Community Developed Resource

Alternative Analgesic and Sedative Agents in the Setting of Drug Shortages during the COVID-19 Pandemic

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The COVID-19 pandemic has triggered a number of medication shortages, including analgesic and sedative agents used in patients who require mechanical ventilation. Given the importance of sedation and prolonged duration of mechanical ventilation experienced by some of these patients, when shortages exist, clinicians must develop alternative strategies to achieve the therapeutic goals while minimizing adverse effects. The purpose of this document is to provide a resource for clinicians who are developing alternative analgesic and sedation strategies in the setting of drug shortages. This document is not intended to be a stand-alone reference. It should be used in concert with other resources. Clinicians should evaluate each alternative in the context of individual patient care needs, the institutional resources available and the team's overall comfort with the alternative agents. Suggestions are not meant to be prescriptive or applied in absolute terms.

The tables below outline suggestions for alternative analgesic and sedative agents for use in adult, mechanically ventilated intensive care unit (ICU) patients with an emphasis on COVID-19 infection. While these medications are often used in other settings (e.g., procedural sedation, surgery), these recommendations are not intended for those scenarios. Clinicians must be cautioned that high-level evidence for these alternative agents in the ICU setting is sparse and, in many cases, drug doses and titration recommendations are derived from a combination of limited published data, tertiary drug information resources, alternative indications, pharmacokinetic properties and expert opinion.

A determination of well-established dosing recommendations for alternative agents is limited by a relative lack of information regarding the impact of critical illness (e.g., changes in volume of distribution, metabolism and elimination) on drug disposition. As such, the recommendations provided represent conservative, initial starting doses that can be adjusted as clinically indicated. Several other overarching themes exist. First, as recommended in the Society of Critical Care Medicine's pain, agitation, and delirium guidelines, is an "analgesia first" strategy whereby pain medications are optimized before sedatives are increased. There is no maximum dose of an opioid but rather the dosing regimen should be designed to balance the benefits and potential adverse drug effects (e.g., respiratory depression, central nervous system alteration, gastrointestinal-related). When developing sedation strategies, non-benzodiazepine medications are preferred over benzodiazepines. If benzodiazepines are necessary and continuous infusions are utilized, bolus doses should be administered with each upward titration. Concomitant enteral therapy may be useful to minimize intravenous requirements. Validated analgesic and sedation scales should be used to guide therapy. Finally, as many institutions are using extension tubing so pumps can be placed outside the room, a shortage of these supplies may influence the alternative strategy chosen by dictating the use of drugs that can be given via intravenous (IV) push.

When a shortage arises with a preferred analgesic or sedative, clinicians should consider an alternative from the same tier listed in the appropriate table. If this is not feasible, then an agent from the next tier should be selected. When switching medications, the preferred method would be to begin the transition before the "last bag" runs out. This will allow for a smoother transition between therapies. In settings where this is not possible and equipotent doses must be calculated, clinicians are advised these are typically derived from single dose pharmacokinetic studies and do not account for factors such as end-organ dysfunction, variability in pharmacokinetics, and presence of active metabolites. Lower doses (i.e., 50 – 75% of the calculated dose) are therefore recommended.

Analgesics									
Drug	**Approximate parenteral equianalgesic dose (mg)**	**Onset (IV)**	**Elimination half-life**	**Initial Dosing Intermittent**	**Initial Dosing (IV) (Loading Dose/Bolus and/or Continuous Infusion)**	**Titration**	**Stability**	**Side Effects and Considerations**	**Special Comments**
Tier 1									
Fentanyl	0.1	1-2 min	2-4 h	25-50 mcg IV every 0.5-1 h	25-100 mcg bolus, then 25-50 mcg/h	Adjust by 25 mcg/h every 30 min; give bolus dose with each rate increase	NS/D5W	Muscle rigidity when administered in high doses	Less hypotension than with morphine; accumulation with hepatic impairment
Hydromorphone	1.5	5-10 min	2-3 h	0.2-0.6 mg IV every 1-2 h	0.2-2 mg bolus, then 0.4-0.8 mg/h	Adjust by 0.2 mg/h every hour; give bolus dose with each rate increase	NS/D5W	Potential for potency-related dosing errors	May work in patients tolerant to morphine/fentanyl; accumulation with hepatic/renal impairment
Tier 2									
Morphine	10	5-10 min	3-4 h	2-4 mg IV every 1-2 h	2-10 mg bolus, then 2-4 mg/h	Adjust by 1 mg/h every hour; give bolus dose with each rate increase	NS/D5W	Hypotension, bronchospasm	Accumulation with hepatic/renal impairment; active metabolite may accumulate in renal failure and contribute to pharmacologic effects including respiratory depression
Ketamine	N/A	30-40 sec	2-3 h	0.1-0.5 mg/kg IV; may repeat as needed	0.1-0.5 mg/kg loading dose, then 0.05-0.4 mg/kg/h	Adjust rate every 30 min	NS/D5W For infusion, dilute to 1-2 mg/mL (may be prepared by adding 500mg to 500mL or 250 mL)	Use caution in presence of poorly controlled hypertension, heart failure, or myocardial ischemia; may cause hallucinations and other psychological disturbances; strongly consider administration of benzodiazepines to attenuate psychological disturbances	COVID-19 may be associated with acute cardiac injury, cardiomyopathy, and renin-angiotensin-aldosterone system (RAAS) activation; ketamine attenuates the development of acute tolerance to opioids; potential for neurotoxicity with prolonged use

Tier 3									
Remifentanil	0.1	1-3 min	3-10 min	N/A	0.5-1.5 mcg/kg loading dose, then 0.5-1 mcg/kg/h	Adjust by 0.5 mcg/kg/h every 5 min	NS/D5W Stable for 24 h at a concentration of 20-250 mcg/mL	Hypotension, muscle rigidity, bradycardia	No accumulation in hepatic/renal failure; short half-life; use ideal body weight (IBW) if weight >130% IBW
Tier 4									
Sufentanil	0.01	1-3 min	2-3 h; dose dependent	0.05 mcg/kg IV over at least 2 minutes; may repeat every hour as needed	0.05 mcg/kg loading dose, then 0.05 mcg/kg/h (see special comments)	Adjust by 0.03 mcg/kg/h every hour	Stable in D5W at 5 mcg/mL (polyolefin plastic infusion bags); stable in NS at 2 mcg/mL (polypropylene syringes)	Elevation of intracranial pressure, bradycardia; serotonin syndrome with concomitant use of serotonergic agents	Drug interactions related to cytochrome P450 (CYP) 3A4 (several medications described for use in COVID-19 are associated with CYP3A4 interactions); dosing is primarily based on potency relative to other opioids; limited data in ICU setting suggests higher doses (see references); available as a 50 mcg/mL solution; use IBW if weight >120% IBW

Sedatives								
Drug	**Onset (IV)**	**Half-life**	**Initial Dosing (IV) Intermittent**	**Initial Dosing (IV) (Loading Dose/Bolus and/or Continuous Infusion)**	**Titration**	**Stability**	**Side Effects and Considerations**	**Special Comments**
Tier 1								
Dexmedetomidine	5-10 min	1.8-3.1 h	N/A	0.2-0.4 mcg/kg/h (see special comments)	Adjust by 0.1 mcg/kg/h at least every 30 min	Dilute in NS/D5W to 4 mcg/mL	Bradycardia, hypotension Hypertension or hypotension with loading dose	Note that dose range listed in product information differs from that in literature specific to the ICU setting; no active metabolites; loading dose of 1 mcg/kg can be considered but may lead to adverse hemodynamic effects; does not provide amnesia or deep sedation and should not be used during neuromuscular blockade
Propofol	1-2 min	1.5-12.4 h	N/A	5-10 mcg/kg/min	Adjust by 10 mcg/kg/min every 5 min	1000mg/100mL lipid emulsion	Hypotension, respiratory depression, hypertriglyceridemia, pain on injection when administered through peripheral veins, pancreatitis, propofol related infusion syndrome (PRIS); risk for PRIS may increase with prolonged durations or higher doses	Acute hypertriglyceridemia reported in patients with COVID-19; use caution when hypotension is likely to occur [e.g., patients with compromised myocardial function, intravascular volume depletion, or abnormally low vascular tone (e.g., sepsis)]
Tier 2								
Midazolam	2-5 min	3-11 h	2-4 mg every 0.5-2 h	2-4 mg bolus, then 2-4 mg/h	Adjust by 1-2 mg/h every 30 min; give bolus with each rate increase	For infusion, dilute in NS or D5W to 1 mg/mL	Respiratory depression	Intermittent dosing preferred; active metabolite prolongs sedation, especially in patients with renal failure

Tier 3								
Lorazepam	15-20 min	8-15 h	1-2 mg every 2-6 h	1-2 mg bolus, then 1-2 mg/h	Adjust by 1 mg/h every 30 min; give bolus dose with each rate increase	For infusion, dilute in NS or D5W to 1mg/mL	Respiratory depression, propylene glycol-related acidosis, renal failure	Intermittent dosing preferred; no active metabolites
Diazepam	2-5 min	20-120 h	2.5-10 mg every 4-6 h	N/A	N/A	N/A	Active metabolite prolongs sedation	Intermittent dosing preferred; consider enteral administration
Ketamine	30-40 sec	2-3 h	0.1-0.5 mg/kg IV; may repeat as needed	0.1-0.5 mg/kg loading dose, then 0.2-0.5 mg/kg/h	Adjust every 30 min	NS or D5W For infusion, dilute to 1-2 mg/mL (may be prepared by adding 500mg to 500mL or 250 mL)	Use caution in presence of poorly controlled hypertension, heart failure, or myocardial ischemia; may cause hallucinations and other psychological disturbances; strongly consider administration of benzodiazepines to attenuate psychological disturbances	COVID-19 may be associated with acute cardiac injury, cardiomyopathy, and RAAS activation; ketamine attenuates the development of acute tolerance to opioids; potential for neurotoxicity with prolonged use
Tier 4								
Phenobarbital	5 min	53-140 h	Bolus with 7.5 mg/kg IV over 1-2 h, then 1-2 mg/kg/day divided every 12 h; for adults <90kg, initiate at 65mg every 12h	N/A	N/A	Generally not considered stable in solution; dilution in NS to 10 mg/mL described	Respiratory depression, potential for drug interactions due to hepatic enzyme induction	May supplement with 65mg every 1 h as needed; consider increasing scheduled dose if frequent supplemental doses are required; do not exceed administration rate of 60 mg/min

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