitation in patients who either cannot receive alternatives due to lack of intravenous access or cannot receive alternatives such as parenteral antipsychotics may benefit from intramuscular ketamine for sedation. Ketamine 100 mg/mL should be reserved for intramuscular administration.

Table 1 describes selected indications for the above-mentioned drug shortage, specifically in critically ill adult patients. Pediatric dosing may be found in drug information resources.

Table 1. Potential Management Strategies for Drug Shortage in Critically Ill Adult Patients

Indication in critically ill patients	Suggested strategies	Key points
Agitated delirium management[11-15]	Ketamine • 2 mg/kg IM × 1 • 0.5 mg/kg – 1 mg/kg IV Alternatives therapies • Droperidol IV/IM • Dexmedetomidine infusion • Haloperidol IV/IM • Midazolam IV/IM • Olanzapine IV/IM • Valproate IV	• Current evidence does not support using ketamine for the prevention of delirium. However, it may be used for sedation in patients with hyperactive delirium. • Ketamine can often result in prolonged sedative effects. • 57% of adult patients with profound prehospital agitation who received ketamine doses of 5 mg/kg IM × 1 became intubated in an observational study. If doses higher than 2 mg/kg are used, closely monitor the patient for respiratory depression. • Optimize nonpharmacologic therapies and control pain to manage delirium (e.g., sleep/wake cycle, early mobilization, reorientation). Eliminate medications that increase the risk for delirium (e.g, BZDs, anticholinergics) • For severe agitation, consider parenteral antipsychotics. BZD exposure should be minimized to prevent worsening of delirium, unless BZD withdrawal is believed to be the cause of agitation. • Agitated delirium caused by withdrawal syndromes should be managed according to the syndrome present. • For persistent severe agitation despite antipsychotics, consider dexmedetomidine.
Alcohol withdrawal[16-18]	Ketamine (as adjunct to GABA agonists) • 0.15-0.3 mg/kg/h Common therapies: • BZDs	• Diazepam, lorazepam, and chlordiazepoxide are the most commonly used BZDs, but others can be used. Doses, including for symptom-based and front-loading strategies, can vary.

	• Phenobarbital	• Escalating doses of BZDs in addition to barbiturates based on symptoms, if necessary, may lead to a decreased need for mechanical ventilation. • Limited data exist at this time to routinely recommend ketamine for the management of alcohol withdrawal. • Multivariable modeling in a small series shows that patients who received ketamine in addition to GABA agonists had lower rates of intubation and shorter ICU length of stay compared to those who did not receive ketamine.
Asthma exacerbation[19-23]	Ketamine (as adjunct to beta$_2$-agonists) • 0.1 mg/kg IV × 1 followed by 0.5 mg/kg/h IV infusion Standard of care: Oxygen + inhaled short-acting beta$_2$-agonists (e.g., albuterol) + inhaled muscarinic antagonists (e.g., ipratropium) + corticosteroids, magnesium	• Ketamine inhibits vagal outflow, relaxes airway smooth muscle, and increases catecholamines, leading to bronchodilation. • There is lack of data showing clear benefit over standard of care.

Endotracheal intubation[5,24-27]	Ketamine
	• 1-2 mg/kg IV × 1
	• 4-10 mg/kg IM × 1
	
	Alternatives:
	• Etomidate 0.3 mg/kg IV × 1
	• Propofol 0.5-1.2 mg/kg IV × 1
	• Lower doses of ketamine and propofol (i.e., ketofol) 0.5 mg/kg each
	• Remimazolam
	  ○ ASA I/II: 5 mg IV with 2.5 mg every 2 min as needed
	  ○ ASA III/IIII: 2.5 mg IV with 1.25-2.5 mg every 2 min as needed
	• Midazolam 0.2-0.3 mg IV × 1
		• Some reports indicate a possible association between etomidate use and decreased survival.
		• Etomidate can lead to adrenal suppression adding to multiorgan failure, the significance of which is still to be determined, with some reports indicating harm.
		• Hemodynamic derangements may be mitigated with lower doses of ketamine when used in conjunction with propofol. Although the data support use in a single syringe, combining both agents in one syringe is not recommended due to the increased risk for medication errors.
		• Fast onset and offset of remimazolam may lead to less potential for hemodynamic complications.
		• Consider delayed sequence intubation if clinically appropriate with local anesthesia and BZDs.

Pain control [28-36]	Ketamine: • 0.5 mg/kg IV × 1 followed by 0.06-0.12 mg/kg/h • 0.3 mg/kg IV × 1 Alternatives: • Methadone (IV or oral) • Opioids (e.g., fentanyl, hydromorphone, morphine, oxycodone) • Non-opioid multimodal analgesia (e.g., NSAIDS, lidocaine, gabapentinoids, muscle relaxants, acetaminophen, nerve blocks) • For refractory pain, consider PCA and/or consult pain anesthesiology Service	• Studies evaluating ketamine for pain control in critically ill patients use varying doses. • Ketamine's impact on pain control and opioid consumption have varied due to differences in study methodology and cause (e.g., sickle cell crisis). • One randomized controlled trial showed a reduction in opioid consumption with continuous-infusion ketamine. • The dosing of methadone and opioids will differ due to pharmacokinetics. Patients with hepatic and renal dysfunction may need reduced doses of opioids due to increased half-lives. Patients with chronic exposure to opioids may need higher doses. • Continuous opioid infusion does not improve analgesia compared to on-demand doses but may be necessary when pain is not controlled with on-demand doses (e.g., 3 boluses in 1 h) or in patients who are chronically exposed to opioids. • Nerve blocks can decrease opioid use. • PCA is useful for maintenance of analgesia rather than breakthrough pain.
Procedural sedation[37-39]	Ketamine • 0.5-2 mg/kg IV × 1 Alternatives: • Consider delaying non-urgent procedures • Attempt local anesthesia/nerve blocks • Propofol • BZDs • Dexmedetomidine	• Hematoma blocks for fracture reductions, intra-articular anesthetic injection for dislocation reduction and other forms of local pain management can obviate the need for procedural sedation. • See SCCM Drug Shortage Alert Alternative Medications for Procedural Sedation for more details.
Sedation of mechanically ventilated patients[28,40,41]	Ketamine • 1-5 mcg/kg/min (0.1-0.5 mg/kg/h) IV infusion as starting dose Alternatives: • Dexmedetomidine propofol, or BZDs at lowest required dose, in combination with analgesia.	• Propofol may cause hypotension, hypertriglyceridemia leading to pancreatitis, and propofol infusion syndrome. • Dexmedetomidine may cause bradycardia and hypotension, and body temperature elevations. • BZDs can lead to prolonged sedation, delirium, tolerance, and withdrawal.

	• Consider treating hyperactive delirium not related to other identified causes (e.g., pain, substance withdrawal) and refractory to nonpharmacologic therapies with antipsychotics such as haloperidol, olanzapine, or quetiapine	• Either dexmedetomidine or propofol are recommended instead of BZDs for sedation of critically ill mechanically ventilated patients. • Routine use of antipsychotics for the management of delirium is not recommended unless the patient has significantly distressing symptoms (e.g., anxiety, fear, hallucinations, delusions, extreme agitation, physically harmful to self or others). Short-term use may be needed for these patients.
Refractory SE/super-refractory SE [9,10,42,43]	Ketamine • 0.05-10 mg/kg/h ± 1.5 mg/kg initial bolus Alternative therapies • Fosphenytoin • Lacosamide • Levetiracetam • Phenobarbital • Valproate • Pentobarbital infusion • Propofol infusion • Midazolam infusion	• Ketamine may be beneficial in patients with refractory SE and super-refractory SE despite first-line (e.g., BZDs) and second-line therapies (e.g., fosphenytoin/phenytoin, valproate, levetiracetam). • For super-refractory SE, dosing optimization of current antiepileptics, addition of third-line antiepileptics (e.g, lacosamide, phenobarbital), increasing dosing of anesthetics, and/or adding another continuous-infusion anesthetic such as pentobarbital or ketamine should occur. • In a series of patients administered ketamine, decreased seizure burden by at least 50% was seen within 24 h; the average ketamine dose was 2.2 ± 1.8 mg/kg/h. • High doses of propofol or phenobarbital may require vasopressor use to maintain adequate blood pressure and/or cerebral perfusion pressure. • Abrupt discontinuation may lead to rebound seizure activity.

ASA, American Society of Anesthesiologists; BZD, benzodiazepine; GABA, gamma-aminobutyric acid; h, hour; ICU, intensive care unit; IM, intramuscular; IV, intravenous; NSAID, nonsteroidal antiinflammatory drug; PCA, patient-controlled analgesia; SE, status epilepticus

PHARMACOTHERAPEUTIC CONSIDERATIONS

- The use of ketamine and management strategies in the setting of drug shortages is indication dependent. Please refer to **Table 1** for more information.
- Monitor daily use of ketamine and assess for appropriate use. Choose an alternative agent when clinical situations allow.

- Compounded bags of ketamine for use as continuous infusions can be made smaller to conserve drug supply.
- Reserving high-concentration ketamine (e.g., 100 mg/mL) is recommended for IM administration.

SAFETY IMPLICATIONS

- When ketamine is unavailable due to shortages and clinicians must select other agents, education of staff and caregivers is important to prevent adverse reactions.
- Benzodiazepines or antipsychotics may be necessary for agitated delirium, although different durations of effect and cumulative dosing can lead to prolonged sedation or arrhythmias.
- Alternative sedative agents for induction of anesthesia for endotracheal intubation may carry more risk of hypotension than ketamine.
- Providers of procedural sedation may be required to utilize propofol (which can have an increased risk of hypotension when used as a single agent) or benzodiazepines with risk of prolonged sedative effects.
- Increasing doses of more traditional pain medications may be required, with associated side effects, when ketamine is not available as an adjunct.
- Institutions may purchase ketamine from different manufacturers, depending on availability. Care must be taken to prevent mixing vials of different strengths and resulting dosing errors.[44]
- Limit different concentrations of ketamine at institutions to reduce potential for medication errors. Sequester certain concentrations within the pharmacy.[44]
- Double-check ketamine dose, route, and dose preparation details (e.g., concentration of vial use, amount drawn up from vial) with a second clinician to minimize the risk of errors.[44]

IMPACT ON ICU CARE

- Routine administration of ketamine for the management of asthma exacerbations and alcohol withdrawal is not supported by existing data.
- Ketamine is a reasonable agent to use for the management of uncontrolled pain if nonpharmacologic and multimodal regimens are optimized. While the incidence of side effects is low with subanesthetic doses of ketamine, tachycardia, hypertension, increased secretions, nystagmus, confusion, and agitation may occur. Patients should be monitored accordingly.
- Patients with super-refractory SE who are already receiving benzodiazepines and second-line antiepileptic agents may benefit from continuous-infusion ketamine.
- When possible, ketamine syringes should be either purchased from compounding pharmacies or batched within the hospital pharmacy to prevent drug waste at the bedside when vials are used. This may also decrease the risk of drug errors caused by improperly labeled syringes made at the bedside.

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