



**Drug Shortage Alert**  
**Alternative Medications for Procedural Sedation (Adults 18 Years and Older)**  
**September 2022**

*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**

- Medications frequently used for procedural sedation are currently being affected by shortages due to manufacturer discontinuation and/or increased demand.<sup>1-2</sup>
- Alternative medication recommendations given below can be considered when a drug shortage arises within a particular class of medications.<sup>3</sup>
- When using less familiar medications for this indication, it is recommended to review basic principles of procedural sedation, including goals for sedation and analgesia and the four different depths of patient procedural sedation:<sup>4-5</sup>
  - Goals for sedation and analgesia:
    - Alteration of patient level of consciousness, mood, and anxiety level
    - Amnesia of unpleasant sensation
    - Increase in pain threshold
    - Patient cooperation with appropriate response to tactile and verbal stimulation
    - Maintenance of intact airway
    - Maintenance of protective airway reflexes
    - Hemodynamic stability
  - Procedural sedation is classified into four categories based on patient assessment:<sup>4-5</sup>
    - Minimal sedation/analgesia: mild anxiolysis or pain control
    - Moderate sedation: purposeful response following voice or light touch
    - Deep sedation: purposeful response following painful stimuli
    - General anesthesia: no purposeful response to repeated painful stimuli

**MANAGEMENT STRATEGIES**

- Depending on your institution's supply, considerations for reserving IV sedative agents for the following scenarios is prudent:
  - Moderate to deep sedation
- Selected anesthetics or sedatives may be considered as an alternative in certain situations (if not also on shortage) based on their adverse effect profile.

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

**Table 1. Potential Management Strategies for Drug Strategies<sup>4-5</sup>**

| Indication in the critically ill | Suggested strategies   | Key points   |
|----------------------------------|--|--|
| Minimal to moderate sedation     | <ul style="list-style-type: none"> <li>• Use oral sedation and analgesia options in advance of procedure.</li> <li>• Consider delay of non-urgent procedures.</li> <li>• Consult anesthesiology.</li> </ul>  | <ul style="list-style-type: none"> <li>• Oral benzodiazepines (e.g., lorazepam) may offer a reasonable adjunct, although they may take up to 30 minutes to work.</li> </ul>                                |
| Moderate to deep sedation        | <ul style="list-style-type: none"> <li>• Combine multiple agents to minimize doses of each.</li> <li>• Round doses to nearest vial size to conserve vials.</li> <li>• Consult anesthesiology.</li> <li>• Consider inhaled anesthetics (e.g., nitric oxide).</li> </ul> | <ul style="list-style-type: none"> <li>• “Ketofol” may decrease requirements of both ketamine and propofol.</li> <li>• There is increasing literature with nitric oxide use in non-OR settings.</li> </ul> |

**PHARMACOTHERAPEUTIC CONSIDERATIONS**

- Characteristics of an ideal drug for procedural sedation and analgesia:
  - Predictable pharmacokinetic profile
    - Medications should be administered incrementally, allowing sufficient time between doses to assess 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, and 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 (**Table 2**) and sedatives that decrease anxiety and promote somnolence (**Tables 3 and 4**).<sup>11</sup>
- If both benzodiazepines and analgesics are used, consider:
  - Dose reduction of both agents due to synergistic side effects of these medication classes
  - Giving an opioid first and titrating benzodiazepine to desired depth of sedation to minimize risk of respiratory depression
- A combination of ketamine and the propofol known as ketofol can be used for procedural sedation and analgesia<sup>11</sup>
  - A 1:1 ratio of ketamine and propofol mixed in a single syringe (concentration 5 mg/mL each of ketamine and propofol when mixing the same concentration of 10 mg/mL of each drug in the same syringe to be given as a 1-3 mL bolus dose; for endotracheal intubation, dosing is 0.5 mg/kg of each ketamine and propofol mixed in the same syringe)
    - Alternatively, individual administration of ketamine followed by propofol can be performed in the recommended doses above.
  - Allow for lower doses of each agent to achieve adequate and consistent sedation for

procedures while decreasing dose-related side effects

### **SAFETY IMPLICATIONS**

- Level of sedation can be an unpredictable, dynamic process based on pharmacokinetic and pharmacodynamic principles; therefore, it is recommended that clinicians using unfamiliar medications should be prepared to rescue patients from a depth of sedation beyond (deeper than) the intended level based on institutional standards.
- Use of anesthetic induction agents, including methohexital, propofol, and ketamine, should be consistent with medication labeling and institutional standards for deep sedation, regardless of route of administration and intended level of sedation.
  - Reversal agents, including naloxone and flumazenil, should be available whenever opiates or benzodiazepines are administered.
- Continued monitoring of effect is recommended because the duration of the reversal agent may be less than that of the agent it is intended to reverse (e.g., flumazenil with benzodiazepine administration).

### **IMPACT ON ICU CARE**

- In general, procedural sedation medications are for short-term use and shortage should not cause disruption in care. If tier 1 agents are unavailable, tier 2 or tier 3 agents may be used (**Tables 2 and 3**).
- Safety concerns include using agents with more adverse effects (e.g., respiratory depression from methohexital) and less familiarity among staff with potential to result in dosing errors or adverse effects.
- Potential cost consequences of shortage should be minimal but vary by institution.

**Table 2** describes selected indications for the above-mentioned drug shortage, specifically in the critically ill.

**Table 2. Opioid Analgesics<sup>7,10</sup>**

| Medication                | Approximate parenteral equianalgesic dose | Onset IV (min) | Duration                                | Initial dosing: intermittent         | Initial dosing: continuous infusion | Repeat dosing/ titration <sup>a</sup>                                  | Side effects   | Reversal | Safety implications                                   | Special comments   |
|---------------------------|---|----------------|---|--------------------------------------|-------------------------------------|--|--|----------|---|--|
| <b>Tier 1<sup>b</sup></b> |   |                |   |                                      |                                     |  |  |          |   |  |
| Fentanyl                  | 0.1 mg (100 mcg)                          | 1-2            | 30-60 min (prolonged with higher doses) | 0.5-1 mcg/kg IV                      | NA                                  | May repeat every 15-30 minutes (consider using ¼ to ½ of initial dose) | Bradycardia, potentiated with propofol, chest wall rigidity                    | Naloxone | Respiratory depression may last longer than analgesia | Less hypotension compared to morphine  |
| <b>Tier 2<sup>b</sup></b> |   |                |   |                                      |                                     |  |  |          |   |  |
| Hydromorphone             | 1.5 mg                                    | 1-3            | 2-4 hours                               | 0.5-1.5 mg IV                        | NA                                  | May repeat every 15-30 minutes   | Nausea, vomiting, bradycardia, pain at injection site, local tissue irritation | Naloxone | Potential for potency-related dosing errors           | Accumulates with hepatic and renal impairment, which leads to increased duration           |
| Morphine                  | 10 mg                                     | 5-10           | 2-4 hours                               | 0.05-0.1 mg/kg IV<br>or<br>2-4 mg IV | NA                                  | May repeat every 15-30 min (max 15 mg)                                 | Hypotension, bradycardia, bronchospasm, pruritis, vomiting                     | Naloxone | Side effects can be due to histamine release          | Accumulates with hepatic and renal impairment, which leads to increased duration of effect |

Tier 3<sup>b</sup>

|              |        |       |          |     |   |  |   |  |   |   |
|--------------|--------|-------|----------|-----|---|--|---|--|---|---|
| Remifentanyl | 0.1 mg | 1-1.5 | 3-10 min | N/A | <p>Loading dose: 0.5 mcg/kg IV</p> <p>Followed by 0.025 mcg/kg/min continuous-infusion IV</p> | <p>Adjust by 0.025 mcg/kg/min every 5 min (max 0.2 mcg/kg/min)</p> | <p>Apnea, respiratory depression, chest wall rigidity, hypotension, bradycardia, post-procedure nausea and vomiting</p> | <p>Discontinue therapy</p> <p>Naloxone</p> | <p>Risk of apnea and hypoventilation; only practitioners trained in airway management and anesthetic agents should administer.</p> <p>Administer only as infusion bolus dosing for general anesthesia only; not recommended due to risk of respiratory depression and muscle rigidity.</p> <p>All IV lines should be flushed since small doses can cause significant adverse effects.</p> | <p>Potency similar to fentanyl</p> <p>Ultrashort-acting</p> <p>Clearance unchanged with renal/hepatic insufficiency</p> <p>Not suitable as sole agent for induction; should be used in conjunction with other agents</p> <p>In obese patients (&gt; 130% IBW), use IBW for dosing</p> |
|--------------|--------|-------|----------|-----|---|--|---|--|---|---|

|            |              |     |         |              |                   |   |   |   |  |   |
|------------|--------------|-----|---------|--------------|-------------------|---|---|---|--|---|
| Sufentanil | 0.01-0.02 mg | 1-3 | 164 min | 10-50 mcg IV | 0.1-0.5 mcg/kg/hr | Adjust by 0.1 mcg/kg/hr; total dose does not exceed 1 mcg/kg/hr | Bradycardia, hypotension, respiratory depression, Chest wall rigidity | Naloxone; because the duration of respiratory depression produced by sufentanil injection may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. | Risk of apnea and hypoventilation<br><br>Risk of chest wall rigidity<br><br>All IV lines should be flushed since small doses can cause significant adverse effects | More potent than fentanyl<br><br>Accumulates with hepatic and renal impairment, which leads to increased duration of effect |
|------------|--------------|-----|---------|--------------|-------------------|---|---|---|--|---|

IBW, ideal body weight; IV, intravenous; NA, not applicable.

<sup>a</sup> Rapid titration of opiates may lead to hypotension and/or respiratory depression.

<sup>b</sup> Tiers represent the order in which alternative agents should be considered.

**Table 3. Sedative Agents for Minimal to Moderate Sedation<sup>6,9</sup>**

| Medication                | Pharmacologic class | Onset (min) | Duration   | Initial dosing: intermittent                     | Initial dosing: continuous infusion  | Repeat dosing/ titration   | Side effects  | Reversal   | Safety implications   | Special comments   |
|---------------------------|---------------------|-------------|------------|--|--|--|---|------------|---|--|
| <b>Tier 1<sup>a</sup></b> |                     |             |            |  |  |  |   |            |   |  |
| Remimazolam (IV)          | Benzodiazepine      | 1-2         | 45 ± 9 min | ASA: 1-2<br>5 mg IV<br><br>ASA: 3-4<br>2.5 mg IV | Off-label use:<br><br>Induction of general anesthesia 6-12 mg/kg/hour with maintenance | ASA: 1-2 2.5 mg every 2 minutes as needed<br><br>ASA: 3-4 1.25-2.5 mg every 2 minutes as | Hypotension, respiratory depression but less than midazolam | Flumazenil | Extremes of hepatic dysfunction → approximately 30% increase in duration due to hydrolysis from carboxylesterase 1 activity | 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 |

|                |                |     |            |                                    |                |   |  |            |  |   |
|----------------|----------------|-----|------------|------------------------------------|----------------|---|--|------------|--|---|
|                |                |     |            |                                    | 1-3 mg/kg/hour | needed  |  |            | (liver)  | solution such as lactated Ringer. Stable for 8 hours once reconstituted; use of flumazenil in patients on chronic benzodiazepines may lead to withdrawal symptoms |
| 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. | Consider patient-specific variables when determining dosage; use of flumazenil in patients on chronic benzodiazepines may lead to withdrawal symptoms             |

|                      |                          |                                  |          |  |                        |  |  |            | Reduce dose by 25%-50% if combined with opioids.   |  |
|----------------------|--------------------------|----------------------------------|----------|--|------------------------|--|--|------------|--|--|
| Tier 2 <sup>a</sup>  |                          |                                  |          |  |                        |  |  |            |  |  |
| Lorazepam (IV)       | Benzodiazepine           | 15-20                            | 6-8 hour | 0.02-0.05 mg/kg IV<br><b>or</b><br>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% if combined with opioids.  | Consider patient-specific variables when determining dosage; use of flumazenil in patients on chronic benzodiazepines may lead to withdrawal symptoms  |
| Dexmedetomidine (IV) | Alpha-2-receptor agonist | 15 (following start of infusion) | 1-2 hour | N/A (see Safety Implications column)         | 0.6-0.7 mcg/kg/hour IV | Adjust by 0.1-0.2 mcg/kg/hour at least every 30 min ( <i>usual range 0.2-1.5 mcg/kg/hour</i> ) | Bradycardia, hypotension                                   | NA         | Use with caution in patients with history of heart block and those dependent on adrenergic tone to maintain blood pressure.<br><br>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<br><br>Can cause loss of oropharyngeal muscle tone; monitor for hypoxemia and hypoventilation (effects can be |



|                           |                |     |       |    |         |    |  |    |   |   |
|---------------------------|----------------|-----|-------|----|---------|----|--|----|---|---|
|                           |                |     |       |    |         |    |  |    |   | enhanced with concomitant benzodiazepine use).  |
| <b>Tier 3<sup>a</sup></b> |                |     |       |    |         |    |  |    |   |   |
| Nitrous oxide (inhaled)   | Anesthetic gas | 2-5 | 5 min | NA | 25%-50% | NA | Decreased myocardial contractility, worsening pulmonary hypertension, nausea, peripheral neuropathy, headache, CNS excitation, increased intracranial pressure | NA | Requires well-ventilated room and has potential for clinician exposure or abuse; gas scavenging system minimizes clinician exposure.<br><br>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). | Administer with 30% oxygen to avoid diffusion hypoxia; oxygen should be continued after nitrous oxide is discontinued.<br><br>Typically used as adjunct to other sedatives. |

ASA, American Society of Anesthesiology; IV, intravenous; NA, not applicable.

<sup>a</sup> Tiers represent the order in which alternative agents should be considered.

**Table 4. Sedative Agents for Moderate to Deep Sedation**<sup>8,15,16</sup>

| Medication                | Pharmacologic class     | Onset (min) | Duration (min) | Initial dosing: intermittent   | Initial dosing: continuous infusion | Repeat dosing/ titration      | Side effects  | Reversal | Safety implications   | Special comments  |
|---------------------------|-------------------------|-------------|----------------|--|-------------------------------------|-------------------------------|---|----------|---|---|
| <b>Tier 1<sup>a</sup></b> |                         |             |                |  |                                     |                               |   |          |   |   |
| 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 reduced with ketamine in combination with propofol) | NA       | Small or large dose changes may result in unpredictable general anesthetic state.<br><br>Initial hypotension exaggerated when administered via central access.  | Clinicians should be prepared to rescue patients from depth of sedation beyond intended level.<br><br>Institutional procedures or state laws may preclude bolus administration by nurses.         |
| Ketamine                  | Dissociative anesthetic | 0.5         | 5-10           | 1-2 mg/kg IV ( <i>0.5 mg/kg when combined with propofol given in aliquots to effect</i> ); 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   | NA       | Use caution in patients with significant coronary artery disease, increased intracranial/intraocular pressure, and excessive respiratory secretions. Consider pretreatment with antisialogogue to minimize secretions.<br><br>Hemodynamic stability | 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).<br><br>Institutional |

|                           |                   |     |      |                  |     |                            |   |    |  |  |
|---------------------------|-------------------|-----|------|------------------|-----|----------------------------|---|----|--|--|
|                           |                   |     |      |                  |     |                            | combination with ketamine)  |    | maintained due to catecholamine release; use with caution in patients with poor reserve (e.g., elderly, trauma) and in patients with poor cardiac reserve due to direct myocardial depression. | procedures or state laws may preclude bolus administration by nurses.                          |
| <b>Tier 2<sup>a</sup></b> |                   |     |      |                  |     |                            |   |    |  |  |
| Etomidate                 | Sedative/hypnotic | 1   | 5-15 | 0.1-0.3 mg/kg IV | N/A | 1-2 mg IV every 10 min     | Emergence, nausea/vomiting, adrenal suppression, myoclonus/seizure activity | NA | Use caution in patients at risk for adrenal insufficiency.   | Due to short duration of action, role in therapy may be for shorter procedures.                |
| <b>Tier 3<sup>a</sup></b> |                   |     |      |                  |     |                            |   |    |  |  |
| 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. |

IV, intravenous; NA, not applicable.

<sup>a</sup> Tiers represent the order in which alternative agents should be considered.

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