Sedation and Analgesia for the Mechanically Ventilated Patient

David R. Brush, MD, John P. Kress, MD*

Up to one third of ICU patients worldwide undergo mechanical ventilation.1 These patients frequently require analgesics and sedatives—potent medications with clear benefits and significant side effects. Sedation and analgesic requirements can vary greatly among critically ill patients. This poses a challenge for clinicians hoping to maximize the benefits from controlled analgesia and sedation while attempting to minimize patient risk.

INDICATIONS FOR SEDATION AND ANALGESIA

Pain

Patients commonly experience pain while undergoing mechanical ventilation.2,3 While pain from trauma, invasive operations, or procedures is often apparent, there are other sources of pain that may be underappreciated by clinicians such as routine nursing care, endotracheal tube suctioning, and prolonged immobility. Pain is associated with numerous adverse effects including increased endogenous catecholamine activity, sleep deprivation, anxiety and delirium.4 Adequate treatment of pain may alleviate some of these adverse effects.5 Although some discomfort may be alleviated by nonpharmacologic means such as patient positioning, minimizing invasive interventions, and prompt removal of unnecessary noxious stimuli, most patients will require opiates to adequately control their pain. Mechanically ventilated patients may be unable to communicate with care providers, and the physiologic variables of critically ill patients are often unreliable indicators of pain. Clinicians should direct their initial attention toward providing adequate analgesia when considering “sedation” in mechanically ventilated patients. Otherwise, agitated patients with pain may be given sedatives—an intervention with suboptimal results.

Anxiety

The intensive care unit can be a frightening place for patients. In addition to the anxiety caused by life-threatening illness, patients can often be isolated and in uncertain surroundings. Inadequately controlled pain, sleep deprivation, isolation, and the presence of invasive tubes and catheters are frequently listed as sources of stress and anxiety.6,7 Although nonpharmacologic interventions such as comfortable positioning, verbal reassurance, and encouraging the presence of family and friends should be attempted, these interventions alone are often inadequate and medications must be employed.

Amnesia

Deep sedation is associated with memory impairment in mechanically ventilated patients.8 Whereas amnesia is of clear benefit during surgical procedures and should be a mandatory goal when using neuromuscular blocking agents, there is growing evidence that critically ill patients may benefit from retaining an awareness of their...
surroundings. Some studies have shown that patients with a greater recall of adverse experiences may be likely to develop posttraumatic stress disorder (PTSD), leading some to suggest that deep sedation be routinely used to blunt patient awareness of the ICU experience. More recently, investigators have demonstrated that patients who were most awake, or the most unresponsive, during mechanical ventilation had the lowest PTSD-like symptoms. Given the increased morbidity associated with deep sedation, we recommend allowing patients to retain an awareness of their surroundings unless neuromuscular blocking agents are being used.

Decrease Oxygen Consumption
Sedatives can be used to decrease patient oxygen consumption. This reduction in oxygen consumption can be particularly important in patients suffering from acute lung injury or shock.

Facilitate Patient Care
Patients undergoing mechanical ventilation are sometimes dysynchronous with the ventilator. This may be more likely to occur with modern mechanical ventilation strategies such as low tidal volume or permissive hypercapnia. However, initial concerns that low tidal volume ventilation may lead to increased sedation requirements have not been substantiated. Strategies involving high-frequency oscillatory ventilation and prone positioning may cause patients to require additional sedation. When ventilator dysynchrony is present, patients should be evaluated for sources of uncontrolled pain or discomfort. Despite adequate analgesia and ventilator-patient optimization, some patients require deeper sedation to meet the goals of care.

COMPLICATIONS ASSOCIATED WITH SEDATION AND ANALGESIA
The pharmacokinetic properties for short-term sedative and analgesic administration are not predictive of pharmacokinetics when the same drugs are used for long-term infusions in critically ill patients. Buildup of active drugs and metabolites, multicompartment tissue saturation, drug-drug interactions, and hepatic and renal dysfunction may result in unpredictable drug pharmacokinetics. Administration of sedatives in the ICU by continuous infusion is associated with a higher risk for oversedation, particularly in the elderly or patients with hepatic dysfunction. Kollef and colleagues studied the outcomes of 240 mechanically ventilated patients who either received continuous sedation or received intermittent/no intravenous sedation. Continuous sedation was associated with prolonged mechanical ventilation, increased ICU and hospital length of stay, and increased rates of organ failure and re-intubation. Continuous sedation has also been shown to be an independent risk factor for developing ventilator-associated pneumonia. Deep sedation may impair proper assessment of a patient’s neurologic status, resulting in increased use of diagnostic procedures and imaging. Long-term administration of sedatives and analgesic medications can also produce physical dependence, leading to withdrawal syndromes when these agents are discontinued.

The role of sedation in the development of central nervous system dysfunction is receiving increased attention from investigators. Central nervous system dysfunction, measured as delirium, has been detected in 60% to 80% of patients undergoing mechanical ventilation. ICU delirium is associated with greater hospital length of stay, and increased 6-month mortality. Pandharipande and others demonstrated that sedation with lorazepam is an independent risk factor for transitioning to delirium in ICU patients. This group also noted recently that newer agents such as dexmedetomidine had a lesser incidence of delirium than more conventional sedatives such as lorazepam. Investigators continue to evaluate which medications (or combinations of medications) can provide effective analgesia and sedation while minimizing unwanted side effects of drug accumulation and its associated risks.

INTRAVENOUS DRUGS FOR ANALGESIA AND SEDATION

Opioids
Opioids bind to receptors in the central nervous system and peripheral tissue. Mu-1 receptors mediate analgesia, while mu-2 receptor binding produces respiratory depression, nausea, vomiting, constipation, and euphoria. Kappa receptor activation causes sedation, miosis, and spinal analgesia. Whereas the primary effect of opioids is analgesia, they also may provide mild to moderate anxiolysis. Opioids have no reliable amnestic effect on patients.

Opioid administration is associated with dose-dependent, centrally mediated respiratory depression. Respiratory rate is depressed first, while tidal volume is initially preserved. Tidal volume is reduced with higher doses of opiates. The ventilatory response to hypoxia is eradicated and the CO₂ response curve is shifted to the right. Opioids are excellent drugs to help palliate coughing and
the subjective sense of dyspnea. This pharmacologic property may be particularly important for many patients who are distressed during mechanical ventilation.

Opioids have little cardiovascular effect in euolemic patients. The provision of opioids may decrease sympathetic tone, and thus may decrease heart rate and systemic vascular resistance. Additionally, opioids increase venous capacitance, thereby decreasing venous return. In hypovolemic patients with reduced cardiac output, this decrease in venous return, reduced sympathetic tone, and reduction in heart rate can result in significant hypotension.

Opioids decrease gastrointestinal motility and may induce ileus. Opioid-induced ileus is a common problem in critically ill patients. Treatment of this problem with stool softeners and/or laxatives is often ineffective. Methylnaltrexone bromide, a specific antagonist of peripheral mu-2 receptors in the gut, was recently approved by the Food and Drug Administration (FDA) for use in patients with late-stage advanced illnesses that are using opioids chronically. Thomas and colleagues recently demonstrated that methylnaltrexone significantly restored bowel function in terminally ill patients on chronic opioid therapy, without adversely impacting analgesia. Currently, there is no literature evaluating this drug in ICU patients.

Morphine

Morphine is poorly lipid soluble, and thus has a relatively slow onset of action (5 to 10 minutes). For a typical single intravenous dose of 5 to 10 mg, the approximate half-life is 4 hours; however, with repeated dosing or continuous infusions, this half-life pharmacology is not applicable. Morphine is conjugated by the liver to metabolites that include morphine-6-glucuronide, a potent metabolite with 20 times the activity of morphine. Both morphine and morphine-6-glucuronide are eliminated by the kidney, thus patients with renal dysfunction may suffer from prolonged drug effect. As such, morphine is a poor choice for patients with renal insufficiency.

Meperidine

Meperidine is more lipophilic than morphine and thus has a more rapid onset of action (3 to 5 minutes). However, meperidine’s duration of action (1 to 4 hours) is shorter than morphine because of redistribution of the drug into peripheral tissues. Like morphine, meperidine is metabolized by the liver and is renally excreted. A metabolite of meperidine, normeperidine, is a potent central nervous system (CNS) stimulant that can precipitate seizures, especially in patients with renal dysfunction. Given the similar onset and half-life to morphine and the increased potential for CNS toxicity, meperidine should not be used routinely for analgesia in the ICU.

Fentanyl

Fentanyl is highly lipid soluble with a rapid onset of action (1 minute) and rapidly redistributes into peripheral tissues, resulting in a short half-life (0.5 to 1 hour) after a single dose. Hepatic metabolism creates inactive metabolites that are renally excreted, making this drug a more attractive choice in patients with renal insufficiency. Continuous administration of fentanyl can result in altered pharmacokinetics, with build-up of drug into peripheral tissues that then reenters the plasma after drug discontinuation, causing a prolonged clinical effect.

Remifentanil

Remifentanil is a selective mu receptor agonist with unique pharmacokinetic properties. It is profoundly lipophilic, with an onset of action of about 1 minute. Unlike other opioids, it is rapidly metabolized by nonspecific blood and tissue esterases to a clinically inactive metabolite with a terminal half-life of approximately 10 to 20 minutes. Remifentanil was first introduced as part of perioperative anesthesia, but its favorable pharmacokinetics have led to increased interest in its use as part of a sedative/analgesic regimen for nonsurgical mechanically ventilated patients. Because rapid metabolism leaves no residual opioid, clinicians should use care to anticipate the emergence of pain and discomfort following remifentanil discontinuation, and should consider using a more long-acting analgesic regimen to bridge patients through this period.

In a double-blind, randomized, controlled trial comparing remifentanil to fentanyl in postsurgical patients undergoing mechanical ventilation 12 to 72 hours, Muellejans and colleagues demonstrated no significant difference in the time patients spent at an optimum level of sedation. Time to recovery from sedation was similar in both groups and both agents were well tolerated. Remifentanil is associated with a shorter time to extubation compared with sedation regimens using morphine. Other studies have demonstrated that the pharmacokinetics of remifentanil are not significantly altered in ICU patients with renal dysfunction, even after continuous administration for up to 3 days. Based on these initial studies, remifentanil shows exciting promise as a new analgesic for use in critically ill patients. However, more data are needed to guide clinicians on the use of this drug in ICU patients.
Midazolam

Midazolam has a rapid onset of action (0.5 to 5 minutes) and a short duration of action after a single dose (2 hours). The drug undergoes oxidation through the cytochrome P450 pathway to form metabolites that are excreted in the urine. The primary metabolite, 1-hydroxymethylmidazolam, is a mild CNS depressant and may accumulate in patients with renal dysfunction. Medications such as itraconazole, calcium channel blockers, and erythromycin may interfere with the cytochrome P450 enzyme and decrease midazolam metabolism. Hepatic dysfunction may also result in drug accumulation.

In critically ill patients undergoing continuous midazolam infusion, clinical recovery following drug discontinuation may take hours to days because of drug accumulation in peripheral tissues. Elderly patients with decreased renal and hepatic function as well as obese patients with a greater volume of distribution are at greater risk for prolonged sedation.

Lorazepam

Intravenous lorazepam has an onset of action of approximately 5 minutes, with duration of action after a single dose of approximately 6 to 10 hours. Lorazepam is metabolized through hepatic glucuronidation to inactive metabolites that are renally excreted. High-dose infusion of lorazepam has been associated with severe metabolic acidosis from propylene glycol toxicity, a suspension agent used to enhance solubility in the intravenous solution. Lorazepam administration has also been found to be an independent risk factor for the development of delirium in ICU patients.

Propofol

Propofol (2, 6 diisopropylphenol) is a sterically hindered phenol that exhibits sedative and hypnotic effects. Propofol acts on the GABA receptor, although at a different binding site than for benzodiazepines. Propofol is highly lipophilic and rapidly crosses the blood-brain barrier resulting in a rapid onset of action (1 to 5 minutes). The duration of action is dose dependent but relatively short (2 to 8 minutes for a bolus injection). The depth of sedation increases in a dose-dependent fashion, and it rapidly redistributes into peripheral tissues resulting in a quick emergence from sedation when the drug is discontinued. Propofol is conjugated by the liver into inactive metabolites that are renally excreted, but unlike with benzodiazepines, the presence of hepatic or renal disease has little impact on its metabolism. Elderly patients require a dosage reduction because of their decreased volume of distribution and decreased clearance of propofol. Like benzodiazepines, propofol exhibits dose-dependent sedation that may range from mild depression of responsiveness to obtundation. It has powerful anxiolytic and amnestic properties. Propofol has no analgesic effect, and patients may require higher doses of opioids compared with patients sedated with benzodiazepines. Propofol may also be used as an effective anticonvulsant.

Propofol causes profound respiratory depression and even apnea in some patients, and should be used only in patients with a secured airway or with personnel immediately available to intubate.
Similar to benzodiazepines, propofol decreases tidal volume with an associated increase in respiratory rate. Propofol administration can be associated with significant decreases in blood pressure, especially in hypovolemic patients. This is mainly because of increased venous capacitance and decreased venous return, although there may be some lesser effect stemming from myocardial depression. Long-term infusions of propofol may be associated with hypertriglyceridemia and subsequent pancreatitis, thus patients receiving propofol should have their serum triglyceride levels monitored. Patients receiving long-term propofol infusion, those receiving parenteral lipids for nutrition, and patients with baseline hypertriglyceridemia are at greatest risk.

Propofol infusion syndrome (PRIS) is a rare, but potentially fatal, complication typically seen with infusion rates of more than 4 mg/kg/h for more than 48 hours. Patients develop refractory bradycardia leading to asystole in the presence of metabolic acidosis, hyperkalemia, rhabdomyolysis, hyperlipidemia, or an enlarged fatty liver. Although the exact mechanism is unknown, current theories implicate impairment of mitochondrial respiratory chain function. Unexplained metabolic acidosis, elevations in serum lactate, creatinine kinase, or serum myoglobin may be early markers for the development of PRIS. Treatment consists of immediate discontinuation of propofol and correction of hemodynamic and metabolic abnormalities.

The pharmacokinetic properties of propofol offer significant advantages over other forms of hypnotic sedatives, such as benzodiazepines. Propofol has been demonstrated to be associated with a shorter duration of mechanical ventilation when compared with intermittent lorazepam in both retrospective studies and a recent randomized trial. When combined with a strategy including daily interruption of sedation, propofol also provides a significant cost savings compared with intermittent lorazepam. In a randomized trial by Barrientos-Vega and colleagues, long-term, continuous sedation with propofol and midazolam were equally effective at achieving goal sedation in patients undergoing mechanical ventilation, but propofol was associated with significantly shorter times from drug discontinuation to extubation. This decreased time to extubation led to a cost savings in the propofol group, despite the higher drug cost of propofol compared with midazolam. Hall and colleagues also demonstrated a decreased time to extubation after drug discontinuation of propofol compared with midazolam in their larger randomized multicenter trial.

**Butyrophenones**

Butyrophenones are sometimes provided for sedation in the ICU. These drugs appear to antagonize dopamine, especially in the basal ganglia, although the exact mechanism remains unclear. Drugs such as haloperidol induce a tranquil state, and patients often have a detached affect. Patients may even demonstrate a cataleptic, immobile state. These drugs offer minimal analgesia, and have no amnestic or anticonvulsant properties. For patients with psychotic agitation resistant to other pharmacologic interventions, butyrophenones are sometimes required to maintain patient safety.

Butyrophenones do not have any significant respiratory effects. There may be some mild, synergistic respiratory depression when butyrophenones are used in combination with opioids. Butyrophenones may cause mild hypotension as a result of the effects of peripheral alpha-1 blockade.

Butyrophenones such as haloperidol are associated with QTc prolongation and, rarely, torsade de pointes. Most reported cases in critically ill patients have occurred when patients were prescribed more than 50 mg/24 hours. If the patient’s baseline QTc interval is prolonged, if electrolyte disturbances are present, or they are receiving other drugs that may prolong the QTc interval, butyrophenones should be prescribed with caution.

**Haloperidol**

An intravenous dose of haloperidol will demonstrate an onset of effect within 2 to 5 minutes and will have a half-life of 2 hours. Doses of 1 to 10 mg are typically used initially, with titration depending on dose effect. In a retrospective cohort analysis of mechanically ventilated patients, Milbrandt and colleagues detected a difference in hospital mortality between patients who received haloperidol within 2 days of initiation of mechanical ventilation when compared with patients who never received haloperidol (20.5% versus 36.1%; \( P = .04 \)) even after adjusting for age, comorbidity, severity of illness, degree of organ dysfunction, and other potential cofounders. While intriguing, these findings must be interpreted with caution until confirmed by randomized, controlled trials.

**Dexmedetomidine**

Dexmedetomidine is a centrally acting alpha2-agonist approved for short-term use (<24 hrs) in patients receiving mechanical ventilation. It is an attractive drug for use in the ICU, given that it demonstrates sedative, analgesic, and anxiolytic
properties without depressing respiratory drive.\textsuperscript{57} Patients remain sedated if left undisturbed, but arouse easily with stimulation. Cardiovascular side effects include bradycardia and hypertension with initial bolus injection and hypotension with continuous infusion due to central sympatholysis.\textsuperscript{39} Most studies involving dexmedetomidine have been in postoperative patients, where it has been shown to decrease requirements for additional sedation and analgesic medications.\textsuperscript{58} Currently, dexmedetomidine is FDA approved only for use up to 24 hours in mechanically ventilated patients, but a recent randomized trial comparing lorazepam to dexmedetomidine in critically ill, mechanically ventilated patients suggests that dexmedetomidine may be safely used for up to 120 hours.\textsuperscript{59} Patients randomized to receive dexmedetomidine spent more days alive without delirium or coma (median days 7.0 versus 3.0, \(P = .01\)) and experienced a lower prevalence of coma (63\% versus 92\%; \(P = .001\)). Further long-term studies of dexmedetomidine are warranted before it can be routinely employed.

**VOLATILE ANESTHETIC SEDATION**

Volatile anesthetics such as isoflurane have been used for sedation in mechanically ventilated patients, but widespread use has been limited because of difficulty in administration. Compared with midazolam or propofol, isoflurane was found to have adequate sedative properties with predictable and quick awakening.\textsuperscript{60,61} Recent technological advances such as the Anesthetic Conserving Device (AnaConDa, Hudson RCI, Uppsland Väsb, Sweden) can convert a standard ventilator to provide volatile sedation. Using this device, Sackey and colleagues\textsuperscript{62} were able to provide prolonged isoflurane to ICU patients, with effective sedation and subsequent awakening times that were significantly shorter than seen with midazolam (time to follow verbal command 10 ± 8 versus 110 ± 132 minutes). In time, volatile sedation may become a viable alternative to routine intravenous sedation for mechanically ventilated patients.

**ANALGOSEDATION VERSUS HYPNOTIC-BASED SEDATION**

Traditional sedation practices focused primarily on hypnotic drugs such as benzodiazepines and propofol, with opioids added as needed to control pain. The introduction of shorter-acting opioids and dexmedetomidine has led to an increased interest in sedative strategies that focus primarily on analgesic medications, with hypnotic agents added on an as-needed basis. In a randomized, multicenter study by Breen and colleagues\textsuperscript{63} of patients undergoing mechanical ventilation for up to 10 days, an analgesia-based sedation regimen using remifentanil reduced the duration of mechanical ventilation by 2 days compared with a midazolam-based sedation strategy where fentanyl or morphine was added as needed for analgesia. In neurosurgical and neurotrauma patients, analgesia-based sedation strategies using remifentanil plus propofol provided significantly faster and more predictable awakening for neurologic assessment compared with standard hypnotic-based regimens using propofol with fentanyl or morphine added for pain control.\textsuperscript{64}

**ASSESSING THE ADEQUACY OF SEDATION**

Individual assessments of sedation adequacy can be hampered by lack of objectivity. The Society of Critical Care Medicine’s Clinical Practice Guidelines for Sustained Use of Sedatives and Analgesics in the Critically Ill Adult recommend that a sedation goal or end point be established and regularly redefined for each patient using a validated sedation assessment scale, with documentation of regular assessment and response.\textsuperscript{16} There are several reliable instruments available to assess the adequacy of sedation. The Ramsay scale has been used for over 30 years in clinical investigations of sedation,\textsuperscript{65} but has attracted criticism because of its lack of clear discrimination and lack of specific descriptors to differentiate between levels.\textsuperscript{66} Other sedation scales such as the Sedation-Agitation Scale and the Richmond Agitation Sedation Scale (RASS) have been extensively tested for reliability and validity in critically ill patients.\textsuperscript{67–69} The RASS has been validated to detect changes in sedation status over several days, to perform reliably in patients with altered levels of consciousness such as delirium, and to correlate with doses of sedatives and analgesic medications administered to critically ill patients. The Adaptation to the Intensive Care Unit Environment (ATICE) is a sedation scoring system that additionally rates patient agitation and ventilator synchrony.\textsuperscript{70} It has demonstrated high internal consistency, inter-rater reliability across disciplines, and validity. Limited data suggest that adoption of routine, structured assessments alone may substantially change patient outcomes, even without pairing assessments to a protocol dictating alteration in sedation administration. In a two-phase, prospective controlled study by Chanques and colleagues,\textsuperscript{71} the implementation of a systematic evaluation of pain and agitation and using the Behavioral Pain Scale (BPS),\textsuperscript{72} Numerical Rating...
Scale (NRS),73 and the Richmond Agitation Sedation Scale (RASS)67 resulted in decreased incidence of pain and agitation in the intervention group (pain 63% versus 42% \( P = .02 \) and agitation 29% versus 12% \( P = .02 \)). Compared with the control group, the patients in the intervention group experienced a decreased duration of mechanical ventilation (120 versus 65 hours, \( P = .01 \)) and decreased nosocomial infection rate (17% versus 8%, \( P < .05 \)). This study met with criticism because of the lack of independent observer scoring in the intervention group, which may have confounded sedation assessment because of lack of blinding. Nevertheless, it does lend support to the notion that a more objective methodology in sedation assessment may lead to improved outcomes.

Despite recommendations from the SCCM and other expert reviews16,74–76 supporting the use of sedation scales and sedation algorithms, several studies suggest that this does not occur routinely in ICUs around the world. For example, a recent, large observational study in 44 French ICUs that had adopted sedation scales found only 43% patients on day 2 and 31% on day 6 had their level of sedation evaluated by a standardized assessment tool. Of the patients who were assessed, 57% on day 2 and 41% on day 6 were found to be deeply sedated.77 In a recent cross-sectional survey of Canadian critical care physicians, only 49% of respondents used a sedation scoring system as part of routine patient assessment.37

**PROTOCOLIZED SEDATION STRATEGIES**

Patient-targeted sedation protocols provide a structured approach to the assessment of patient pain and distress, combined with an algorithm that directs drug escalation and de-escalation based on assessments. In a randomized, controlled trial of 321 patients receiving mechanical ventilation, Brook and colleagues78 found that the use of protocol-directed sedation decreased the duration of mechanical ventilation, as well as hospital length of stay, compared with nonprotocol-directed sedation. In patients assigned to receive protocol-directed sedation, nurses were allowed to determine type of sedation used (sedatives, analgesics, or both), type of administration (intermittent or continuous), and dosages to target an “ideal level” of sedation (Ramsay score of 3: patient awake—responds to commands only). In contrast, patients in the nonprotocol-directed arm of the study had their sedation managed by treating physicians only. Nurses in this control group were allowed to communicate their observations and opinions to the treating physicians, but were not allowed to make changes without a physician order. De Jonghe and colleagues79 recently paired “Adaptation to the ICU Environment” (ATICE) assessments with a sedation protocol leading to a decreased time to arousal and decreased duration of mechanical ventilation. In addition to reducing duration of mechanical ventilation, nurse-implemented sedation protocols have also been shown to reduce the incidence of ventilator-associated pneumonia.80 But even when protocols have been designed and put in place at an institution, they may not be optimally used. In a study by Marshall and others,81 daily pharmacist-enforced intervention aimed at improving sedation guideline adherence resulted in further decreases in mechanical ventilation and ICU length of stay.

There have been some exceptions to the improvements seen with sedation protocols. In a study by Bucknall and colleagues,82 protocol-directed sedation management did not change outcomes compared with usual local practice in an Australian ICU, where nurses are usually free to assess level of sedation, titrate sedative and analgesic medications, and stop sedation if the patient was deemed to be oversedated. Reasons for a lack of difference between the two groups may have been lack of blinding, and the significant increase in propofol prescribing in the control arm, which itself has been associated with decreased duration of mechanical ventilation.

**DAILY INTERRUPTION OF SEDATION**

Daily interruption of sedative infusion (DIS) allows a focused downward titration of sedative drugs over time, thus minimizing the tendency for drug accumulation to allow early patient awakening. Analgesic and sedative medications are interrupted once daily until the patient awakens to follow commands or exhibits distress that requires drug resumption. With drug interruption, the ICU team must be vigilant for the development of patient distress manifested by overt agitation, hemodynamic instability, or ventilator asynchrony. If excessive agitation is noted, providers should administer drugs as a bolus to de-escalate symptoms, and resume the sedatives and analgesics at half the previous doses. Further titration can then be performed to achieve the desired level of sedation. Alternatively, patients who awaken and are not agitated should have their sedatives restarted only as needed, thereby allowing them to spend some of their ICU time awake and interactive.

When mechanically ventilated patients undergoing DIS were compared with a control group where care was directed by the primary ICU team, the
mean duration of mechanical ventilation was 4.9 days, compared with 7.3 days in the control group for whom drug infusions were only interrupted at the discretion of the ICU clinicians (P = .004)19 (Fig. 1). The median length of stay in the ICU was 6.4 days in the intervention group versus 9.9 days in the control group (P = .02), and patients in the DIS intervention spent more days awake and following commands (85.5% versus 9.0%, P < .001). Complications as a result of undersedation (eg, patient removal of endotracheal tube) were not different between groups.

This study met with criticism because of its single-center application and concerns for unrecognized patient harm such as psychologic distress, myocardial ischemia, and the risk of precipitating dangerous drug and alcohol withdrawal syndromes as a result of daily interruption of sedation.83 Subsequent investigations into the long-term effects of DIS have shown no adverse psychologic outcomes, a reduction in PTSD symptoms after approximately 1 year, and a trend toward reductions in the incidence of PTSD.10 In a subsequent cohort study of 74 mechanically ventilated patients undergoing DIS with coronary risk factors, sedative interruption was not associated with increased risk for ischemia determined by continuous three-lead Holter monitoring.84 A recent trial by de Wit and colleagues85 noted that a nursing-directed sedation protocol resulted in better outcomes than DIS. This study was hindered by early cessation. There was the suggestion that certain groups of patients, such as those with substance abuse histories, should have sedation strategies such as DIS undertaken with extreme caution. Further investigation into the safety of DIS in patients with alcohol and other drug use disorders is needed.

A recent multicenter, randomized trial assessed a protocol pairing spontaneous awakening trials (SATs), ie, daily interruption of sedatives, with spontaneous breathing trials (SBTs).86 Patients in the intervention group (n = 168) underwent awakening with SAT before SBT, whereas patients in the control arm (n = 168) received patient-targeted sedation using a validated sedation scale and SBTs alone. Patients in the intervention group had more ventilator-free days during the 28-day study period (14.7 versus 11.6 days, P = .02), spent fewer days in the ICU (median time 9.1 days versus 12.9 days, P = .01), and were discharged from the hospital earlier (hospitalized 14.9 days versus 19.2 days, P = .04). There were more self-extubations in the intervention group compared with controls (16 patients versus 6 patients, P = .03), but the reintubation rates for both groups were similar. Last, patients in the intervention group were less likely to die than were patients in the control group (hazard ratio 0.68, 95% confidence interval [CI] 0.50 to 0.92,

Fig. 1. Duration of mechanical ventilation: DIS versus control. Shown is a Kaplan-Meier analysis of the duration of mechanical ventilation, according to study group: an intervention group, in which sedative infusions were interrupted on a daily basis (DIS) until the patients were awake; and a control group, in which the infusions were interrupted only at the discretion of the clinicians in the intensive care unit. After adjustment for baseline variables (age, sex, weight, Acute Physiology and Chronic Health Evaluation II score, and type of respiratory failure), mechanical ventilation was discontinued earlier in the intervention group than in the control group (relative risk for extubation = 1.9, 95% CI 1.3 to 2.7; P < .001). (From Kress JP, Pohlman AS, O’Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med 2000;342(20):1471–7; with permission. Copyright © 2000, Massachusetts Medical Society.)

Fig. 2. Survival at 1 year. Events indicate the number of deaths in each group in the year after enrollment. (From Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomized controlled trial. Lancet 2008;371(9607):126–34; with permission.)
$P = .01$ (Fig. 2). For every seven patients treated with both SATs and SBTs, one life was saved (number needed to treat 7.4, 95% CI 4.2 to 35.5).

**SUMMARY**

Providing adequate sedation and analgesia to mechanically ventilated patients while avoiding the hazards of oversedation is challenging. Careful drug selection and frequent evaluation of the adequacy of sedation and analgesia can help minimize the risks of oversedation. Sedation scales, sedation protocols, and daily interruption of sedative can help minimize unwanted sedative effects, minimize the duration of mechanical ventilation, and may reduce ICU mortality. Further studies are warranted to determine how best to combine these tools as part of an overall sedation strategy, and new medications are being investigated that may also help minimize oversedation.

**REFERENCES**

27. Pasternak GW, Bodnar RJ, Clark JA, et al. Morphine-
6-glucuronide, a potent mu agonist. Life Sci 1987; 
29. Gehlbach BK, Kress JP. Sedation in the intensive care 
30. Westmoreland CL, Hoke JF, Sebel PS, et al. Pharma-
cokinetics of remifentanil (GI87084B) and its major 
metabolite (GR90291) in patients undergoing elec-
versus fentanyl for analgesia based sedation to 
provide patient comfort in the intensive care unit: a 
randomized, double-blind controlled trial. Crit 
Care 2004;8(1):R1–11.
32. Dahaba AA, Grabner T, Rehak PH, et al. Remifentanyl 
versus morphine analgesia and sedation for 
mechanically ventilated critically ill patients: a 
randomized double blind study. Anesthesiology 
33. Pitsiu M, Wilmer A, Bodenheim A, et al. Pharmacoki-
netics of remifentanil and its major metabolite, remi-
fentanil acid, in ICU patients with renal impairment. 
pharmacodynamic effects and safety of remifentanil 
in intensive care unit patients with various degrees 
35. Rhoney DH, Murry KR. National survey of the use of 
sedating drugs, neuromuscular blocking agents and 
reversal agents in the intensive care unit. J Intensive 
Care Med 2003;18(3):139–45.
36. Martin J, Franck M, Sigel S, et al. Changes in seda-
tion management in German intensive care units 
37. Mehta S, Burry L, Fischer S, et al. Canadian survey of 
the use of sedatives, analgesics, and neuromus-
cular blocking agents in critically ill patients. Crit 
38. George KA, Dundee JW. Relative amnesiac actions 
of diazepam, flunitrazepam and lorazepam in man. 
39. Gammer D, Bakker J. Medications for analgesia and 
sedation in the intensive care unit: an overview. Crit 
40. Byatt CM, Lewis LD, Dawling S, et al. Accumulation of 
midazolam after repeated dosage in patients receiving 
mechanical ventilation in an intensive care unit. BMJ 
1984;289(6448):799–800.
41. Tayar J, Jabbour G, Saggi SJ. Severe hyperosmolar 
metabolic acidosis due to large dose of intravenous 
42. Barr J, Zomorodi K, Bertaccini EJ, et al. A double-
blind, randomized comparison of i.v. lorazepam 
versus midazolam for sedation of ICU patients via 
a pharmacologic model. Anesthesiology 2001; 
95(2):324–33.
43. James R, Glen JB. Synthesis, biological evaluation 
and preliminary structure-activity considerations of 
a series of alkylphenols as intravenous anaesthetic 
44. Mirenda J, Broyles G. Propofol as used for sedation 
45. Kress JP, O’Connor MF, Pohlman AS, et al. Seda-
tion of critically ill patients during mechanical ven-
tilation: a comparison of propofol and midazolam. 
46. Marik PE, Varon J. The management of status epilepticus. 
47. Devlin JW, Lau AK, Tanios MA. Propofol-associated 
hypertriglyceridemia and pancreatitis in the inten-
sive care unit: an analysis of frequency and risk 
with a shorter duration of mechanical ventilation than 
scheduled intermittent lorazepam: a database anal-
ysis using Project IMPACT. Ann Pharmacother 2007; 
ized trial of intermittent lorazepam versus propofol 
with daily interruption in mechanically ventilated 
51. Cox CE, Reed SD, Govert JA, et al. Economic eval-
uation of propofol and lorazepam for critically ill pa-
tients undergoing mechanical ventilation. Crit Care 
52. Barrientos-Vega R, Mar Sánchez-Soria M, Morales-
García C, et al. Prolonged sedation of critically ill pa-
tients with midazolam or propofol: impact on wean-
midazolam for ICU sedation: a Canadian multicenter 
54. Glassman AH, Bigger JT Jr. Antipsychotic drugs: 
prolonged QTc interval, torsade de pointes, and sudden 
1774–82.
55. Lawrence KR, Nasraway SA. Conduction distur-
bances associated with administration of butyrophen-
one antipsychotics in the critically ill: a review of the 
versus fentanyl for analgesia based sedation to 
provide patient comfort in the intensive care unit. 


