



**Drug Shortage Alert
Etomidate**

Date of last update: July 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

- Etomidate supply is currently limited due to a combination of manufacturer delays, increased demand, and discontinuation of production.¹
- Etomidate acts as a positive allosteric modulator on the gamma-aminobutyric acid (GABA) type A receptor, enhancing the effect of the inhibitory neurotransmitter GABA.²
- Etomidate is FDA-approved for rapid sequence intubation (RSI) and induction of anesthesia. Off-label uses include procedural sedation and the management of Cushing syndrome.
- This summary provides information in the event of a shortage and its impact on adult and pediatric patients by providing potential management strategies, pharmacotherapeutic considerations, and safety implications.
- The recommendations provided within this document 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, considerations for reserving etomidate for the following scenarios is prudent:
 - For procedural sedation, general anesthesia, or RSI: if alternatives are contraindicated or undesirable due to the risk of adverse events
 - Cushing syndrome: in situations where surgery may not be feasible and the patient cannot take medications by enteral route (e.g., mouth)
- Other anesthetics such as ketamine, propofol, or midazolam can be considered as an alternative sedative in certain situations (if also not on shortage).

Table 1 describes selected indications for the above-mentioned drug shortage, specifically in critically ill patients.

Table 1. Potential Management Strategies for Drug Shortage

| Indication in critically ill patients | Suggested strategies | Key points |
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| RSI | <ul style="list-style-type: none"> • Consider alternatives such as ketamine, midazolam, or propofol in appropriate patients • In patients that require etomidate, consider rounding the dose to optimize the vial size (e.g., for a 70-kg patient with a calculated dose of 21 mg, dose would be rounded to 20 mg, which is 1 vial) | <ul style="list-style-type: none"> • The ACEP RSI policy statement recommends for appropriate sedative and induction agents to be immediately available in the ED and accessible to all clinicians performing RSI in the ED.³ • Clinicians performing RSI should be made aware of the etomidate shortage in advance and familiarize themselves with alternatives. • Propofol 1-2 mg/kg, ketamine 1-2 mg/kg, or midazolam 1-2 mg IV are commonly utilized. • The addition of fentanyl 1-3 mcg/kg can provide analgesia and blunt the patient's sympathetic response.⁴ |
| Procedural sedation | <ul style="list-style-type: none"> • Consider alternatives such as ketamine, midazolam, propofol, or dexmedetomidine infusion in appropriate patients • Combine sedation with analgesia to reduce sedative doses and to provide pain control | <ul style="list-style-type: none"> • Propofol can be administered as an initial bolus of 0.5-1 mg/kg with additional boluses 0.25-0.5 mg/kg every 1-3 minutes to maintain and achieve sedation. • Given propofol's lack of analgesic properties, combination with ketamine 0.1-0.5 mg/kg or fentanyl is common. • Coadministration of ketamine with propofol can quickly achieve deep sedation and analgesia. Higher ratios of ketamine to propofol doses may lead to prolonged recovery time.⁵ |
| Cushing syndrome | <ul style="list-style-type: none"> • Reserve for when surgery is not feasible or delayed, and the patient cannot take medications enterally • Consult endocrinologist for recommendations | <ul style="list-style-type: none"> • Cushing syndrome is primarily treated surgically. However, if immediate surgery cannot be performed, medical treatment can be provided to decrease cortisol production and to antagonize cortisol activity at the glucocorticoid receptor.⁶ • Oral medications such as ketoconazole, metyrapone, and mitotane inhibit cortisol synthesis, which can also decrease ACTH-dependent cortisol production. • Etomidate is the only IV agent that decreases endogenous cortisol synthesis. It is administered as a continuous infusion, with low dose (0.04-0.05 mg/kg/h) producing partial blockade, while high dose (0.5-1 mg/kg/h) provides complete blockade. • A case series describes a protocol of utilizing 2.5 mg/hr for a mean of 8.2 days. The implementation of this protocol would utilize 60 mg of etomidate per day.⁷ |

ACEP, American College of Emergency Physicians; ACTH, adrenocorticotropic hormone; ED, emergency department; IV, intravenous; RSI, rapid sequence intubation.

PHARMACOTHERAPEUTIC CONSIDERATIONS

- The use of etomidate and management strategies in the setting of drug shortages is indication-dependent. Please refer to the above review for more information.

- RSI is a method of securing the airway utilizing pharmacologic agents in quick succession to avoid pain, aspiration, and increase in intracranial pressure that are associated with the process of intubation.
 - Sedation must occur prior to the administration of paralytic agents to avoid consciousness while intubation is occurring. Because of its quick onset, short duration of action, and minimal effects on a patient's hemodynamic status, etomidate has become a standard agent for induction of RSI by anesthesia, critical care, and ED clinicians.
 - Ketamine is considered an alternative and may be preferred to etomidate in certain clinical scenarios⁸:
 - Status asthmaticus or bronchospasms
 - Adrenal insufficiency
 - Hemodynamic compromise
 - Propofol is a reasonable alternative in patients with low risk of hemodynamic compromise or when combined with vasopressors (e.g., norepinephrine, phenylephrine) to mitigate hypotensive effects.
- Procedural sedation:
 - Consider the use of a benzodiazepine and an analgesic.
 - Administer an opioid first and titrate the benzodiazepine to desired depth of sedation to minimize risk of respiratory depression.
 - A combination of ketamine and propofol can be used for procedural sedation and analgesia.
 - It is recommended to not combine these two agents in one syringe to prevent medication errors, such as visual identification of dose for these visibly different medications.
 - The use of combination therapy allows lower doses of each agent to achieve adequate and consistent sedation for procedures while decreasing dose-related side effects.
- Characteristics of an ideal drug for RSI and procedural sedation:
 - Predictable pharmacokinetic profile
 - Medications should be administered incrementally, allowing sufficient time between doses to assess its effect.
 - Rapid onset of action
 - Analgesic and anxiolytic effects
 - Match medication duration of action with length of procedural stimulation.
 - Short recovery time
 - Minimal associated risks
 - Consider the patient's comorbidities when selecting drug, dose, and administration interval since patients with comorbid disease, extreme age, obesity, sleep apnea, or renal or hepatic insufficiency are more likely to develop complications associated with procedural sedation.
 - May be administered in the absence of an anesthesiologist
 - Clinicians should make a distinction between analgesics that relieve pain and sedatives that decrease anxiety and promote somnolence (**Table 2**).
- Cushing syndrome:
 - Etomidate inhibits 11-beta-hydroxylase, which converts cholesterol to cortisol, resulting in a marked decrease in circulating cortisol.¹ In critically ill and trauma patients, sedation using etomidate infusions were found to result in a threefold increase in mortality.^{9,10}

- Given the impact of etomidate on circulating cortisol, it can be utilized to manage severe Cushing syndrome. It is currently the only IV option for patients who are unable to take medications enterally.
- Alternative pharmacotherapy management of Cushing syndrome includes mifepristone, ketoconazole, and metyrapone; however, all these drugs can only be administered enterally.¹¹

SAFETY IMPLICATIONS

- Etomidate has limited effects on hemodynamic and respiratory functions, making it an ideal agent for rapid, short-term sedation in critically ill or hemodynamically unstable patients requiring intubation or procedural sedation.
- Concerns persist about the potential effects on adrenal suppression, especially in critically ill patients with sepsis. However, single-dose administration of etomidate for endotracheal intubation in patients with sepsis or septic shock has not been shown to increase morbidity or mortality.¹²
- Published guidelines on procedural sedation discuss the relative merits of the available sedatives but do not recommend the use of any particular agent.¹³ Multiple studies comparing one agent to another have not proven any to be superior to another.¹³⁻¹⁷ The choice of sedation agent should take into account patient-specific factors.
- Understanding of institutional policies of the administration of these medications and credentialing/monitoring requirements is important to consider when determining alternative medications

IMPACT ON ICU CARE

- There are several alternative agents that can be used for RSI and/or procedural sedation in the ICU. With judicious use of alternative agents in appropriate situations, the shortage of etomidate may have minimal overall impact on the provision of care in ICUs and EDs. The lack of etomidate may have bearing on hemodynamically unstable patients requiring intubation or sedation.
- Some alternative agents can have potentially deleterious effects on blood pressure. For those patients with hemodynamic instability, the best alternative may be ketamine.^{11,14,17}
- The use of etomidate for the treatment of acute severe Cushing syndrome is uncommon and most patients are able to take a medication enterally. Since there is no currently available alternative IV medication for the treatment of Cushing syndrome, the lack of availability of etomidate will impact the rare patient who is unable to take medications enterally and for whom surgery is not feasible. Institutions are encouraged to develop a mitigation strategy in conjunction with an endocrinologist.

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Table 2. Alternative Rapid Sequence Intubation and Procedural Sedation Agents

| Medication | Pharmacologic class | Onset (min) | Duration | Initial dosing: intermittent | Initial dosing: continuous infusion | Repeat dosing/titration | Side effects | Reversal | Safety implications | Special comments |
|------------------|---------------------|-------------|------------|--|---|---|---|------------|---|--|
| Remimazolam (IV) | Benzodiazepine | 1-2 | 45 ± 9 min | ASA: 1-2 5 mg IV ASA: 3-4 2.5 mg IV | Off-label use: Induction of general anesthesia 6-12 mg/kg/hour with maintenance 1-3 mg/kg/hour | ASA: 1-2 2.5 mg every 2 minutes ASA: 3-4 1.25-2.5 mg every 2 minutes | Hypotension, respiratory depression but less than midazolam | Flumazenil | Extremes of hepatic dysfunction → approximately 30% increase in duration due to hydrolysis from carboxylesterase 1 activity (liver) | Reconstitute in normal saline, 8.2 mL, to obtain 2.5 mg/mL due to pH (2.5-3.5), otherwise can precipitate in balanced salt solution such as lactated Ringer. Stable for 8 hours once reconstituted; use of flumazenil in patients on chronic benzodiazepines may lead to withdrawal symptoms |

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| Midazolam (IV) | Benzodiazepine | 1-3 | 30-120 min | 0.02 mg/kg IV (2 mg IV increments) | NA | May repeat every 3-5 min (max 0.2 mg/kg IV total) | Hypotension, respiratory depression, paradoxical agitation | Flumazenil | Use with caution in patients who are obese or have acute kidney injury/chronic renal failure due to risk of accumulation of active metabolite with repeated dosing; clearance is reduced when administered with medications that inhibit cytochrome P450 enzyme systems. Reduce dose by 25%-50% if combined with opioids. | Consider patient-specific variables when determining dosage; use of flumazenil in patients on chronic benzodiazepines may lead to withdrawal symptoms |
| Lorazepam (IV) | Benzodiazepine | 15-20 | 6-8 hour | 0.02-0.05 mg/kg IV or 1-2 mg IV | NA | 0.5-1 mg IV every 15-20 min (max 4 mg IV) | Hypotension, respiratory depression, paradoxical agitation | Flumazenil | Due to slower onset and longer duration, has limited utility in procedural sedation. Reduce dose by 25%-50% | Consider patient-specific variables when determining dosage; use of flumazenil in patients on chronic |

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| | | | | | | | | | if combined with opioids. | benzodiazepines may lead to withdrawal symptoms |
| Dexmedetomidine (IV) | Alpha-2-receptor agonist | 15 (following start of infusion) | 1-2 hour | NA | 0.6-0.7 mcg/kg/hour IV | Adjust by 0.1-0.2 mcg/kg/hour every 30 min (usual range 0.2-1.5 mcg/kg/hour) | Bradycardia, hypotension | NA | Use with caution in patients with history of heart block and those dependent on adrenergic tone to maintain blood pressure. Bolus dose increases risk of bradycardia, hypotension, and/or hypertension. | While dexmedetomidine provides mild analgesia, it will not blunt noxious stimuli and should not be used without adequate analgesia Can cause loss of oropharyngeal muscle tone; monitor for hypoxemia and hypoventilation (effects can be enhanced with concomitant benzodiazepine use). |
| Nitrous oxide (inhaled) | Anesthetic gas | 2-5 | 5 min | NA | 25%-50% | NA | Decreased myocardial contractility, worsening pulmonary hypertension, nausea, peripheral neuropathy, | NA | Requires well-ventilated room and has potential for clinician exposure or abuse; gas scavenging system minimizes clinician | Administer with 30% oxygen to avoid diffusion hypoxia; oxygen should be continued after nitrous oxide is discontinued. |

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| | | | | | | | headache, CNS excitation, increased intracranial pressure | | exposure. Can increase pressure in closed gas-containing spaces or air pockets (e.g., pneumothorax, pneumoperitoneum/bowel obstruction, intraocular pressure, inner ear pressure, endotracheal tube cuff pressure). | Typically used as adjunct to other sedatives. |
| Propofol | Sedative/hypnotic | 1 | 5-10 | 0.5-1 mg/kg IV (<i>0.5 mg/kg when combined with ketamine given in aliquots to effect</i>) | NA | 0.5-1 mg/kg IV every 5 min | Pain at injection site, hypotension, myocardial depression, bradycardia, apnea, hypersensitivity reaction (allergy to eggs, soy, or peanuts (product-specific), hypertriglyceridemia (side effects are generally | NA | Small or large dose changes may result in unpredictable general anesthetic state. Initial hypotension exaggerated when administered via central access. | Clinicians should be prepared to rescue patients from depth of sedation beyond intended level. Institutional procedures or state laws may preclude bolus administration by nurses. |

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| | | | | | | | reduced with ketamine in combination with propofol) | | | |
| Ketamine | Dissociative anesthetic | 0.5 | 5-10 | 1-2 mg/kg IV (0.5 mg/kg when combined with propofol given in aliquots to effect); IM dosing: 6.5-13 mg/kg | NA | 0.2-0.5 mg/kg IV every 10 min | Emergent delirium, increased systemic and pulmonary pressures, and intraocular pressures, laryngospasm, hypersalivation, tachycardia (side effects are generally reduced with propofol in combination with ketamine) | NA | Use caution in patients with significant coronary artery disease, increased intracranial/intraocular pressure, and excessive respiratory secretions. Consider pretreatment with antisialagogue to minimize secretions. Hemodynamic stability maintained due to catecholamine release; use with caution in patients with poor reserve (e.g., elderly, | Consider pretreatment with benzodiazepines to prevent associated emergent reactions (not needed if using with propofol (e.g., ketofol) as propofol acts as a GABAa agonist). Institutional procedures or state laws may preclude bolus administration by nurses. |

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| | | | | | | | | | trauma) and in patients with poor cardiac reserve due to direct myocardial depression. | |
| Methohexital | Barbiturate | 1-3 | 5-10 | 0.75-1 mg/kg IV | NA | 0.5 mg/kg IV every 2-5 min | Hypotension, myocardial depression, CNS and respiratory depression | NA | Unpredictable general anesthetic state may result, particularly with large doses. | Clinicians should be prepared to rescue patients from depth of sedation beyond intended level. |

ASA, American Society of Anesthesiology; CNS, central nervous system; IV, intravenous; NA, not applicable.