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Critical Connections

The Complete News Source for Critical Care Professionals

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In This Issue…

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See brochure inside.

Clinical Spotlight

Critical Care Medicine:

The Bench Perspective

The clinical care we provide today absolutely could not exist without the research performed at the laboratory bench. From the diabetes research of Banting and Best to Jonas Salk's polio vaccine, examples of previous discoveries that have revolutionized how we care for patients are seemingly endless. Many investigators dedicate their lives to the pursuit of discovering new proteins, therapeutic targets, or physiologic mechanisms that will also lead to new treatments – or even cures – for the hundreds of major diseases that affect us on a daily basis. We have highlighted some important recent studies that may one day significantly influence therapy in humans.

Mesenchymal Stem Cells Following Tissue Injury

Multipotent bone marrow-derived stem cells, or multipotent stem cells (MSC), have been investigated throughout the past decade for the treatment of graft-versus-host disease, sepsis, hepatic failure, and acute renal failure. Originally characterized by Friedenstein and colleagues in 1968, these cells are derived from bone marrow and can differentiate into muscle, fat, cartilage, bone, and fibroblasts. They also appear to have both an immunomodulatory effect influencing the function of lymphocytes and neutrophils, as well as a beneficial effect

"Critical Care Medicine: The Bench Perspective" p16

Recommendations for Alternative Analgesic and Sedative Agents in the Setting of Drug Shortages

Drug shortages are increasingly common occurrences that threaten the quality and safety of care provided by the multispecialty care team in the intensive care unit (ICU). The U.S. Food and Drug Administration (FDA) has reported an ever-increasing number of drug shortages over the past decade with more than 200 shortages reported in 2011, including several sedatives and opioids commonly used in the ICU. As members of the Society of Critical Care Medicine's (SCCM) Anesthesiology and Clinical Pharmacy and Pharmacology sections, we have compiled a reference for those coping with shortages in analgesic and sedation drugs. This guide outlines first-, second- and third-tier drug recommendations for those faced with shortages during their everyday practice.

Additionally, the Society has been participating in various outreach and educational activities in an attempt to address the issue on a broader scale. A position paper published at www.sccm.org/advocacy outlines concerns for patient safety and endorses the Preserving Access to Life-Saving Medication Act, which would give the FDA improved capacity to prevent shortages. Recently, SCCM participated in a drug shortages summit, which facilitated discussion among several healthcare associations, pharmaceutical manufacturers, supply chain entities, and the FDA.

Find easy-to-reference tables on page 10 and 11, detailing suggestions for alternative analgesics and sedatives for use in adult, mechanically ventilated intensive care unit patients.

Despite these efforts, critical care professionals can expect to face shortages well into the foreseeable future, as the underlying factors are multifaceted and numerous. The inconsistent supply source for raw materials, inventory practices that offer little or no cushion in supply, and regulatory and legislative factors – including the lack of requirements for reporting impending shortages to the FDA – are among the most pressing issues contributing to the current situation. Solutions will be complex and far-reaching. Until then, preparation is key and an outline of available alternatives and supplements is vital for those administering and prescribing drugs in the ICU.

"Recommendations for Alternative Analgesic and Sedative Agents in the Setting of Drug Shortages" p10

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Has your ICU experienced drug shortages this year?

"Recommendations for Alternative Analgesic and Sedative Agents in the Setting of Drug Shortages" continued from p1

The tables below outline suggestions for alternative analgesics and sedatives for use in adult, mechanically ventilated ICU patients. Although analgesics and sedatives are often used in other settings (e.g., procedural sedation, surgery), these recommendations were 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 were derived from a combination of limited published data, tertiary drug information resources, alternative indications, pharmacokinetic properties and expert opinion. 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 and elimination) on drug disposition. As such, the recommendations provided represent conservative, initial starting doses that can be adjusted as clinically indicated. This approach (i.e., start low and go slow), as well as efforts to optimize therapy while minimizing waste, are strongly advised. Dosing weight considerations are provided for select agents that may be less familiar to ICU clinicians. Finally, appropriate monitoring for common adverse drug events, like respiratory depression and coma, is essential, particularly with agents of limited familiarity and comfort.

When a shortage arises in a preferred analgesic or sedative, clinicians should consider an alternative from the same tier listed in the appropriate table (e.g., hydromorphone if fentanyl and morphine are not available). If this is not feasible, then an agent from the next tier should be selected. Global principles for the use of analgesics and sedatives must be adhered to and standard evidence-based practices followed. For example, nonopioid agents can be considered to reduce opioid requirements where appropriate. Validated scales should be used to guide sedation therapy, and daily wake-up assessments should be performed as clinically indicated. Clinicians can also consider an analgesic-first sedation strategy when primary sedatives are unavailable. When use of less-familiar agents is necessary, specialized calculators from validated drug information resources can assist with conversions and infusion rate calculations.

References and disclosures are available at www.sccm.org/criticalconnections.

Table 1.

ANALGESICS

Drug	Approximate Parenteral Equianalgesic Dose (mg)	Onset (IV)	Elimination Half-Life	Initial Dosing Intermittent	Initial Dosing Continuous Infusion	Titration	Stability	Side Effects and Considerations	Special Comments
Tier 1									
Fentanyl	0.1	1-2 min	2-4 h	25-50 µg IV every 0.5-1 h	25-50 µg/h (#)	Adjust by 25 µg/h every 30 min; give bolus dose with each rate increase	NS or 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	0.4-0.8 mg/h (#)	Adjust by 0.2 mg/h every hour; give bolus dose with each rate increase	NS or D5W	Potential for potency-related dosing errors	May work in patients tolerant to morphine/fentanyl; accumulation with hepatic/renal impairment
Morphine	10	5-10 min	3-4 h	2-4 mg IV every 1-2 h	2-4 mg/h (#)	Adjust by 1 mg/h every hour; give bolus dose with each rate increase	NS or D5W	Hypotension, bronchospasm	Accumulation with hepatic/renal impairment
Tier 2									
Remifentanil	0.1	1-3 min	3-10 min	N/A	0.5 µg/kg loading dose, then 0.5-1 µg/kg/h	Adjust by 0.5 µg/kg/h every 5 min	NS or D5W Stable for 24 h at a concentration of 20-250 µg/mL	Hypotension, muscle rigidity	No accumulation in hepatic/renal failure; short half-life; use IBW if weight >130% IBW
Methadone	N/A	10-20 min	15-60 h	10-40 mg po every 6-12 h	Not recommended	N/A	N/A	QT prolongation; unpredictable pharmacodynamic profile in opiate-naïve patients	Unpredictable pharmacokinetics; long half-life; IV dosage form available (conversion from oral to parenteral based on 2:1 ratio)
Tier 3									
Alfentanil	0.75	Immediate	1.5 h	5-7.5 µg/kg IV over 3-5 min; may repeat as needed	0.1-0.2 µg/kg/min (#)	Adjust by 0.1 µg/kg/min every 15-30 min	NS or D5W For infusion, dilute to 25-80 µg/mL	Hypotension, elevation of intracranial pressure, bradycardia	Use IBW; pharmacokinetics altered when used for ICU sedation
Sufentanil	0.01	1-3 min	2-3 h; dose dependent	0.05 µg/kg IV; may repeat every hour as needed	0.05 µg/kg/h (#; see special comments)	Adjust by 0.03 µg/kg/h every hour	Stable in D5W at 5 µg/mL (polyolefin plastic infusion bags); stable in NS at 1 µg/mL (polypropylene syringes)	Elevation of intracranial pressure, bradycardia	Dosing primarily based on potency relative to other opioids; limited data in ICU setting suggest higher doses (see references); available as a 50 µg/mL solution; use IBW if weight >120% IBW
Oxymorphone	1	5-10 min	Duration: 3-6 h	0.2-0.5 mg IV over 2-5 min; may repeat every 4 h as needed	0.2 mg/h (#)	Adjust by 0.2 mg/h every hour	NS For infusion, dilute to 0.25 mg/mL	Respiratory depression, hypotension, elevation of intracranial pressure	Intermittent dosing preferred; approximately 10 times more potent than morphine
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 5-20 min	NS or D5W For infusion, dilute to 1-2 mg/mL (may be prepared by adding 500 mg to 500 mL or 250 mL)	May cause hallucinations and other psychological disturbances; consider administration of benzodiazepines to attenuate psychological disturbances	Attenuates the development of acute tolerance to opioids; potential for neurotoxicity with prolonged use

#May administer bolus prior to start of continuous infusion for more rapid analgesic effect.
Abbreviations: IV, intravenous; N/A, not applicable; po, by mouth; NS, normal saline; D5W, 5% dextrose in water; ICU, intensive care unit; IBW, ideal body weight.

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Additional Resources

Additional resources related to drug shortages in the intensive care unit are available at LearnICU.org.

- Judith Jacobi, PharmD, BCPS, FCCM, discusses drug shortages in the intensive care unit and how such shortages affect critical care patients and those requiring anesthesia. She discusses reasons for various drug shortages, the Society of Critical Care Medicine's recent participation in an information summit on the matter, and the U.S. Food and Drug Administration's limited ability to help resolve the situation. In a robust and insightful conversation, Jacobi addresses the potential unintended consequences of shortages and the future of drug availability. Jacobi is a clinical pharmacy specialist at Methodist Hospital/Clarian Health in Indianapolis, Indiana.
- Authors John J. Lewin III, PharmD, MBA, BCPS, and Judith Jacobi, PharmD, BCPS, FCCM, detail the reasons and possible solutions for alleviating drug shortages affecting critical care in the April 2011 issue of *Critical Connections*.

Table2.

SEDATIVES

Drug	Onset After IV Loading Dose	Half-Life	Initial Dosing (IV) Intermittent	Initial Dosing (IV) [LD and/or CI]	Titration	Stability	Side Effects and Considerations	Special Comments
Tier 1								
Dexmedetomidine	5-10 min	1.8-3.1 h	N/A	LD: 1 µg/kg over 10 min (optional) CI: 0.2-0.8 µg/kg/h (see special comments)	Adjust by 0.1 µg/kg/h at least every 30 min	Dilute in NS or D5W to 4 µg/mL	Bradycardia, hypotension	Note that dose range listed in product information differs from that in literature specific to the ICU setting; no active metabolites; administer LD only in those patients in whom hypotension is unlikely to occur
Propofol	1-2 min	1.5 - 12.4 h	N/A	5-50 µg/kg/min	Adjust by 10 µg/kg/min every 5 min	1000 mg/100 mL lipid emulsion	Hypotension, respiratory depression, hypertriglyceridemia, pain on injection when administered through peripheral veins, pancreatitis, propofol-related infusion syndrome	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								
Lorazepam	15-20 min	8-15 h	1-2 mg q2-6h	CI: 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 1 mg/mL	Respiratory depression, propylene glycol-related acidosis, renal failure	Intermittent dosing preferred; no active metabolites
Midazolam	2-5 min	3-11 h	2-4 mg q0.5-2h	CI: 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								
Diazepam	2-5 min	20-120 h	2.5-10 mg q4-6h	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	LD: 0.1-0.5 mg/kg, then CI: 0.05-0.4 mg/kg/h	Adjust every 5-20 min	NS or D5W; for infusion, dilute to 1-2 mg/mL (may be prepared by adding 500 mg to 500 mL or 250 mL)	May cause hallucinations and other psychological disturbances; consider administration of benzodiazepines to attenuate psychological disturbances	Attenuates the development of acute tolerance to opioids; potential for neurotoxicity with prolonged use
Pentobarbital	3-5 min	22 h	100 mg IV; may repeat as needed (allow 1 min to see full effect)	100 mg LD (may repeat up to 500 mg), then 0.5 mg/kg/h	Adjust by 0.5 mg/kg/h every hour; if bolus needed, may give hourly dose	For infusion, dilute to 8 mg/mL in NS or D5W	Hypotension, decreased cardiac output, respiratory depression, potential for drug interactions due to hepatic enzyme induction	Reduce dose in the elderly and patients with hepatic impairment; highly alkaline (avoid extravasation); do not exceed administration rate of 50 mg/min
Phenobarbital	5 min	53-140 h	Bolus with 7.5 mg/kg IV over 1 -2 h, then 1-2 mg/kg/day divided q12h; for adults <90kg, initiate at 65mg q12h	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 65 mg every 1 h as needed and consider increasing scheduled dose if frequent supplemental doses are required; do not exceed administration rate of 60 mg/min

#May administer bolus prior to start of continuous infusion for more rapid achievement of sedative effect.
Abbreviations: IV, intravenous; N/A, not applicable; NS, normal saline; D5W, 5% dextrose in water; ICU, intensive care unit; LD, loading dose; CI, continuous infusion