

Sedation in the ICU: Shifts and Strategies



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Over the past decade, intensive care units (ICUs) worldwide have adopted the goal of maintaining an optimal level of comfort and safety for critical care patients.^{1,2} Guidelines and protocols for the sedation of ICU patients now also are mandated by accreditation agencies. As a result, sedation and pain management are being tracked as vital signs throughout a patient's hospital stay.

Recently, clinicians have been faced with multiple shortages of sedative drugs, most notably propofol, which have significantly affected protocols in ICUs throughout the world. Our growing understanding of the importance of delirium in critically ill patients, and how it affects outcomes, also has influenced how clinicians plan ICU sedation and has led to shifts in how patients are evaluated and how they are treated, pharmacologically or otherwise.

The large number of modern sedatives and analgesics has given critical care practitioners the ability to titrate specific agents for specific patient types, allowing patients to be comfortable throughout their stay in the ICU. This wide selection of drugs also has reduced the length of hospital stays and permitted patients to wean from therapy earlier, enabling them to participate in physical and occupational therapy.

As the customized care of patients continues to evolve, a common language is mandated for the titration and use of sedative agents. With this language also comes the development of protocols and guidelines to better use these drugs and to maximize the unique pharmacodynamic profile of each drug for individual patients.

No longer is it necessary to be trapped by the all-or-none effect of very long-acting compounds that depress respiration and prolong the ICU stay. Titratable sedation also may modulate the immune system. Evidence now shows that high levels of anxiety and pain may influence morbidity and mortality, and specific compounds may modulate the release of cytokines and vasoactive compounds.^{1,2}

Evaluation for Agitation and Anxiety

Agitation and anxiety are common in ICU patients of all ages, occurring at least once in 71% of patients admitted to a medical-surgical ICU.³ Agitation can be caused by multiple factors, such as extreme anxiety, delirium, adverse drug effects, and pain. Inadequate pain control is a significant factor in the development of agitation in critically ill patients, predominantly in the postoperative period. Insufficient pain management often results from suboptimal dosing of opioids because of concerns about respiratory depression and the development of dependence. Normally, these side effects are unlikely to develop over the short term if the medication is properly titrated to patient comfort.

Hypoxemia has long been associated with agitation. It is crucial for ICU staff to monitor the oxygen levels of all patients. A partial pressure of oxygen of 60 mm Hg or lower (or oxygen saturation <90%) can contribute to agitation secondary to hypoxemia. Hypotension also can lead to agitation due to hypoperfusion of the brain. Common metabolic problems such as hyperglycemia and, especially, hypoglycemia can promote severe agitation. Uremia and elevated levels of heavy metals (eg, lead, mercury) have been identified as causes of significant agitation. Sepsis also is a common cause of agitation and must be immediately ruled out.

Table 1. Medications Associated With Agitation in ICU Patients

Antibiotics	
Acyclovir	Ketoconazole
Amphotericin B	Metronidazole
Cephalosporins	Penicillin
Ciprofloxacin	Rifampin
Imipenem-cilastatin (Primaxin, Merck)	Trimethoprim-sulfamethoxazole
Anticonvulsants	
Phenobarbital	Phenytoin
Cardiac drugs	
Captopril	Nifedipine
Clonidine	Nitroprusside
Digoxin	Procainamide
Dopamine	Propranolol
Labetalol	Quinidine sulfate
Lidocaine	
Corticosteroids	
Dexamethasone	Methylprednisolone
Opioid analgesics	
Codeine	Morphine sulfate
Meperidine	
Miscellaneous drugs	
Anticholinergics	Metoclopramide
Benzodiazepines	Nonsteroidal anti-inflammatory drugs
Hydroxyzine	Theophylline
Ketamine	

The trauma patient with a closed head injury may have minor to severe agitation. Patients without traumatic head injury, including those with subarachnoid bleeds, also may present with agitation. Thrombotic stroke may cause agitation, and patients with brain neoplasms, brain seizures, infections such as meningitis, or air embolism also may have associated persistent and severe agitation.

One of the most common problems confronting providers of critical care is a patient's withdrawal from alcohol or other agents, including cocaine, opioids, and sedatives such as benzodiazepines; all of these substances contribute to brain injury and agitation.⁴ Withdrawal in cigarette smokers, who can suffer agitation from lack of nicotine, should be ruled out.

Another common cause of agitation in the ICU patient is significant ventilator desynchronization in patients on mechanical ventilation. This is frequently the result of poorly set ventilators that delay response

Table 2. Ramsay Scale for Assessing Level of Sedation

Level	Response
1	Patient awake and anxious, agitated, and/or restless
2	Patient awake, cooperative, accepting ventilation, oriented, and tranquil
3	Patient awake; responds to commands only
4	Patient asleep; brisk response to light glabellar tap or loud auditory stimulus
5	Patient asleep; sluggish response to light glabellar tap or loud auditory stimulus but responds to painful stimulus
6	Patient asleep; no response to light glabellar tap or loud auditory stimulus

Based on reference 5.

to the patient's efforts at spontaneous breathing. The problem is becoming less common because of the availability of advanced computer-controlled ventilators and the use of graphic displays to titrate ventilation. Patients who undergo short- or long-term intubation also become agitated because of the stimulus of the endotracheal tube itself. Patients who are alert and intubated may become frustrated by their inability to communicate with staff and family and descend into a cycle of continued agitation. The ICU itself, with its high levels of technology, lights, noise, and continuous stimuli, can significantly contribute to further agitation.

Numerous drug interventions, drug reactions, and drug-drug interactions, as well as drug withdrawal, all increase the incidence of patient agitation in the modern ICU. The occurrence of undesirable drug-drug interactions always should be considered when multiple drugs are being used for pain, anxiety, infection, and cardiac arrhythmias (a brief list of medications associated with agitation appears in Table 1). Even after the withdrawal of a pharmacologic compound suspected of increasing agitation, a positive response may not be seen for several days while the drug and its metabolites clear from the patient's system.

A differential diagnosis of agitation begins with a review of the patient's disease process, mechanism of injury, laboratory values, treatments, baseline medications, and history of chronic diseases (eg, hepatic or renal). Only after this type of rapid evaluation can the process move toward proper treatment for agitation.

Evaluation and Titration of Sedative Agents

ICU patients typically demonstrate a complex disease state and a rapidly changing spectrum of

hemodynamic parameters, so the requirements to treat agitation fluctuate over time. Bedside clinicians must frequently reassess and redefine the goals of therapy, to evaluate ICU patients and their levels of sedation in real time. Tools and scales to monitor agitation in the ICU should be simple to apply yet should describe clearly graded changes between levels of sedation to allow the titration of both pharmacologic and nonpharmacologic interventions, depending on the patient's condition.

Many scales and tools for the evaluation of ICU patients described in the literature assess the level of consciousness with descriptive responses to interventions. Most ICUs use modifications of these scales and tools to develop customized unit-based scales, protocols, and guidelines. This customization is highly important to facilitate acceptance of the guidelines by all members of the health care team.

Sedation Scales

The most commonly used sedation scale is the Ramsay Sedation Scale, which identifies 6 levels of sedation ranging from severe agitation to deep coma (Table 2).⁵ Despite its frequent use, the Ramsay Scale has some shortcomings when applied at the bedside of patients with complex problems. For example, a patient who appears to be asleep with a sluggish response to glabellar tap (Ramsay 5) also may be restless and anxious (Ramsay 1). The Ramsay Scale is simple, however, and is widely used throughout the world.

The Riker Sedation-Agitation Scale (SAS) was the first scale formally tested and developed for reliability in the ICU (Table 3).^{2,6} The SAS identifies 7 symmetric levels, ranging from dangerous agitation to deep sedation. This scale provides descriptions of patient behavior that can assist the bedside practitioner in distinguishing between levels.

The Motor Activity Assessment Scale (MAAS), which is similar in structure to the SAS, uses patient behaviors to describe the different levels of agitation.⁷ The MAAS identifies 7 levels, ranging from unresponsive to dangerously agitated (Table 4).

Ely et al described a newer assessment tool for the ICU, the Confusion Assessment Method for the ICU (CAM-ICU).⁸ This tool is being validated in critically ill patients with delirium. It is used in combination with the Glasgow Coma Scale to evaluate highly complex, agitated patients. The CAM-ICU is simple to apply at the bedside and has been found to have high levels of reliability, sensitivity, and specificity.

There is hope that real-time, computer-based monitors of brain function may remove human variability from the evaluation of patients with agitation. One such monitor that is popular in the operating room is the Bispectral Index (BIS, Covidien). This objective monitor is especially helpful for the deeply sedated patient receiving neuromuscular blockade. The BIS monitor provides discrete values from 100 (completely awake) to less than 60 (deep sedation) to 40 or below (deep hypnotic state or barbiturate coma) by

Table 3. Riker Sedation-Agitation Scale

Score	Diagnosis	Description
7	Dangerously agitated	Pulls at endotracheal tube; tries to remove catheters; climbs over bed rail; strikes at staff; thrashes from side to side
6	Very agitated	Does not calm down despite frequent verbal reminding of limits; requires physical restraints; bites endotracheal tube
5	Agitated	Anxious or mildly agitated; attempts to sit up; calms down in response to verbal instructions
4	Calm and cooperative	Calm; awakens easily; follows commands
3	Sedated	Difficult to arouse; awakens to verbal stimuli or gentle shaking but drifts off again; follows simple commands
2	Very sedated	Arouses to physical stimuli but does not communicate or follow commands; may move spontaneously
1	Unable to be aroused	Minimal or no response to noxious stimuli; does not communicate or follow commands

Based on references 2 and 6.

incorporating several electroencephalographic components.⁹ Although the technique has been shown to be valid in the operating room, it has not been studied to any great extent in the ICU. This device should be carefully evaluated in the wide spectrum of critically ill patients in all types of ICUs.

Establishing and Implementing Sedation Guidelines/Protocols

One of the most important goals for any ICU is the development of protocols and guidelines for the use of pain medications and sedative drugs. The development of such protocols requires multidisciplinary input and should be unit-specific. All staff, including physicians, nurses, and pharmacists, need to agree on which monitoring scales and tools to use and then ensure that they are applied reliably across disciplines. It is key for staff to agree on documentation, frequency of assessment, predefined end points of therapy, and evaluation of patient outcomes. Tools to evaluate sedation and pain should be added to flow sheets placed at the bedside. The use of these types of protocols with documentation in daily practice can foster communication between disciplines and shifts. Each hospital should develop guidelines based on current pharmacologic and pharmacokinetic recommendations and supported by national standards.^{1,2}

Several studies have shown that when ICUs institute protocol-driven sedative use, patients spend less time on mechanical ventilation and have shorter stays in the ICU and the hospital.¹⁰ Another easy bedside strategy for optimizing outcome in patients receiving therapy for agitation is to implement a daily schedule for

the reassessment and interruption of sedation infusions.¹¹ This practice is common in the trauma-burn ICU at the University of Rochester in Rochester, NY, where daily interruptions of sedative infusions are found to decrease the duration of mechanical ventilation and decrease time in the ICU. A “sedation holiday” improves clinicians’ ability to perform daily neurologic examinations, thereby reducing the need for diagnostic studies to evaluate unexplained alterations in mental status.¹² This practice also allows the maximal use of bed resources in a busy hospital.

It is important that pharmacologic colleagues—hospital pharmacists and PharmDs—be involved in the development of sedation guidelines. Pharmacists can provide guidance and educational input regarding specific pharmacodynamic profiles of individual agents. The participation of pharmacists on rounds and as members of the ICU team improves care, especially in complex cases.

The implementation of guidelines and protocols has the added benefit of decreasing the use of sedative drugs, thereby enhancing hospital finances. Sedatives and narcotic agents are the most commonly prescribed drugs in the ICU and may account for a major percentage of patients’ pharmacy charges.

Review of Agents Commonly Used In Sedation

Analgesics and sedatives are the mainstays of supportive patient care in the ICU, where they are the most commonly used drugs. Over the past few years, several novel, highly titratable agents have been introduced that have greatly altered patient care. The pharmacology of several of these widely used agents, along with

Table 4. Motor Activity Assessment Scale

Score	Description	Definition
0	Unresponsive	Does not move with noxious stimulus
1	Responsive only to noxious stimuli	Opens eyes or raises eyebrows or turns head toward stimulus or moves limbs with noxious stimulus
2	Responsive to touch or name	Opens eyes or raises eyebrows or turns head toward stimulus or moves limbs when touched or name is loudly spoken
3	Calm and cooperative	Does not require external stimulus to elicit movement; adjusts sheets or clothes purposefully; follows commands
4	Restless but cooperative	Does not require external stimulus to elicit movement; picks at sheets or clothes or uncovers self; follows commands
5	Agitated	Does not require external stimulus to elicit movement; attempts to sit up or moves limbs out of bed; does not consistently follow commands
6	Dangerously agitated, uncooperative	Does not require external stimulus to elicit movement; pulls at tubes or catheters, thrashes from side to side, strikes at staff, or tries to climb out of bed; does not calm down when asked

Based on references 7 and 16.

that of classic drugs with long-use profiles, is reviewed in Table 5.

OPIOIDS

Opioids are the main agents used for analgesia in the ICU. Analgesia greatly affects the need for sedation and other therapies. Unrelieved pain induces a powerful stress response characterized by tachycardia, increased myocardial oxygen consumption, hypercoagulability, immunosuppression, and persistent catabolism.¹³ Effective analgesia also can diminish pulmonary complications in postoperative patients.

Opioids are lipid-soluble and bind to opiate receptors in the central nervous system (CNS) and peripheral nervous system. At low doses, opioids provide analgesia but not anxiolysis, whereas at higher doses, they act as sedatives. All the opioids share therapeutic properties, but they vary in potency and pharmacokinetics.

Although opioids can be given via several routes, the IV method is the most common in the ICU. It is important to consult with anesthesiologists when developing pathways for novel uses of these agents, such as epidural placement. When given intravenously in therapeutic doses, opioids cause sedation by clouding the sensorium, but they do not possess amnestic properties.¹⁴

Comparative trials of opioids have not been performed in critically ill patients. The selection of a specific agent depends on its pharmacology and potential for causing adverse effects. For opioids, desirable attributes include a rapid onset of effect, ease of titration, lack of accumulation of the parent drug or its metabolites, and low cost.

Morphine sulfate is the preferred opioid analgesic in patients with stable hemodynamics. Its relatively low

lipid solubility may result in a delayed onset of action. Morphine also induces the release of histamine, increasing the likelihood of hypotension secondary to vasodilation. Morphine-6-glucuronide, a metabolite of morphine, is excreted in the urine and may accumulate in patients with renal failure. The opiate activity of this metabolite is several times greater than that of morphine, and its accumulation in patients with renal failure has been reported to prolong narcosis.

Fentanyl has the most rapid onset and shortest duration of action of the opioids, but repeated dosing may cause accumulation and prolonged effects. Fentanyl, a synthetic narcotic analgesic, is up to 100 times more potent than morphine, is highly lipid-soluble, and has a rapid onset of action because it quickly crosses the blood-brain barrier. Fentanyl has no active metabolites and is not associated with histamine release or venodilating effects. Because of these characteristics, fentanyl has become a widely used agent in the ICU. It is ideal for use in patients with unstable hemodynamics. Fentanyl should be administered by continuous infusion for sustained effect because of its short duration of action.¹⁵

Remifentanyl (Ultiva, Abbott), a newer agent, has not been widely studied in ICU patients. The drug has a very short half-life and may be best used in patients requiring serial examinations or neurologic evaluations. Because of its short duration of action, continuous infusion is necessary for pain management.¹⁶

Hydromorphone is a highly potent opioid with no active metabolites. It can be used in the ICU but has not found broad-based application in this setting.

Meperidine is not recommended for repeated use; it has an active metabolite that causes neuroexcitation (apprehension, tremors, delirium, and seizures) and

may interact with antidepressants (contraindicated with monoamine oxidase inhibitors and best avoided with selective serotonin reuptake inhibitors). Because of risks from multiple interactions with other medications, meperidine should not be used in the ICU.

Certain adverse effects of opioid analgesics occur frequently in ICU patients. Of greatest concern are respiratory, hemodynamic, CNS, and gastrointestinal effects. Respiratory depression is a concern in spontaneously breathing patients or in those receiving partial ventilatory support. Opioids also may increase intracranial pressure in patients with traumatic brain injury, although the data are inconsistent and the clinical significance is unknown.¹⁷

NONOPIOIDS

Gabapentin. Increasing evidence suggests that non-benzodiazepine γ -aminobutyric acid (GABA)-ergic compounds have promise for the treatment of alcohol withdrawal syndrome. GABA represents the major inhibitory neurotransmitter of the CNS. Ethanol, benzodiazepines, and some anticonvulsants directly affect GABA receptors, inducing similar anxiolytic, sedative-hypnotic, and anticonvulsant effects.

Benzodiazepines (see below) are widely used to treat alcohol withdrawal syndrome and continue to be considered the drugs of choice for this condition. Because of their addictive potential and lack of safety when combined with alcohol, benzodiazepines usually are not recommended for maintenance treatment.

A 2009 study compared gabapentin with lorazepam in a double-blind randomized clinical trial. Gabapentin was well tolerated and decreased symptoms of alcohol withdrawal in an outpatient population. Gabapentin reduced the probability of drinking during alcohol withdrawal and in the postwithdrawal week compared with lorazepam.¹⁸

A more recent study showed that gabapentin loaded up to 3,200 mg in the first 24 hours was helpful in reducing less severe and less complicated acute alcohol withdrawal syndrome.¹⁹

Gabapentin is structurally related to GABA but does not bind to GABA_A or GABA_B receptors and does not appear to influence GABA synthesis or uptake. Binding sites have been located throughout the brain, corresponding to the presence of voltage-gated calcium channels possessing the α_2/δ_1 subunit. This channel appears to be located presynaptically and is thought to modulate the release of excitatory neurotransmitters involved in epileptogenesis and nociception.²⁰

Gabapentin is not highly protein-bound, is excreted renally, and is absorbed mainly from proximal small bowel. Its half-life is 5 to 7 hours.²⁰ The most common adverse reactions to the drug (occurring in fewer than

10% of patients) relate to the CNS and include somnolence, dizziness, ataxia, and fatigue. Gabapentin may enhance the effects of other CNS depressants, including herbal agents such as valerian and St. John's wort. There is no labeled use or dosage recommendation for alcohol withdrawal.

The daily dose range for labeled and unlabeled use of gabapentin (seizures and neuropathic pain, respectively) is adjusted based on creatinine clearance (CrCl) as follows: CrCl greater than or equal to 60: 300 to 1,200 mg 3 times daily; CrCl 30 to 59: 200 to 700 mg twice daily; CrCl 15 to 29: 200 to 700 mg daily; CrCl 15: 100 to 300 mg daily with dose reduction in proportion to reductions in clearance. For hemodialysis, the dose ranges between 125 and 350 mg after each 4 hours of hemodialysis.

Benzodiazepines are the most widely used sedative drugs in medicine.²¹ They are sedative and hypnotic—but not analgesic—agents that block the acquisition and encoding of new information and potentially unpleasant experiences (anterograde amnesia), but

they do not induce retrograde amnesia. They have an opioid-sparing effect by moderating the anticipatory pain response.²² Benzodiazepines vary in potency, onset, duration of action, uptake, and number of active metabolites. The 2 predominant mechanisms of action of benzodiazepines in the nervous system involve activity at GABA receptors. Potentiation of GABA-mediated transmission by benzodiazepines is apparently responsible for somnolent, anxiolytic, and anticonvulsant effects, whereas the amnestic property appears to correlate with GABA agonist activity in the limbic cortex.^{21,15}

Benzodiazepines are metabolized in the liver, where they are extensively cleared. The effects of these drugs may be prolonged in critically ill patients (because of reduced metabolism) or in patients with liver disease. A prolonged and continuous infusion of benzodiazepines should proceed with caution; an accumulation of the parent drug or active metabolites may produce inadvertent and prolonged oversedation, as is seen in elderly patients. It is therefore paramount that these drugs be titrated carefully and used in low doses, or the patient will be somnolent for several days after the infusion is stopped.

Benzodiazepines should be titrated to a predefined end point, often by using a series of loading bolus doses. Hypotension may develop in hemodynamically unstable patients with the initiation of sedation. Intermittent or “as needed” doses of diazepam, lorazepam, or midazolam may be adequate to maintain sedation because of the relatively long half-life of these drugs.^{21,23}

The clinical practice guidelines of the Society of Critical Care Medicine (SCCM) recommend lorazepam for the sedation of most patients, administered by either

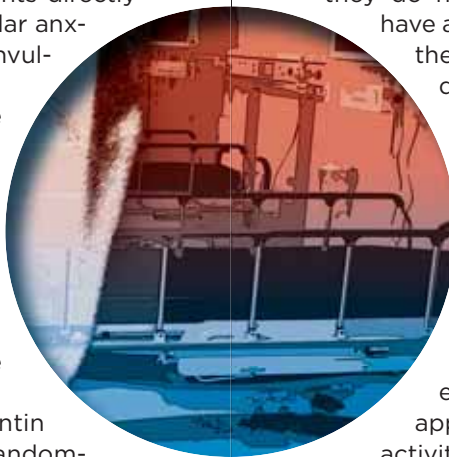


Table 5. Pharmacology of Selected Analgesics and Sedatives

	Agent	Equianalgesic Dose (IV)	Distribution Half-life	Metabolic Pathway	Active Metabolites (Effect)
Analgesics	Acetaminophen	NA	2 h	Conjugation	NA
	Codeine	120 mg	3 h	Demethylation and glucuronidation	Yes (analgesia, sedation)
	Fentanyl	200 mcg	1.5-6 h	Oxidation	No metabolite, parent accumulates
	Hydromorphone	5 mg	2-3 h	Glucuronidation	None
	Ibuprofen	NA	1.8-2.5 h	Oxidation	None
	Ketorolac	NA	2.4-8.6 h	Renal	None
	Meperidine	75-100 mg	3-4 h	Demethylation and hydroxylation	Yes (neuroexcitation, especially with renal insufficiency or high doses)
	Morphine	10 mg	3-7 h	Glucuronidation	Yes (sedation, especially with renal insufficiency)
	Remifentanyl (Ultiva, Abbott)	NA	3-10 min	Plasma esterase	None
Analgesic-Sedative	Dexmedetomidine (Precedex, Hospira)	NA	~6 min	Hydroxylation, methylation, and glucuronidation	None (glucuronidation); undetermined for P450-mediated pathways
Sedatives	Diazepam	NA	30-66 min	Hepatic microsomal enzymes	Yes
	Lorazepam	NA	3-20 min	Glucuronidation	None
	Methohexital (Brevital, JHP)	NA	4 h (for adults; may be up to 5 h in younger patients)	Demethylation and oxidation	NA
	Midazolam	NA	6-15 min	Hydroxylation	Yes
	Propofol	NA	2-3 min	Glucuronidation	None

CNS, central nervous system; D5W, 5% dextrose in water; GI, gastrointestinal; MAOIs, monoamine oxidase inhibitors; NA, not applicable; SSRIs, selective serotonin reuptake inhibitors

intermittent IV dosing or continuous infusion.^{1,2} Lorazepam, an intermediate-acting benzodiazepine, is less lipophilic than diazepam and, thus, has lower potential for accumulation. Lorazepam is associated with a stable hemodynamic profile, even when opioids are concurrently administered. It has no active metabolites, and its metabolism is less affected by advanced age or liver dysfunction than that of midazolam.²⁴ Lorazepam, however, should be used with caution; propylene glycol toxicity, marked by acidosis and renal failure,

has occurred with high doses or prolonged infusions of this drug.²⁵

The other commonly prescribed benzodiazepine is midazolam, more widely used in the operating room than in the ICU. Midazolam is a short-acting, water-soluble benzodiazepine that is transformed into a lipophilic compound in the blood. Midazolam exhibits dose-related hypnotic, anxiolytic, amnestic, and anti-convulsant actions. This drug produces dose-related respiratory depression, and larger doses may cause

Adverse Effects	Intermittent Dose ^a	Infusion Dose Range (Usual, Continuous)
NA	325-650 mg PO q4-6h; avoid >4 g/d	NA
Lacks potency, histamine release	Not recommended	Not recommended
Rigidity with high doses	0.35-1.5 mcg/kg IV q0.5-1h	0.7-10 mcg/kg/h
NA	10-30 mcg/kg IV q1-2h	7-15 mcg/kg/h
Risk for bleeding, GI and renal adverse effects	400 mg PO q4-6h	NA
Risk for bleeding, GI and renal adverse effects	15-30 mg IV q6h; decrease if age >65 y or weight <50 kg or renal impairment; avoid using >5 d	Infusion not FDA-approved
Avoid with MAOIs and SSRIs	Not recommended	Not recommended
Histamine release	0.01-0.15 mg/kg IV q1-2h	0.07-0.5 mg/kg/h
NA	NA	0.6-15 mcg/kg/h (0.1 mcg/kg/min)
Hypotension, transient hypertension, bradycardia	Intermittent dosing not FDA-approved	0.2-0.7 mcg/kg/h
CNS depressant, "paradoxical" reactions	5 mg as needed q2-5 min; maximum dose 0.25 mg/kg	2 mg/kg/d
Respiratory depression	2 mg as needed q2-5 min; maximum dose 1 mg/kg	2-4 mg (0.044-0.05 mg/kg)
Include cardiac and respiratory depression, neurologic and emergence delirium	1% solution (10 mg/mL) 1-1.5 mg/kg induction, then 20-40 mg as required (for adults)	0.2% solution (2 mg/mL) 6 mg/min (for adults)
Respiratory depression, respiratory arrest, hypotension	25% of induction dose	0.02-0.10 mg/kg/h (1-7 mg/h)
Apnea, hypotension ^b	Increments of 20-50 mg as needed	100-200 mcg/kg/min

^a More frequent doses may be needed for acute pain management in mechanically ventilated patients.

^b Strict aseptic technique required.

hypotension and vasodilation. Midazolam is metabolized in the liver to an active compound that is less potent and more transient than the parent compound. The SCCM guidelines recommend midazolam for the rapid sedation of actively agitated patients¹ for short-term use only; it is associated with unpredictable awakening and prolonged time to extubation when infusions continue for longer than 48 to 72 hours.

Paradoxical agitation has been observed with the use of benzodiazepines during light sedation and in the

elderly; this may be the result of drug-induced amnesia or disorientation. The effects of these drugs can be reversed with the benzodiazepine-receptor antagonist flumazenil. However, the routine use of flumazenil is not recommended after prolonged benzodiazepine therapy; there is a risk for inducing withdrawal symptoms and increasing myocardial oxygen consumption with as little as 0.5 mg of flumazenil.²⁶ A starting dose of 0.15 mg of flumazenil is recommended and is associated with fewer withdrawal symptoms.

Propofol has a rapid onset of action, within 1 to 2 minutes after a single IV dose, and a short duration of action, only 10 to 15 minutes, when discontinued.^{12,27} This is a result of its rapid penetration of the CNS and subsequent redistribution. Therefore, in the ICU, propofol is used by continuous infusion for sedation. Long-term infusions result in accumulation within lipid stores, a prolonged elimination phase, and a half-life of 300 to 700 minutes. Note, however, that subtherapeutic plasma concentrations of the drug are maintained after discontinuation because of rapid clearance; this limits the clinical significance of the drug's half-life value. Although the mechanism of action of propofol still is not completely understood, the drug appears to activate the GABA receptor within the CNS.

Propofol alters the sensorium in an extremely rapid dose-dependent manner, from light sedation to general anesthesia, making it a highly useful drug. It also is a potent respiratory depressant, causing a reduction in systemic vascular resistance and possible hypotension, especially when given as a bolus. Propofol should be administered with caution in hypovolemic patients. It has highly interesting effects on neurophysiology, parallel with the patient's level of arousal. Propofol decreases cerebral metabolism, resulting in a coupled decline in cerebral blood flow and decrease in intracranial pressure.

One of the most important benefits associated with propofol is a decrease in weaning time from mechanical ventilation. A large Spanish study using a cost-of-care approach, compared propofol and midazolam with regard to ICU costs for prolonged sedation of critically ill patients and weaning time from mechanical ventilation.²⁸ Although the 2 drugs provided equivalent sedation, propofol was associated with a shorter weaning time than midazolam, resulting in a more favorable economic profile. Because of its associated rapid wake-up time, propofol is considered the fundamental drug in many fast-track surgical programs, including cardiovascular surgery.¹²

Within a year of its introduction in the United States in 1990, reports appeared of clusters of infections in surgical patients treated with propofol.²⁹ The majority of cases were due to contamination of the drug resulting from poor aseptic techniques. To prevent contamination, the additive ethylenediamine tetraacetic acid (EDTA) was included to help inhibit the growth of microorganisms. EDTA, at a concentration of 0.005%, has no effect on the physical or chemical stability of the emulsion compound. In the years following the introduction of the EDTA-containing formulation, the incidence of fevers and infections was reduced to zero.

EDTA is a chelator of various ions, including calcium. In a randomized multicenter trial, patients were treated with either the original propofol formulation or the formulation with EDTA.³⁰ The EDTA-containing formulation had no effect on calcium or magnesium homeostasis, renal function, or sedative efficacy compared with the original formulation.

One of the interesting aspects of propofol with EDTA is its ability to modulate the systemic inflammatory response. In a study of surgical ICU patients, those receiving propofol with EDTA had significantly lower mortality rates at 7 and 28 days than patients receiving the original formulation.³¹ This potential positive effect of propofol with EDTA may be related to the ability of EDTA to bind cations. The EDTA-containing formulation of propofol increases the excretion of zinc; this, in turn, can diminish the inflammatory response to stress by decreasing the release of cytokines involved in inflammation (eg, tumor necrosis factor) and the generation of free radicals and other oxidants. The authors of this review are part of a group in Rotterdam, the Netherlands, that has investigated the release of cytokines and the transmigration of bacteria in an animal model, as modulated by various sedative agents. The full scope of the use of sedative agents to modulate the systemic inflammatory response is a highly interesting avenue of research for the future.

Propofol is not recommended for pediatric patients in the ICU because of reports of metabolic acidosis with accompanying lipemic serum, bradyarrhythmias, and fatal myocardial failure with excessively high doses.³² In adults with massive head trauma, prolonged use of propofol at very high doses may have contributed to cardiac failure³³; however, these were highly complex cases with a high mortality index.

The SCCM guidelines recommend propofol as the agent of choice for rapid awakening and early extubation.¹ Because propofol is formulated as a lipid emulsion, triglyceride concentrations should be monitored after 2 days of propofol infusion. The total caloric intake from the lipids should be included in the nutritional support prescription and may decrease hospital costs for added nutritional support.

Fospropofol (Lusedra, Eisai Inc.) is a prodrug that is hydrolyzed to yield propofol, which then interacts with the GABA_A receptor, the presumed mechanism of propofol's sedative/hypnotic effect. No data are available on the use of fospropofol use for sedation in the ICU. Most studies of fospropofol concern its use in procedural sedation for various endoscopic procedures. Indeed, its sole indication is as a sedative/hypnotic for monitored anesthesia care in adult patients undergoing diagnostic or therapeutic procedures. There are no absolute contraindications to its use.^{34,35} The onset of effect of fospropofol is delayed compared with propofol due to the need for conversion to its active form. This lag may create a risk for dose stacking, which could result in deeper sedation than intended.^{34,35}

The most common adverse reactions to fospropofol are paresthesia and pruritis.^{34,35} The drug is in pregnancy category B, and it is not known whether it crosses the placenta. Propofol, however, does cross the placenta and enters breast milk.^{34,35}

Fospropofol is 98% protein-bound. It is completely metabolized by plasma alkaline phosphatases to propofol, formaldehyde (which is rapidly converted to

formate), and phosphate. Although formate accumulation is the main mechanism of the toxicity seen with methanol ingestion, there have been no reports of toxicity due to fospropofol.³⁶ There are no dosage adjustments recommended with hepatic or renal impairment, but limited data regarding this are available.^{34,35}

Haloperidol, a butyrophenone neuroleptic drug, is the agent of choice for the treatment of delirium in critically ill patients. Patients treated with haloperidol generally appear calmer and are better able to respond appropriately to commands.¹² Haloperidol does not cause major respiratory depression. The drug, however, cannot be used alone in intubated critically ill patients.

The adverse effects associated with haloperidol include occasional hypotension resulting from the α -adrenergic-blocking properties of the drug. Although it is rare with IV use, haloperidol may cause extrapyramidal effects such as drowsiness, lethargy, a fixed stare, rigidity, and akathisia. A highly dangerous side effect is neuroleptic malignant syndrome (NMS), with a mortality rate of 20% to 30%. NMS develops slowly over 24 to 72 hours and can last up to 10 days after discontinuation of the drug.³⁷ The incidence of NMS may be higher when haloperidol is given by continuous infusion, which is not recommended.

Dexmedetomidine (Precedex, Hospira), a selective α_2 -adrenergic receptor agonist, exhibits sympatholytic, sedative, and analgesic effects and has 8 times the affinity for the α_2 -adrenergic receptor as clonidine. Dexmedetomidine is approved for continuous IV sedation of initially intubated and mechanically ventilated patients in the intensive care setting for use for up to 24 hours, as well as in nonintubated patients before or during surgery. Its combined sedative and analgesic effects make it a highly promising therapy.

Dexmedetomidine acts at 2 adrenergic sites. It works by presynaptic activation of the α_2 -adrenoceptor, thereby inhibiting release of norepinephrine and terminating propagation of pain signals; it also affects postsynaptic activation of these receptors in the CNS. Dexmedetomidine inhibits sympathetic activity, resulting in a decrease in blood pressure and heart rate. Together, these 2 effects can produce sedation, anxiolysis, sympatholysis, and analgesia.³⁸

Dexmedetomidine has several advantages as a sedative in the ICU. Because the drug does not cause respiratory depression, a patient can be extubated without prior discontinuation. This property also makes it ideal for use in extubated patients. The drug provides great flexibility. It also may be ideal for use in weaning off mechanical ventilation. Another advantage of dexmedetomidine is the easy awakening of treated patients, making it useful for those with head injury.³⁹

Because dexmedetomidine lowers the requirement for opioids, it can decrease opioid side effects. At the University of Rochester, the drug is widely used in burn patients, allowing complex wound care without the need for intubation.

One of the greatest challenges in administering sedatives to patients who have a history of alcohol or drug abuse is to maintain the correct balance—avoiding both excessive sedation and agitation/withdrawal syndromes. The α_2 -adrenergic receptor properties of dexmedetomidine may be highly useful in this patient population. We have had great success in weaning patients with dexmedetomidine in the ICU—especially those with heavy alcohol or cocaine use. Further studies in this large population are necessary to map out the physiologic effects of sedation.

Dexmedetomidine in the neurologic ICU offers a unique quality of sedation described as similar to normal sleep. Several investigators have noted that their patients were in a tranquil state but were able to understand and communicate their needs on verbal stimulation by the medical staff (including through the use of pen and paper).⁴⁰ This particular profile of sedation may allow a more accurate evaluation of the neurophysiologic status of mechanically ventilated patients, which is difficult to accomplish with any other available sedative agents. Thus, dexmedetomidine may be the preferred sedative for neurosurgical patients who require a real-time assessment of their neurologic status.

Another interesting population for further investigation is patients with head injuries, many of whom are highly agitated and expressing sympathetic outflow. With dexmedetomidine, we have been able to blunt the response of these patients and increase their rate of successful extubation. Dexmedetomidine has decreased the length of ICU stay and the rate of tracheotomies in patients with closed head injuries.⁴¹

A 2009 trial of dexmedetomidine versus midazolam for sedation in the ICU concluded that although no difference in time-to-targeted sedation was observed, at comparable sedation levels, patients treated with dexmedetomidine spent less time on a ventilator, experienced less delirium, and developed less tachycardia and hypertension.⁴²

Because elimination is primarily hepatic, dexmedetomidine dosing should be lowered in patients with hepatic dysfunction. Also, the inappropriate use of dexmedetomidine may induce or aggravate cardiac conduction defects. Dexmedetomidine should not be used in hypovolemic or bradycardic patients, or in patients with low cardiac output or heart conduction blocks.

The administration of this compound for more than 24 hours to critically ill patients has been found to be safe and effective in the ICU.⁴³ An initial loading dose of 1 mcg/kg over 10 minutes can be prescribed; however, this dose is not frequently used because it may cause transient hypotension or hypertension. These phenomena occur, depending on whether vasodilatation (central α_{2a} -receptor stimulation) or vasoconstriction (peripheral α_{2b} -receptor stimulation) predominates. The usual maintenance dose is 0.2 to 0.7 mcg/kg per hour, with increases no more frequently than every 30 minutes. Doses up to 1.4 mcg/kg per hour have been reported.⁴² For patients older than 65 years, the suggested loading

dose is 0.5 mcg/kg over 10 minutes with a maintenance infusion of less than 0.6 mcg/kg per hour. No specific guidelines exist for altering the dose for elderly patients or patients with hepatic or renal impairment.⁴⁴

Dexmedetomidine is a promising agent with multiple actions that reduce analgesic and other sedative requirements, and it produces a cooperatively sedated patient. It may open a whole new arena in the sedation of extubated patients who have high levels of anxiety. The compound may also enhance our ability to evaluate lung function and perform bronchoscopy in nonintubated patients, critically ill patients, and patients with moderate to severe chronic obstructive pulmonary disease or emphysema.⁴⁵ Dexmedetomidine needs to be further studied and its place in the ICU identified by well-designed research to evaluate both its short- and long-term effects.

Methohexital (Brevital, JHP Pharmaceuticals) is a short-acting IV barbiturate anesthetic. The literature is not robust regarding use of the drug for ICU sedation. Continuous IV infusion should use a 0.2% solution with a dose of 5 to 120 mcg/kg per minute for maintenance of anesthesia.⁴⁶ Use for Wada testing is an unlabeled indication. Doses should be lowered in patients with hepatic impairment and renal impairment may prolong or potentiate its hypnotic effect.⁴⁶

Several adverse reactions of methohexital are known, but their frequency has not been defined. Contraindications to its use include hypersensitivity to methohexital (or any component formulation) or other barbiturates and porphyria (latent or manifest).⁴⁶ Extravasation or intra-arterial injection may cause necrosis. Many drug reactions are associated with methohexital. Methohexital is pregnancy category B; it crosses the placenta, and it enters breast milk. It is metabolized via a hepatic route and excreted in urine.⁴⁶

Quetiapine. Oral atypical antipsychotics have drawn recent interest for the treatment of critically ill patients with agitation due to delirium. Few trials have compared the efficacy and safety of these agents with haloperidol, but a recent prospective randomized trial revealed that quetiapine added to as-needed haloperidol resulted in faster resolution of delirium, less agitation, and a greater rate of transfer to home or rehabilitation. The dosing recommendation for quetiapine by this study was 50 mg twice daily, increased as needed daily in 50-mg increments to a maximum dose of 400 mg per day.⁴⁷ A 2007 study concluded that 25 to 100 mg per day of quetiapine improved delirious conditions within 24 hours of treatment, was well tolerated, and had a low propensity to induce extrapyramidal side effects.⁴⁸

Quetiapine is a dibenzothiazepine atypical antipsychotic. Its antipsychotic activity is believed to be

mediated via dopamine type 2 (D2) and serotonin type 2 (5-HT₂) antagonism. Other CNS antagonist sites are the 5HT_{1A}, dopamine D₁, histamine H₁, and α_1 - and α_2 -adrenergic receptors. Quetiapine does not appear to have affinity for benzodiazepine or muscarinic M₁ cholinergic receptors, although norquetiapine, an active metabolite, does have affinity for M₁ receptors.⁴⁹

The main indication of quetiapine is for the treatment of patients with schizophrenia and acute manic or depressive episodes associated with bipolar disorder. Treatment for delirium in the critically ill patient is an unlabeled use. Significant adverse reactions include central (somnolence, headache), cardiovascular (orthostatic hypotension, tachycardia), and metabolic (hyperglycemia) effects.⁴⁹ A boxed warning cautions about an increased risk for death compared with placebo in elderly patients with dementia-related psychosis treated with antipsychotic agents.⁴⁹

Quetiapine is rapidly absorbed, is approximately 80% protein-bound, and is metabolized primarily by cytochrome P4503A4 (CYP3A4) hepatic enzymes with a half-life of 6 hours. The metabolite *N*-desalkyl quetiapine has a half-life of 9 to 12 hours. Excretion occurs renally, mainly as its metabolite and less than 1% as unchanged parent compound. Fecal excretion is approximately 20%.

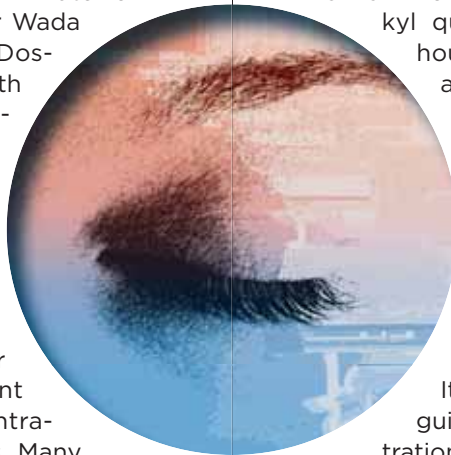
Conclusion

The most important aspect of ICU sedation is understanding the drugs given to patients and their specific advantages and disadvantages. Each drug is ideal for a specific use. It is crucial for the clinician to develop guidelines and pathways for the administration of these drugs within a specific environment. Each unit should develop protocols that grade effect based on the type of patient population in the unit. Newer drugs like dexmedetomidine should be introduced and studied in controlled trials in specific populations. In this way, protocols can be developed that enable patients to be comfortable and anxiety-free in the ICU. Poor levels of sedation should be a thing of the past.

The immunomodulating properties of sedative drugs also must be explored because these properties may greatly affect outcome. An increased understanding of sedative drugs will improve clinicians' ability to use multiple drugs at specific times during the patient's hospital stay.

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