Sedation Practices in the ICU

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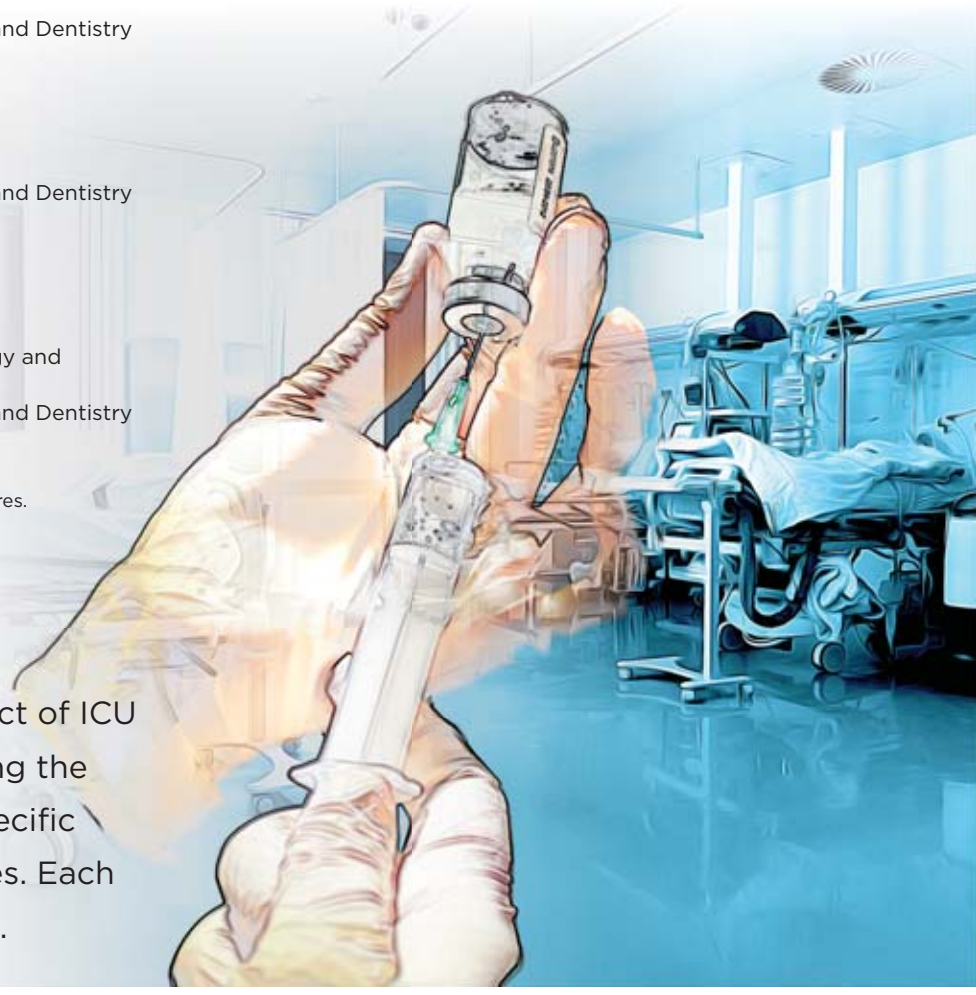

The most important aspect of ICU sedation is understanding the drugs used and their specific advantages and disadvantages. Each drug is ideal for a specific use.

The goal of ICUs worldwide is to maintain an optimal level of comfort and safety for critical care patients.[1,2] Sedation guidelines and protocols now also are mandated by accreditation agencies for ICU patients. Sedation and pain management are being tracked as a vital sign in the care of patients over their entire hospital admission. This has led to widespread efforts to optimize sedation and pain control in this patient population.

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 has also reduced the lengths of hospital stays and permitted patients to participate in drug weaning and such procedures as 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 each drug's unique pharmacodynamic profile for individual patients.

It is no longer necessary to be trapped by the all-or-none effect of very long-acting compounds that depress respiration and prolong ICU stay. Titratable sedation may also modulate the immune system. There

Table 1. Medications Associated With Agitation in ICU Patients

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

is now evidence 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 of 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. Failure to provide adequate pain control is a significant factor in the development of agitation in critically ill patients, predominantly in the postoperative period. Inadequate pain management is often a result of suboptimal dosing of opioids because of concerns about respiratory depression and the development of dependence. Normally, these side effects are unlikely over the short term if the medication is properly titrated to patient comfort.

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

The trauma patient with a closed head injury may have minor to severe agitation. Patients with no traumatic head injury, including patients with subarachnoid bleeds, may also present with agitation. Thrombotic stroke may cause agitation, and patients with brain neoplasms, brain seizures, infections such as meningitis, and air embolism may also have associated persistent and severe degrees of 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 these substances contribute to brain injury and agitation.[4] Withdrawal in cigarette smokers, who can suffer agitation from the lack of nicotine, should be ruled out.

Another common cause of agitation in the ICU is significant ventilator desynchronization in patients on mechanical ventilation. This is frequently the result of poorly set ventilators that delay responding to the patient's efforts at spontaneous breathing. This problem is becoming less common because of advanced computer-controlled ventilators and the use of graphical displays to titrate ventilation. Patients who undergo short- or long-term intubation also develop agitation because of the stimulus of the endotracheal tube itself. Patients who are alert and intubated may also become frustrated by their inability to communicate with staff

and family, and may descend into a cycle of continued agitation. The ICU itself, with its high levels of technology, lights, and noise, and thus continuous stimuli, can significantly contribute to further agitation.

Numerous drug interventions, drug reactions, drug–drug interactions, and drug withdrawal all increase the incidence of agitation in the modern ICU. The occurrence of undesirable drug–drug interactions should always 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, it may take several days for the drug and metabolites to clear from the patient's system before a positive response can be seen.

A differential diagnosis of agitation begins with a review of the patient's disease process, mechanism of injury, laboratory values, therapy and treatments, baseline medications, and a 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

The disease state complexity of ICU patients typically demonstrates a rapidly changing spectrum of hemodynamic states, so the requirements to treat agitation fluctuate over time. Bedside clinicians must frequently reassess and redefine the goals of therapy, implying that ICU patients and their sedation levels must be evaluated in real time. Tools and scales to monitor agitation in the ICU should be simple to apply, yet describe clearly graded changes between sedation levels to allow titration of both pharmacologic and nonpharmacologic interventions, depending on the condition of the patient.

Several scales and tools for ICU evaluation are described in the literature. Many of these evaluate the level of consciousness with descriptive responses to interventions; for example, if the level of a drug is raised, the patient's condition will change. There is no gold standard scale, but most ICUs use modifications of those described in the literature. The development of customized unit-based scales, protocols, and guidelines is highly important for promoting their acceptance by all members of the healthcare team.

Sedation Scales

The most commonly used sedation scale is the Ramsay sedation scale,[5] which identifies 6 levels of sedation ranging from severe agitation to deep coma (Table 2). 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) may also 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). The SAS identifies 7 symmetrical 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.[6]

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

A newer assessment tool for the ICU was described by Ely and colleagues as 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 for highly complex, agitated patients. The CAM-ICU is simple to apply at the bedside and has been found to have a high level of reliability, sensitivity, and specificity.

There is hope that real-time, computer-based monitors of brain function might remove human variability from the evaluation of patients with agitation. One such monitor popular in the operating room is the Bispectral Index (BIS, Medtronic). 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 less (deep hypnotic state or barbiturate coma) by incorporating several electroencephalogram 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 against the wide spectrum of critically ill patients in all types of ICUs.

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.

Establishing and Implementing Sedation Guidelines and Protocols

One of the most important goals for any ICU is the development of protocols and guidelines for pain medication 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 these scales are used 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. Sedation and pain evaluation tools should be added to flow sheets in use at the bedside. Using these types of protocols and documenting their use 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]

Studies have shown that when ICUs institute protocol-driven sedative usage, patients spend less time on mechanical ventilation, have shorter stays in the ICU, and have shorter stays in the hospital.[10] Another easy bedside strategy for optimizing outcome in patients receiving therapy for agitation is to institute a daily schedule for reassessment and interruption of sedation infusions.[11] This is a common practice in the trauma–burn ICU at the University of Rochester, New York, where daily interruptions of sedative infusions are found to decrease the duration of mechanical ventilation and decrease the time in the ICU. This practice allows maximal use of bed resources in a busy hospital. A "sedation holiday" improves the ability of clinicians to perform daily neurologic examinations, thereby reducing the need for diagnostic studies to evaluate unexplained alterations in mental status.[12]

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

The institution 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 used drugs in the ICU and may account for a major percentage of pharmacy charges.

Review of Common Agents 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 classic drugs with long-use profiles, is reviewed in Table 5.

Opioids

Opioids are the primary agents used for analgesia in the ICU. Analgesia greatly affects the need for sedation and other therapies. Unrelieved pain evokes a powerful

Table 3. Riker Sedation–Agitation Scale

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

Based on references 2 and 6.

stress response characterized by tachycardia, increased myocardial oxygen consumption, hypercoagulability, immunosuppression, and persistent catabolism.[13] Effective analgesia can also 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 vary in potency and pharmacokinetics.

Even though opioids can be given via several routes, the intravenous method is the most common in the ICU. It is important to consult with anesthesiologists when developing pathways for novel usage 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 adverse effects. For opioids, desirable attributes include rapid onset, ease of titration, lack of accumulation of the parent drug or its metabolites, and low cost.

Morphine sulfate, the prototypic opioid, has long been a preferred agent for analgesia in the ICU population. In the last decade, the increased preference for other longer acting and more hemodynamically stable agents with fewer side effects has led to a decreased use of morphine as the primary analgesic in the ICU setting. Morphine has lower lipid solubility, which may result in a delayed onset of action. Morphine also induces the release of histamine, increasing the likelihood of hypotension secondary to vasodilatation. 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 a rapid onset and shortest duration of the opioids, but repeated dosing may cause accumulation and prolonged effects. Fentanyl citrate, 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]

Remifentanil has not been widely studied in ICU patients. The drug is exceptionally short acting, and even prolonged infusions yield a context-sensitive half-life of only 3 minutes.[16] As such, remifentanil infusions can be turned on and off with nearly immediate termination of opioid-induced respiratory depression and sedation, making this an attractive agent for use in patients needing serial exams or neurologic evaluations.

Hydromorphone is a highly potent opioid with no active metabolites. It has seen increased use recently in the ICU population, as it lacks morphine's restrictions in the renally impaired patient or hemodynamically

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 or thrashes from side to side or strikes at staff or tries to climb out of bed; does not calm down when asked

Based on references 7 and 16.

Table 5. Pharmacology of Selected Analgesics and Sedatives

	Agent	Equianalgesic Dose (IV)	Distribution Half life	Metabolic Pathway	Active Metabolites (Effect)	Adverse Effects
Analgesics	**Acetaminophen**	NA	2 h	Conjugation	NA	NA
	Codeine	120 mg	3 h	Demethylation and glucuronidation	Yes (analgesia, sedation)	Lacks potency, histamine release
	Fentanyl	200 mcg	1.5-6 h	Oxidation	No metabolite, parent accumulates	Rigidity with high doses
	Hydromorphone	1.5 mg	2-3 h	Glucuronidation	None	NA
	Ibuprofen	NA	1.8-2.5 h	Oxidation	None	Risk for bleeding, GI and renal adverse effects
	Ketorolac	NA	2.4-8.6 h	Renal	None	Risk for bleeding, GI and renal adverse effects
	Meperidine	75-100 mg	3-4 h	Demethylation and hydroxylation	Yes (neuroexcitation, especially with renal insufficiency or high doses)	Avoid with MAOIs and SSRIs
	Morphine	10 mg	3-7 h	Glucuronidation	Yes (sedation, especially with renal insufficiency)	Histamine release
	Remifentanil	NA	3-10 min	Plasma esterase	None	NA
Analgesic-Sedative	**Dexmedetomidine**	NA	~6 min	Glucuronidation, hydroxylation, and methylation	None (glucuronidation); undetermined for P-450–mediated pathways	Hypotension, transient hypertension, bradycardia
	Ketamine	NA	10-15 min	Oxidation	Yes (antinociceptive)	Dysphoria, sialagogue, direct myocardial depressant, nausea
Sedatives	**Diazepam**	NA	30-66 min	Hepatic microsomal enzymes	Yes	CNS depressant, "paradoxical" reactions
	Lorazepam	NA	3-20 min	Glucuronidation	None	Respiratory depression
	Midazolam	NA	6-15 min	Hydroxylation	Yes	Respiratory depression, respiratory arrest, hypotension
	Propofol	NA	2-3 min	Glucuronidation	None	Apnea, hypotension[c]

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

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

[b] Cost data based on Average Wholesale Price to infuse for 24-h period in a 70 kg patient at lowest anticipated dose; costs may vary among institutions.

[c] Strict aseptic technique required.

Intermittent Dose[a]	Infusion Dose Range (Usual, Continuous)	Infusion Cost Per Day—70 kg[b]
325-650 mg PO q4-6h; avoid >4 g/d	NA	NA
Not recommended	Not recommended	NA
0.35-1.5 mcg/kg IV q0.5-1h	0.7-10 mcg/kg/h	$14.40
10-30 mcg/kg IV q1-2h	7-15 mcg/kg/h	$12.30
400 mg PO q4-6h	NA	NA
15-30 mg IV q6h; decrease if age >65 y or weight <50 kg or renal impairment; avoid use >5 d	Infusion not FDA-approved	NA
Not recommended	Not recommended	NA
0.01-0.15 mg/kg IV q1-2h	0.07-0.5 mg/kg/h	$1.68
NA	0.6-15 mcg/kg/h (0.1 mcg/kg/min)	$73.55
Intermittent dosing not FDA-approved	0.2-0.7 mcg/kg/h	$161.78
0.2-0.5 mg/kg for analgesia; 0.8-1.0 mg/kg for induction	0.2-3.0 mk/kg/h	$6.62
5 mg as needed q2-5 min; maximum dose 0.25 mg/kg	2 mg/kg/d	$120.68
2 mg as needed q2-5 min; maximum dose 1 mg/kg	2-4 mg (0.044-0.05 mg/kg)	$16.46
25% of induction dose	0.02-0.10 mg/kg/h (1-7 mg/h)	$4.48
Increments of 20-50 mg as needed	100-200 mcg/kg/min	$3.52

unstable patient. Some studies have additionally suggested improved analgesia over morphine.[17]

Meperidine is not recommended for repetitive use since it has an active metabolite that causes neuroexcitation (apprehension, tremors, delirium, and seizures) and may interact with antidepressants (contraindicated with monoamine oxidase inhibitors, and is 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 from 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 may also increase intracranial pressure in patients with traumatic brain injury, although the data are inconsistent and the clinical significance is unknown.[18]

Nonopioids

Nonsteroidal anti-inflammatory drugs (NSAIDs). The use of nonopioid agents is increasing in the ICU. NSAIDs provide analgesia via the nonselective, competitive inhibition of cyclooxygenase (COX), a critical enzyme in the inflammatory cascade. COX-2 inhibitors were reevaluated as the result of reports of cardiovascular complications, and some have been withdrawn from the market by manufacturers. Therefore, COX-2 agents should not be recommended for critically ill patients. NSAIDs have many positive attributes, including reducing opioid requirements, but they also have many adverse effects and so must be used with caution. A more complete discussion of the use of NSAIDs is not within the scope of this review.

Benzodiazepines. Benzodiazepines are the most widely used sedative drugs in medicine.[19] 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 do not induce retrograde amnesia. They have an opioid-sparing effect by moderating the anticipatory pain response.[20] Benzodiazepines vary in their potency, onset and duration of action, uptake, and absence of active metabolites. The 2 predominant mechanisms of action of benzodiazepines on the nervous system involve activity at the gamma-aminobutyric acid (GABA) receptors. Potentiation of GABA-mediated transmission by benzodiazepines is apparently responsible for somnolent, anxiolytic, and anticonvulsant actions, whereas the amnestic property seems to correlate with GABA agonist activity in the limbic cortex.[2,15]

Metabolism of benzodiazepines occurs in the liver, where they are extensively cleared. The effects of these drugs may be prolonged in critically ill patients (because of decreased metabolism) or in patients with liver disease. Prolonged and continuous infusion of benzodiazepines should proceed with caution; 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 dosages, or the patients will be somnolent for several days after stopping the infusion. It is widely accepted now that there is a correlation between benzodiazepine use in the elderly ICU population and increased incidence of delirium.[21] Furthermore, recent studies suggest that benzodiazepine use may even prolong time spent on a ventilator and the length of ICU stay, and increase mortality compared to other sedatives.[22] For this reason, the once widespread use of these agents in the ICU population is no longer considered the standard of care. The most recent Society of Critical Care Medicine (SCCM) guidelines on sedation and treatment of delirium in the ICU recommend using propofol or dexmedetomidine over benzodiazepines due to research indicating improvement in outcomes.[23]

Benzodiazepines should be titrated to a predefined end point, often using a series of loading bolus doses. Hemodynamically unstable patients may experience hypotension with the initiation of sedation as conscious sympathetic drive is diminished from anxiety, wakefulness, and discomfort. Maintenance of sedation with intermittent or as-needed doses of diazepam, lorazepam, or midazolam may be adequate to accomplish the goal of sedation, secondary to the relatively long half-life of these drugs.[19,24]

Lorazepam, an intermediate-acting benzodiazepine, is less lipophilic than diazepam and thus has less 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.[25] 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 the drug.[26]

The other commonly used benzodiazepine is midazolam, widely used in the operating room but not as widely accepted in the ICU. Midazolam is a short-acting, water-soluble benzodiazepine that is transformed to a lipophilic compound in the blood. Midazolam exhibits dose-related hypnotic, anxiolytic, amnestic, and anticonvulsant actions. The drug produces dose-related respiratory depression, and larger doses may cause 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 rapid sedation of actively agitated patients,[1] but for short-term use only; it produces unpredictable awakening and prolonged time to extubation when infusions continue for longer than 48 to 72 hours.

Paradoxical agitation has been observed from use of benzodiazepines during light sedation and in the elderly, and 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.[27] A starting dose of 0.15 mg flumazenil is recommended, and is associated with fewer withdrawal symptoms.

Propofol. 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.[12,28] 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, with 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 is still 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. The drug is also 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, those with hypotension, shock states, severe cardiac disease, or patients in whom awake sympathetic drive is suspected to be masking an underlying hypotensive process, such as normotensive trauma patients in acute pain with underlying hypovolemia. It has highly interesting effects on neurophysiology, parallel with its level of arousal in the patient. 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,[29] using a cost-of-care approach, evaluated the impact on ICU costs of prolonged sedation of critically ill patients with midazolam or propofol, and weaning time from mechanical ventilation. Although the 2 drugs provided equivalent sedation, the administration of propofol was associated with a shorter weaning time than midazolam, resulting in a more favorable economic profile. Because of its rapid wake-up time, propofol is considered the fundamental drug in many fast-track surgical programs, including cardiovascular surgery.[12]

Within 1 year of its introduction in the United States in 1990, reports started appearing of clusters of infections in surgical patients treated with propofol.[30] The majority of cases were due to contamination of the drug from poor aseptic technique. This contamination resulted in the inclusion of the additive ethylenediaminetetraacetic acid (EDTA) to help retard 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,[31] patients were treated with either the original propofol formulation or the formulation with EDTA. 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,[32] those receiving propofol with EDTA had significantly lower mortality rates at 7 days and 28 days than did patients receiving the original formulation. 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 (such as tumor necrosis factor), and the generation of free radicals and other oxidants.

In the United States, 3 generic formulations of propofol are now available. The major difference with the first generic product is the presence of sodium metabisulfite (0.025%); it carries an FDA warning about use in patients sensitive to sulfite compounds, and therefore should not be used in this group of patients. This generic formulation also has a lower pH (4.5-6.4) compared with the formulation with EDTA. It is highly important for clinical staff to know which propofol formulation is being used in their facility.

The other 2 generic formulations of propofol contain benzyl alcohol as a preservative. These formulations should not be used in neonates because of previous problems with benzyl alcohol in that patient population. Further studies are needed to also evaluate the long-term use of benzyl alcohol–containing formulations by continuous infusion in critically ill patients. There are also several 2% formulations in development for use in both the operating room and the ICU.

The use of 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.[33] In adults with massive head trauma, prolonged use of propofol at very high doses may have contributed to cardiac failures[34]; 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 also be included in the nutritional support prescription and therefore may decrease hospital costs for added nutritional support.

Ketamine. Ketamine is a relatively older and cost-effective agent that has seen increased use for analgosedation in the ICU setting in recent years. The mechanism of action of ketamine is primarily *N*-methyl-D-aspartate (NMDA) blockade, although other potential mechanisms include opioid receptor blockade and GABA inhibition.[35] Ketamine is metabolized to its active metabolite, norketamine, by the P450 system. It provides analgesia and sedation at smaller doses, and anesthesia at higher doses.

Ketamine preserves airway reflexes and does not depress respiratory drive. Unlike NSAIDs, ketamine does not appear to be associated with acute renal injury and gastrointestinal tract damage. In early studies, there was concern that ketamine had pro-convulsant properties.[36] Follow-up investigations, however, have shown that ketamine suppressed or eliminated electroencephalogram discharges in patients having seizures.[37] Thus the current thinking is that it need not be avoided in patients with seizure disorders or seizure potential. In fact, there are ongoing investigations on its use in treating status epilepticus due to possible anti-convulsant properties. Unlike opioids and benzodiazepines, ketamine is sympathomimetic and thus usually increases heart rate and blood pressure, making it a particularly attractive analgosedative choice in the hypotensive patient. Ketamine should be cautiously titrated in patients with ischemic cardiomyopathy, however, due to its direct myocardial depressant properties.

Ketamine is a dissociative agent and can cause hallucinations, a particularly concerning side effect in the ICU population, which is already at risk for delirium. It should be avoided in patients with a history of psychosis and is relatively contraindicated in patients with post-traumatic stress disorder.

Dosing recommendations vary by institution, but ketamine can be administered both as an IV bolus and infusion. A standard analgesic bolus dose ranges from 0.2-0.5 mg/kg IV, and if desired can be followed by an infusion of 0.2-1.2 mg/kg/hr. High doses can produce a temporary state of dissociative consciousness desirable in a patient requiring sedation for a painful procedure who is at risk for respiratory depression, such as the morbidly obese or patients with obstructive sleep apnea.

At high doses, infusions will be limited by patient dysphoria, hypertension, tachycardia, tonic–clonic movements, unpleasant mental sensations, or psychomimetic episodes, and thus patients should be monitored while receiving ketamine. High infusion rates can also lead to excessive sedation. Due to ketamine's lipophilic properties, accumulation also becomes an issue when infusions are continued over many days. Small boluses (0.1-0.5 mg/kg) can be administered as adjuncts in a multi-modal pain treatment approach.

Haloperidol. Haloperidol, a butyrophenone neuroleptic drug, is the agent of choice for treatment of delirium in critically ill patients. Patients treated with haloperidol generally seem to be 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 alpha-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.[38] There may be a higher incidence of NMS when haloperidol is used by continuous infusion, which is not recommended.

Dexmedetomidine. Dexmedetomidine is a selective alpha-2-adrenergic receptor agonist. It exhibits sympatholytic, sedative, and analgesic effects, and is 8 times more potent for the alpha-2 receptor than clonidine. Dexmedetomidine has been approved for sedation and analgesia in the ICU. Its combined sedation and analgesic effects make it a highly promising therapy.

Dexmedetomidine acts at 2 adrenergic sites. It works by presynaptic activation of the alpha-2 adrenoceptor, thereby inhibiting the release of norepinephrine and terminating the 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.[39]

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. Recent studies have shown that the use of dexmedetomidine in critically ill adults reduces the duration of mechanical ventilation and ICU length of stay, with few side effects.[40] Another advantage of dexmedetomidine is the easy awakening of treated patients, making it useful for those with head injury.[41]

Since dexmedetomidine also 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 problems in administering sedation is the proper sedation of patients who have a history of alcohol and drug abuse. These patients are balancing on a tightrope of receiving too much sedation or experiencing agitation and withdrawal syndromes. The alpha-2-adrenergic receptor properties of dexmedetomidine may be highly useful in this patient population. We have had great success in the weaning of these patients in the ICU—especially patients with heavy alcohol and cocaine use. Further studies in this large patient population are necessary to further elucidate dexmedetomidine's role as an adjunct in the management of withdrawal.

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 upon verbal stimulation by the medical staff (including the use of pen and paper).[42] This particular profile of sedation may allow for a more accurate evaluation of the neurophysiology status of these mechanically ventilated patients, which is difficult to accomplish with any other available sedative agents. Hence dexmedetomidine may be the preferred sedative for neurosurgical patients who require real-time assessment of their neurologic status.

Another interesting population for further investigation are patients with head injuries, many of whom are highly agitated and expressing sympathetic outflow. Through the use of dexmedetomidine, we have been able to blunt the response of these patients and increase their rate of successful extubation. In patients with closed head injuries, the use of dexmedetomidine thus has decreased the length of stay in the ICU and the rate of tracheotomies.[43]

Because elimination is primarily hepatic, dexmedetomidine dosing should be lowered in patients with hepatic dysfunction. Also, 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 use of this compound for over 24 hours in critical illness has been found to be safe and effective in ICU patients.[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 open up our ability to evaluate lung function and perform bronchoscopy in non-intubated 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.

Multimodal Pain in the ICU

Systemic opioids are among the most effective analgesic agents available for the treatment of moderate to severe pain. Many negative side effects, including respiratory depression, gastrointestinal dysmotility, nausea, confusion, oversedation, hyperalgesia, dependence, and addiction, have been well described. Recent research additionally implicates opioids as possibly linked to immunosuppression[46] and even certain types of cancer progression.[47,48] Considering these numerous downsides, a multimodal, opioid-sparing pain management approach that fully incorporates non-opioid adjuncts is

recommended. For instance, such an approach would favor initiating a standing dose of acetaminophen in patients requiring opioids for pain control, which has been shown to reduce opioid consumption.[49] Other tactics include early introduction of gabapentinoids, clonidine, lidocaine, short courses of NSAIDs when appropriate, and the use of regional anesthesia.

Many institutions have included these principles in surgical subspecialties, in enhanced recovery protocols. Colorectal surgery especially has embraced postoperative multimodal pain treatment, and research in surgical journals suggests quicker return of normal gut function when an opioid-sparing approach is implemented.[50] Although to our knowledge there are currently no major studies on opioid-sparing analgesia in the ICU population, there is a growing body of literature favoring these techniques in the perioperative setting. Regional anesthesia modalities are especially applicable in the ICU patient with discrete locations of pain and injury. There is some research suggesting favorable results in applying regional techniques to the trauma ICU patient with rib fractures,[46] patients with pancreatitis,[51] and in postoperative patients generally.

Conclusion

The most important aspect of ICU sedation is understanding the drugs used and their specific advantages and disadvantages. Each drug is ideal for a specific use. It is crucial for clinicians to develop guidelines and pathways for the use of these drugs within a specific environment. Each unit should develop use protocols that grade effect, based on the type of patient population in the unit. The role of dexmedetomidine in the treatment of acute withdrawal-associated agitation is yet to be defined, but the results of a few small studies have been optimistic. The last 2 decades of critical care medicine have seen a beneficial shift from a propensity to heavily sedate patients with benzodiazepines to strategies of light sedation, sleep hygiene implementation, early mobilization, multimodal analgesia, and the proactive treatment of delirium.

The immunomodulation properties of sedative drugs must also be explored, as these properties may greatly affect outcome. With an increased understanding of these drugs will come an increased ability to use multiple drugs at specific times during the hospital stay.

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