# Drug shortage mitigation pearls

This document provides mitigation strategies for handling ongoing drug shortages to participants in the Vizient® Pharmacy Program. Information is compiled from mitigation strategies of institutions that serve on the Vizient Clinical Council and is reviewed by a panel of pharmacists. **Information provided refers to adult patients unless otherwise specifically noted**.

For more information, contact pharmacyquestions@vizientinc.com.

Drug name or class: Analgesics and Sedatives

| Background |
|---|
| Please refer to ASHP's Drug Shortage website and the weekly Drug Shortages Digest in Pharmacy Hot Info for the most up-to-date information.<br>• There has been an increased demand for analgesics and sedatives during the COVID-19 pandemic.<br>• Sedatives: Multiple manufactures have reported shortages of injectable propofol, dexmedetomidine (Precedex) - both vials and premix, ketamine, midazolam, and lorazepam.<br>• Analgesics: Multiple manufacturers have reported shortages of injectable morphine - both injection and PCA vials, hydromorphone, fentanyl, and sufentanil. |

| Type(s) of mitigation strategies | |
|---|---|
| Check all that apply: | |
| ☒ Therapeutic alternative/interchange | ☒ Restriction criteria |
| ☒ Compounding (insourcing) | ☒ Change in dosage or administration schedule |
| ☒ Compounding (outsourcing) | ☐ Other; specify: _____ |

| Detailed information |
|---|
| **Ordering/procurement - Best Practices**<br>• Shift ordering practices to more frequent orders (Example: daily vs. weekly)<br>• Work with Distributor and Supplier Account Manager to secure needed product from other suppliers if trouble sourcing drug from historical supplier. If unable to secure historical usage despite working with local supplier and Distributor representatives, email DisasterResponse@vizientinc.com.<br>**Operational pearls/ conservation strategies**<br>• Assess alternate supply availability via 503B compounding partner(s).<br>• Return stock from low use areas. If procedure volumes are reduced, reduce OR levels and reallocate to patient care areas of high need and the pharmacy. |

**Detailed information**

- Cease any routine PCA preparation to maintain stock for patients requiring sedation and for emergent procedures.
- In consultation with infection control prevention, consider extending dating on compounded sterile preparations of sedatives/opioids (except propofol) for up to 96 hours.
    - Propofol pearls (Consult Appendix 1 for additional information)
        - Consider extension tubing sets with smaller priming volume; use the 20 mL vial to prime tubing and save the larger vials for infusions.
        - If needed, repackage a larger propofol vial into smaller unit of use doses to avoid waste or repackage (pool) smaller propofol vials into a larger bag or bottle for infusions.[a]
        - Following the current USP Chapter <797> guidelines (2008) and adhering to aseptic technique procedures, repackaged propofol preparations should be assigned a beyond-use date (BUD) of 6 hours due to its high nutrient content and lack of preservatives with extended antimicrobial activity.
        - However, stability, sterility, and sorption data support the extension of the BUD to 12 hours. The increased dating also corresponds with the paradigm shift for the BUD of single-dose vials that appeared in the 2019 draft version of USP Chapter <797>, which revised dating from 6 hours to 12 hours.
- In patients with lighter sedation goals, consider intermittent bolus dosing (may add scheduled enteral if unable to achieve pain or sedation goals) rather than continuous. If on a continuous infusion, consider a PRN dose or scheduling enteral doses prior to increasing the infusion rate.
    - Sedation example: Start with boluses (eg, midazolam, fentanyl). If sedation goal not achieved, add a scheduled enteral benzodiazepine (eg, diazepam 10-20 mg every 6 or 8 hours or lorazepam 2 mg every 4 to 6 hours).
- As above, use enteral and non-injectable formulations where appropriate, based on clinical picture (Appendix 2).
    - Enteral opioids (oxycodone, hydromorphone, morphine) and sedatives (lorazepam, diazepam)[2] may be used if enteral route accessible.
    - Although not ideal, sites are considering transdermal fentanyl in mechanically ventilated patients during COVID-19. Transdermal fentanyl should be used in combination with PRN or scheduled IV opioid boluses or enteral opioid doses (Appendix 2, table 2).
- Consider multimodal analgesia (eg, acetaminophen, gabapentin, ketamine, etc) to minimize opioid use.[1]
    - The Society of Critical Care Medicine (SCCM) recommends use of low-dose ketamine if used as an adjunct to reduce opioid use (0.5 mg/kg IV push x 1 dose, followed by 1-2 mcg/kg/min infusion).[1]

**Restrictions**

- Consider reserving opioid/sedative drips to areas of greatest patient need (eg, critically ill, mechanically ventilated patients that require deep sedation (RASS -4 or -5), paralyzed patients, or patients that are being weaned off mechanical ventilation and require a titratable infusion).

## Detailed information

**Therapeutic alternatives**

**ICU, mechanically ventilated**

*Please follow SCCM's guidance on pain, sedation, and delirium in ICU patients. Treat to pain and sedation goals.*[1]

- Consider alternative treatment agents for pain and sedation in ICU patients based on availability, patient clinical status, and ability to tolerate alternative agent (Appendix 3, Appendix 4, Appendix 5).
- COVID-19 specific:
    - Per WHO guidance on management of COVID-19: Weaning protocols should include daily assessment for readiness to breathe. Minimize continuous or intermittent sedation, utilizing light sedation with daily interruption of continuous sedative infusions.[3]

**Rapid sequence intubation**

- Consider switching to other sedative-hypnotic agents for rapid sequence intubation (Appendix 6).

Footnotes: [a] Comment from Vizient Clinical Council Shortage members: Propofol repackaging, defined as transferring volume from manufacturers bottles to another container, is not recommended by these clinicians. A common example would be to transfer five 20-mL vials into one sterile container of 100 mL. The reasons for this recommendation include: 1. incompatibilities between manufacturer products when combined; 2. short BUD; 3. ease of connecting an infusion set to a 20 mL or 50 mL vial.

## References


1. Devlin, John W, et al. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility and Sleep disruption in Adult Patients in the ICU. Society of Critical Care Medicine website. www.SCCM.org. Accessed March 27, 2020.
2. Cigada M, Pezzi A, Di Mauro P, et al. Sedation in the critically ill ventilated patient: possible role of enteral drugs. *Intensive Care Med*. 2005;31(3):482-486.
3. Clinical management of severe acute respiratory infection (SARI) when COVID-19 is suspected. Interim Guidance World Health Organization. World Health Organization website. https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected. Published March 13, 2020. Accessed March 27, 2020.


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## Appendix 1: Compounding pearls for propofol

**Stability**:
The propofol products from the current suppliers are therapeutically equivalent (AB rated), however their formulations vary due to differing antimicrobial agents and pH levels. The stability of each formation is affected by the antimicrobial agent used and its pH level. Fresenius Kabi's products contain disodium edetate 0.05 mg/mL as its antimicrobial agent. The antimicrobial agent used by Dr. Reddy's Laboratories in its formulation is benzyl alcohol 1.5 mg/mL. Pfizer's propofol products also contain benzyl alcohol 1.5 mg/mL as well as sodium benzoate 0.7 mg/mL. Sodium benzoate is also the antimicrobial agent in Teva's products but at a concentration of 1 mg/mL. Sagent's formulations contain the antimicrobial agent sodium metabisulfite 0.25 mg/mL.

The pH of the metabisulfite-containing formulation of propofol ranges from 4.5 to 6.6. The benzyl alcohol-containing formulation has a pH ranging from 5.5 to 7.4. The pH of the benzyl alcohol- and sodium benzoate-containing products and the sodium benzoate-containing products both range from 6 to 8.5.[1] Per the USP monograph, propofol should be packaged in tight containers under an atmosphere of inert gas. Propofol undergoes oxidative degradation when exposed to oxygen, therefore it is packaged under nitrogen to avoid oxygen exposure.[2] Due to the instability of propofol once the product is exposed to oxygen (after puncturing or spiking of the vial or being drawn into another container), administration should be completed within 12 hours and the dedicated tubing and unused drug discarded. Propofol formulations that contain sodium metabisulfite undergo a faster rate of oxidation. The stability data from the branded generic propofol product cannot be extrapolated to other products.

**Sterility**:
Propofol products are single-dose vials intended for single-use administration to one patient. Even though the formulations contain antimicrobial agents, propofol is not a multi-dose vial or a preserved product under USP standards because the lipid emulsion supports the growth of microorganisms (*Escherichia coli* and *Candida albicans*). There have been reports in which accidental extrinsic contamination when handling propofol was associated with fever, infection/sepsis, other life-threatening illness, and death.[3] The antimicrobial agents in the propofol products inhibit the rate of growth of microorganisms for up to 12 hours. The package insert recommends assigning a 6 hour beyond-use date accounting for drug adsorption in the transferred container if it is not glass or polyolefin-based and if the propofol formulation contains sodium metabisulfite. A small observational study found that propofol drawn aseptically into uncapped syringes and stored at room temperature remained sterile for at least one day.[4]

**Compatibility**:
Propofol is a lipophilic, un-ionized drug. Propofol's properties create the potential for it to be absorbed into some medical plastics. Significant drug loss has been demonstrated when propofol products are stored in plastic or polypropylene syringes for at least 5 days. Propofol products have been shown to be more stable in glass containers than in plastic ones. Polyvinyl chloride (PVC) tubing has been demonstrated to have up to a 30% loss of diluted propofol when held statically for 120 minutes and an 8% loss when flowing. Therefore, the use of non-PVC administration sets has been traditionally recommended. However, undiluted propofol was subject to minimal sorption in the same PVC delivery system in another study. A slower rate of infusion was associated with a greater rate of sorption.[5]

**Processes**:
Strict aseptic technique must always be maintained during handling of propofol. Propofol should be repackaged within an ISO 5 or better primary engineering control by properly garbed, competent compounding personnel. A technique that has been used is drawing propofol from the original vial via a sterile syringe and injecting through a port into a sterile bag. The repackaging of propofol via a repeater pump is a technique that has been utilized to provide a more "closed system" throughout the process.

Prior to administration, propofol should be inspected for particulate matter, discoloration, or evidence of separation of the emulsion. When performing an intermittent propofol bolus technique, the ideal setup is to have a needleless port that is backflow protected to which the syringe can be continuously attached to protect from dilution of the drug with IV fluid. The port is kept as sterile as possible because the syringe is not removed and replaced for every dose administration. After syringe removal, the port is decontaminated with 70% alcohol or another acceptable disinfectant. Stopcocks can also be used but are harder to disinfect.

The IV line should be flushed every 12 hours and at completion of therapy to remove residual propofol from the tubing. If extension tubing is used for COVID-19 patients, a flush bag should be run at the same rate as the previous propofol infusion so the line is not cleared too quickly.

## Compounding Guidance During The COVID-19 Pandemic

Due to the increased demand for propofol injectable emulsion products to support COVID-19 patients who have been sedated and intubated or for other procedures involved in the care of these patients, the FDA extended enforcement discretion on the compounding of FDA-approved 10 mg/mL propofol products as outlined in the guidance, Temporary Policy on Repackaging or Combining Propofol Drug Products During the COVID-19 Public Health Emergency. The guidance for industry, Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities, mandates that propofol be repackaged according to its approved labeling. Propofol's approved labeling requires packaging under nitrogen to eliminate oxidative degradation. The Temporary Policy allows the repackaging of propofol in the presence of oxygen on an emergency basis.

Based on product availability, many pharmacies are removing the contents of different manufacturers' propofol products and placing them in the same container. The FDA does not consider the combining or pooling of different propofol formulations as repackaging. However, the Temporary Policy addresses the conditions in which the process can be performed. Propofol products with the same preservatives and antioxidants may be assigned a beyond-use date (BUD) of not more than 12 hours. The tubing and any unused portions of the pooled propofol should be discarded after 12 hours. If there is a difference in the preservative or antioxidant components listed in the propofol products, the combined products should be used as close to preparation time as possible, and the shorter BUD of not more than 4 hours should be assigned mitigating the risk of microbial growth in the presence of reduced preservative content. The tubing and any unused portions of the pooled propofol should also be discarded after 4 hours.

Propofol products manufactured by Fresenius Kabi or Sagent Pharmaceuticals should not be combined with any other propofol product containing a different formulation because these two products have more significant differences in formulation, which may result in unknown physicochemical compatibility and reduced preservative effectiveness if combined with any other product. Please refer to the Propofol Injectable Emulsion Side-By-Side Comparison for additional information about each of the available propofol formulations.

Table 1: Information on combining propofol products

| Propofol product | Propofol formulations the product may be combined | BUD of combined products during pandemic |
|---|---|---|
| Dr. Reddy's Laboratories | May be combined with propofol 10 mg/mL formulations from Hikma, Pfizer, and Teva | 12 hours if only Dr. Reddy's formulations combined<br><br>4 hours if combined products from multiple suppliers |
| Fresenius Kabi USA (Diprivan®/ NOVAPLUS Diprivan®) | May only be combined with other Fresenius Kabi USA (Diprivan®/ | 12 hours |

| | | |
|---|---|---|
| | NOVAPLUS Diprivan®) 10 mg/mL formulations | |
| Fresenius Kabi AG (Fresenius Propoven) | May only be combined with other Fresenius Kabi USA (Fresenius Propoven) 20 mg/mL formulations | 12 hours |
| Hikma | May be combined with propofol 10 mg/mL formulations from Dr. Reddy's, Pfizer, and Teva | 12 hours if only Hikma formulations combined<br>4 hours if combined products from multiple suppliers |
| Pfizer | May be combined with propofol 10 mg/mL formulations from Dr. Reddy's, Hikma, and Teva | 12 hours if only Pfizer formulations combined<br>4 hours if combined products from multiple suppliers |
| Sagent | May only be combined with other Sagent 10 mg/mL propofol formulations | 12 hours |
| Teva/Watson | May be combined with propofol 10 mg/mL formulations from Dr. Reddy's, Hikma, and Pfizer | 12 hours if only Teva formulations combined<br>4 hours if combined products from multiple suppliers |

**Safety Considerations**:
Anesthetic agents (general, inhaled and IV), including propofol, are classified as high-alert medications that require special safeguards to reduce the risk of errors, which can cause significant patient harm. When handling propofol, risk mitigation strategies should be implemented to avoid drug diversion.

References


1. Trissel LA. Drug compatibility differences with propofol injectable emulsion products. *Crit Care Med.* 2001; 29:466–468.
2. Food and Drug Administration. Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities: Guidance for Industry. FDA website. https://www.fda.gov/media/90978/download.
3. Zorrilla-Vaca A, Arevalo JJ, Escandón-Vargas K, Soltanifar D, Mirski MA. Infectious disease risk associated with contaminated propofol anesthesia, 1989–2014. *Emerg Infect Dis*. 2016;22(6):981-992.
4. Smith I. Total intravenous anesthesia: Is it worth the cost? *CNS Drugs*. 2003;17(19):609-619.
5. Parsons. No loss of undiluted propofol by sorption into administration systems. *Pharmacol Commun*. 1999;5:377-381.

## Appendix 2

Table 1: Equi-analgesic Opioid Doses [a,b]

| Opioid Agonist | Oral Dose | Parenteral Dose |
|---|---|---|
| Morphine | 30 mg | 10 mg |
| Hydrocodone | 30 mg | NA |
| Hydromorphone | 7.5 mg | 1.5 mg |
| Oxycodone | 20-30 mg | NA |
| Fentanyl | NA | 0.1 mg (100 mcg) |

Note there are no universally accepted opioid dose conversion tables. The above is extrapolated from multiple references.

**References**: [a] Baumann TJ, Herndon CM, Strickland JM. Chapter 44: Pain Management. DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. *Pharmacotherapy: A Pathophysiologic Approach*. 9th ed. New York, NY: McGraw Hill; 2015:557-577. [b] Mariano ER. Management of acute perioperative pain. In: Post T, ed. UpToDate. Waltham, MA: UpToDate; 2020. www.uptodate.com. Accessed March 30, 2020.

Table 2: Published methods for converting from IV fentanyl infusion (IVF) to transdermal fentanyl - Ventilated patients only

| Kornick et al[a] | Nomura et al[b] | Samala et al[c] |
|---|---|---|
| **Step 1**: 1:1 conversion ratio (infusion to transdermal; eg, If IVF 50 mcg/h started, apply 50 mcg/h transdermal patch). Apply patch(es) at the start of the infusion (immediately after intubation). Give bolus and start IVF at the same time patch is applied. **Subsequent steps**: After patch is applied and IVF initiated, refer to individual strategies below for titrating IVF down and transitioning fully to transdermal patch.[d] | | |
| **12 h strategy**<br>• Overlap IVF for 6 h<br>• Reduce IVF dose by 50%<br>• Continue IVF for another 6 h<br>• Stop IVF<br>Pain intensity was well controlled; however, significant decrease in pain intensity noted at 12 h. Three of 15 patients (25%) experienced mild adverse events. | Compared 12 h vs. **6 h strategy outlined below**<br>• Overlap IVF for 3 h<br>• Reduce IVF dose by 50%<br>• Continue IVF for another 3 h<br>• Stop IVF<br>6 h strategy associated with fewer opioid-related adverse events (25.6% vs. 2.3%). Pain intensity well controlled in both groups (although significant decreases in pain intensity noted in 12 h group at 6 and 12 h after patch application). | **6 h strategy**<br>• Overlap continuous dose of IVF for 6 h<br>• Stop IVF after 6 h<br>Pain intensity significantly increased at 12 h and 18 h after patch placement. There was no significant difference in the number of rescue doses. One patient (n = 17) experienced a significant adverse event. |

**References:** [a] Kornick CA, Santiago-Palma J, Khojainova N, Primavera LH, Payne R, Manfredi PL. A safe and effective method for converting cancer patients from intravenous to transdermal fentanyl. *Cancer.* 2001;92(12):3056-3061. [b] Nomura M, Kamata M, Kojima H, Hayashi K, Kozai M, Sawada A. Six-versus 12-h conversion method from intravenous to transdermal fentanyl in chronic cancer pain: a randomized study. *Support Care Cancer*. 2011;19(5):691-695. [c] Samala RV, Bloise R, Davis MP. Efficacy and safety of a six-hour continuous overlap method for converting intravenous to transdermal fentanyl in cancer pain. *J Pain Symptom Manage*. 2014;48(1):132-136. [d]After patch is removed, some effects may last 72 to 96 hours due to extended half-life and absorption from the skin; fentanyl concentrations decrease by roughly 50% in 20-27 h.

**Appendix 3**: Alternative intravenous analgesics for use in adult, mechanically ventilated ICU patients[a]

| Drug | Onset and Duration | Initial Dosing Intermittent | Initial Dosing Continuous | Titration | Considerations |
|---|---|---|---|---|---|
| Fentanyl[c,d] | Onset<br>2-5 min<br>Duration<br>30-60 min | 25-50 mcg IV every 0.5-1 h | 25-50 mcg/h[b] | Adjust by 25 mcg/h every 30 min; give bolus dose with each rate increase | Highly fat soluble, accumulates with prolonged infusion; Hepatic metabolism - accumulation with hepatic impairment. No active metabolites. Ideal for patients with AKI or CKD; Less hypotension than with morphine (due to relative lack of histamine release). |
| Hydromorphone[c,d] | Onset<br>5-10 mins<br>Duration<br>240 to 300 min | 0.2-0.6 mg IV every 1-2 h | 0.4-0.8 mg/h[b] | Adjust by 0.2 mg/h every h; give bolus dose with each rate increase | Non-CYP (glucuronidation) metabolism – may be useful for patients with potential for drug interactions; Potentially neurotoxic (excitatory) metabolites in renal or hepatic failure- requires dose adjustment. |
| Morphine[c,d] | Onset<br>5-10 mins<br>Duration<br>240- 300 min | 2-4 mg IV every 1-2 h | 2-4 mg/h[b] | Adjust by 1 mg/h every h, give bolus dose with each rate increase | Renal metabolism with active metabolites-reduce dose in renal impairment; May accumulate in hepatic and renal dysfunction prolonging effects; Histamine release with vagally mediated venodilation, hypotension and bradycardia may be significant. |
| Remifentanil[c,d] | Onset<br>1-3 min<br>Duration<br>5-10 min | N/A | 0.5 mcg/kg loading dose, then 0.5-1 mcg/kg/h | Adjust by 0.5 mcg/kg/h every 5 min | Ultra short acting. Anticipate pain upon abrupt cessation. (May be considered as an alternative to patients that require frequent neurologic assessments); Does not accumulate; Use IBW if weight > 130% IBW |
| Sufentanil[e] | Onset<br>1 to 3 min<br>Duration<br>60 to 90 min | 0.05 mcg/kg IV; may repeat every hour as needed | 0.05 mcg/kg/h[b] | Adjust by 0.03 mg/kg/h every h | Risk of hypotension; Metabolized-CYP 3A4 risk of drug interactions |
| Ketamine[f]<br>Note: Sub anesthetic dose for pain is not well defined in literature | Onset<br>< 1 min<br>Duration<br>10-15 min | Bolus up to a max of 0.3 mg/kg | 0.1-1 mg/kg/h<br>Majority of acute pain studies dose at < 0.5 mg/kg/h[f] | | Causes sympathetic stimulation, leading to increased heart rate and myocardial oxygen demand; caution in hepatic dysfunction; relative contraindication in pulmonary infection or disease - may increase secretions |

Abbreviations: AKI = acute kidney injury; CKD = chronic kidney disease; CYP = cytochrome; IBW = ideal body weight

[a] Options not listed on table - Alfentanil, oxymorphone, transdermal fentanyl, enteral formulations; [b] May administer bolus prior to start of continuous infusion for more rapid analgesic effect.

**References**: [c]Tietze KJ, Fuchs B. Sedative-analgesic medications in critically ill adults: Properties, dosage regimens, and adverse effects. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. www.uptodate.com. Accessed March 30, 2020. [d] Gesin G, Barletta J, Brown D, Shander A. Recommendations for alternative analgesic and sedation agents in the setting of drug shortages. https://pdfs.semanticscholar.org/ef0e/1a09c9e18b5f1d7e7caecf3a00ef8157cb16.pdf. Accessed April 2, 2020. e Ethuin F, Boudaoud S, Leblanc I, et al. Pharmacokinetics of long-term sufentanil infusion for sedation in ICU patients. *Intensive Care Med*. 2003;29(11):1916-1920.[f]Schwenk ES, Viscusi ER, Buvanendran A, et al. Consensus guidelines on the use of intravenous ketamine infusions for acute pain management from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. *Reg Anesth Pain Med*. 2018;43(5):456-466.

**Appendix 4**: Alternative intravenous sedatives for use in adult, mechanically ventilated ICU patients[a]

| Drug | Onset after IV LD and Duration | Initial Dosing (IV) Intermittent | Initial Dosing (IV) [LD and/or CI] | Titration | Considerations |
|---|---|---|---|---|---|
| Dexmedetomidine | Onset<br>5-10 mins<br><br>Duration<br>60-120 mins | N/A | LD: 1 mcg/kg over 10 min (optional)<br><br>CI: 0.2-0.8 mcg/kg/h[a] | Adjust by 0.1 mcg/kg/h at least every 30 min | Potential for significant hypotension and bradycardia; hepatic impairment - reduce dose for hepatic impairment |
| Propofol | Onset<br><1-2 min<br><br>Duration<br>3-10 min | N/A | 5-50 mcg/kg/min | Adjust by 10 mcg/kg/min every 5 min | Adverse effects include hypotension, bradycardia, respiratory depression, decreased myocardial contractility; rates exceeding 70 mcg/kg/min may increase risk of propofol infusion syndrome. |
| Lorazepam | Onset<br>15-20 min<br><br>Duration<br>360-480 min | 1-2 mg every 2-6 h | CI: 1-2 mg/h[b] | Adjust by 1 mg/h every 30 min; give bolus dose with each rate increase | Hepatically metabolized; Slow onset with risk of accumulation; IV incompatibilities and risk of precipitate; risk of polyethylene glycol toxicity. |
| Midazolam | Onset<br>2-5 min<br><br>Duration<br>60 min | 2-4 mg every 0.5-2 h | CI: 2-4 mg/h[b] | Adjust by 1-2 mg/h every 30 min; give bolus with each rate increase | Amnestic and anxiolytic; hepatic metabolism by CYP3A4; Potential for prolonged duration due to drug interactions, as well as in hepatic and renal impairment; dose adjust and reduce titration for renal or hepatic impairment |
| Diazepam | Onset<br>2-5 min<br><br>Duration<br>20-60 min | 2.5-10 mg every 4-6 h | N/A | N/A | Hepatic metabolism to active metabolites can prolong sedation; risk of delirium<br><br>Intermittent dosing preferred; consider enteral administration |
| Ketamine | Onset<br>< 1 min<br><br>Duration<br>10-15 min | 0.1-0.5 mg/kg; may repeat as needed | LD: 0.1-0.5 mg/kg then CI: 0.05-0.4 mg/kg/h | Adjust every 5-20 min | Causes sympathetic stimulation, leading to increased heart rate and myocardial oxygen demand; caution in hepatic dysfunction; relative contraindication in pulmonary infection or disease - may increase secretions |

[a] Dose range listed in product information differs from that in literature specific to the ICU setting; [b] May administer bolus prior to start of continuous infusion for more rapid achievement of sedative effect  Abbreviations: CI = continuous infusion; LD = loading dose; IV = intravenous

**References**: [a]Gesin G, Barletta J, Brown D, Shander A.  Recommendations for alternative analgesic and sedation agents in the setting of drug shortages. https://pdfs.semanticscholar.org/ef0e/1a09c9e18b5f1d7e7caecf3a00ef8157cb16.pdf. Accessed April 2, 2020.

**Appendix 5**: Alternative intravenous analgesics/sedatives for use in pediatrics, mechanically ventilated ICU patients [a,b]

| Drug and dose | Onset and duration | Considerations |
|---|---|---|
| **Opioids** | | |
| Fentanyl 0.5-2 mcg/kg/hr | Onset: 2-5 min<br>Duration: 30-60 min | Highly fat soluble, accumulates with prolonged infusion<br>Hepatic metabolism; accumulation with hepatic impairment. No active metabolites. Ideal for patients with AKI or CKD.<br>Risk of chest wall rigidity in higher doses. |
| Hydromorphone 0.018 mg/kg/h titrate carefully to a maximum of 0.043 mg/kg/h | Onset: 5-10 min<br>Duration: 240-300 mins | Metabolism is not dependent on CYP (glucuronidation) - may be useful for patients with potential for drug interaction.s<br>Potentially neurotoxic (excitatory). |
| Morphine 0.01-0.04 mg/kg/h | Onset: 5-10 min<br>Duration: 240-300 min | Renal metabolism with active metabolites - reduce doses in renal impairment.<br>May accumulate in hepatic and renal dysfunction, prolonging effects.<br>Histamine release with vagally mediated venodilation, hypotension, and bradycardia may be significant. |
| Remifentanil: Dosing is age, weight and clinical scenario dependent; refer to tertiary reference for guidance | Onset: 1-3 min<br>Duration: 5-10 min | Ultra short acting. Anticipate pain upon abrupt cessation (May be considered as an alternative to patients that require frequent neurologic assessments)<br>Does not accumulate. |
| Sedatives | | |
| Propofol - Not recommended in pediatric patients for ICU sedation[b] | N/A | N/A |
| Ketamine 0.3-0.6 mg/kg/h | Onset: <1 min<br>Duration: 10-15 min | Causes sympathetic stimulation leading to increased heart rate and myocardial oxygen demand.<br>Caution in hepatic dysfunction.<br>Relative contraindication in pulmonary infection or disease. May increase sections. |
| Midazolam 0.03-0.12 mg/kg/h | Onset: 2-5 min | Amnestic and anxiolytic. |

| Drug and dose | Onset and duration | Considerations |
|---|---|---|
| | Duration: 60 min | Prolonged duration potential due to drug interactions, as well as in hepatic and renal impairment.<br><br>Dose adjust and reduce titration for renal or hepatic impairment. |
| Lorazepam 0.05 mg/kg/h | Onset: 15-20 min<br><br>Duration: 360-480 min | Hepatically metabolized. Slow onset with risk of accumulation.<br><br>IV incompatibilities and risk of precipitate. Risk of polyethylene glycol toxicity. |
| Dexmedetomidine 0.2-0.7 mcg/kg/h | Onset: 15 min<br><br>Duration: 60-20 min | Potential for significant hypotension and bradycardia.<br><br>Hepatic metabolism: Reduce dose for renal and hepatic impairment.<br><br>Note: Does NOT induce deep sedation as required for neuromuscular blockade.<br><br>Does NOT have analgesic properties |

Abbreviations: AKI = acute kidney injury; CKD = chronic kidney disease

**References**: [a]Beckman EJ. Analgesia and sedation in hospitalized children. American College of Clinical Pharmacy. *PSAP Pharmacotherapy Self-Assessment Program*. Kansas City, MO: ACCP, 2017. [b]Propofol. In: Lexi-Drugs. Hudson, OH: Lexi-Comp, Inc. [Last updated April 3 2020; Accessed April 8, 2020]

**Appendix 6**: Alternative sedative-hypnotic agents for rapid sequence intubation in adults

| Drug | Mechanism of action | Dose | Onset/duration of action |
|---|---|---|---|
| Etomidate | Acts directly on the gamma amino butyric acid (GABA) receptor complex, blocking neuroexcitation and producing anesthesia | 0.2 to 0.3 mg/kg intravenous push (IVP) | Onset: 5 to 45 secs<br>Duration: 3 to 12 mins |
| Ketamine | Stimulates the N-methyl-D-aspartate receptor at the GABA receptor complex, causing neuroinhibition and anesthesia; Excites opioid receptors within the insular cortex, putamen, and thalamus, producing analgesia | 1 to 2 mg/kg intravenously (IV) | Onset: 45 to 60 secs<br>Duration: 10 to 20 mins |
| Methohexital | Interacts with the barbiturate component of the GABA receptor complex, causing profound amnesia and sedation | 1 to 3 mg/kg IV | Onset: Less than 30 secs<br>Duration: 5 to 10 mins |
| Midazolam | Acts on the GABA receptor complex causing sedation and amnesia | 0.1 to 0.3 mg/kg IVP | Onset: 30 to 60 secs<br>Duration: 15 to 30 mins |

Reference: Fuchs B, Bellamy C. Sedative-analgesic medications in critically ill adults: Selection, initiation, maintenance, and withdrawal. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. www.uptodate.com. Accessed March 30, 2020