Sedation in the intensive care unit

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Although the administration of sedatives is a commonplace activity in the ICU, few guidelines are available to aid the clinician in this practice. The first principle of sedative administration is to define the specific problem requiring sedation and to rationally choose the drug and depth of sedation appropriate for the indication. Next, the clinician must recognize the diverse and often unpredictable effects of critical illness on drug pharmacokinetics and pharmacodynamics. Failure to recognize these effects may lead initially to inadequate sedation and subsequently to drug accumulation. Drug accumulation may result in prolonged encephalopathy and mechanical ventilation and may mask the development of neurologic or intra-abdominal complications. Daily interruption of continuous sedative infusions is a simple and effective way of addressing this problem. A glossary of sedative drugs commonly used in the ICU is included in this review. Curr Opin Crit Care 2002, 8:290–298

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Critically ill patients requiring mechanical ventilatory support are frequently treated with sedatives and analgesics. The approach to sedation of these patients varies widely, partially because of institutional bias and partially because requirements for sedation can vary greatly from patient to patient. The principles and goals of sedation in the ICU will be discussed, and the drugs currently available to achieve these goals will be reviewed.

Indications for sedation

Analgesia

Pain is a common experience in critically ill patients [1] and often originates from sources such as surgical incisions, vascular catheter placement, and endotracheal suctioning. In addition to suffering, adverse effects of pain in critically ill patients may include increased endogenous catecholamine activity, myocardial ischemia, induction of hypermetabolic states, and anxiety. There is some evidence that inadequate analgesia may be associated with adverse outcomes [2]. Achieving adequate analgesia is the first priority when administering sedation in the ICU [3••].

Anxiety

Anxiety and agitation may arise from innumerable psychologic and physical sources and may be more commonly recognized than pain. Anxiety that is difficult to remedy may be a result of inadequately treated pain.

Dyspnea

The subjective sense of dyspnea is common in ICU patients and may be a source of severe anxiety and distress. Likewise, coughing is common in intubated ICU patients, particularly during endotracheal suctioning. Excessive coughing may contribute to patient–ventilator dyssynchrony. Dyspnea may be exacerbated by the use of lung-protective strategies that result in hypercapnia.

Delirium

Potential causes of delirium include drugs, sepsis, sleep deprivation, electrolyte disturbances, hepatic encephalopathy, withdrawal syndromes, and many others. Ely *et al.* [4•] have recently reported the incidence of delirium to be extremely high in critically ill patients.

To facilitate care

Sedatives are often used to facilitate the delivery of nursing care (dressing wounds, administering baths, and so forth), to prevent adverse events such as self-extubation, and to ensure synchrony with mechanical ventilation.

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To decrease excess oxygen consumption

Sedatives are commonly used to decrease the volume of oxygen utilization associated with analgesia, anxiety, dyspnea, and delirium. Minimizing the volume of oxygen utilization is particularly important in patients with acute hypoxemic respiratory failure and shock.

To achieve amnesia

Although this seems intuitively desirable for critically ill patients, data supporting this notion are lacking. Rather, there are reports of adverse psychological sequelae in patients unable to recall factual memories from their illness [5,6•]. The only circumstance in which amnesia is mandatory is when neuromuscular blocking agents are being administered.

Properties of the ideal sedative

The ideal sedative would have a rapid onset of action with rapid recovery so that a thorough physical examination and communication with the patient could occur. It would lack the problem of drug accumulation and would be easy to titrate to varying levels of sedation. It would exhibit no tachyphylaxis or withdrawal symptoms, cause no hemodynamic instability, and would be inexpensive. It is clear that no single drug has all of these properties, and that combinations of drugs are essential to meet these objectives [7]. Using a drug to attain a goal for which that drug is not particularly well suited often results in rapidly escalating doses of the drug with suboptimal effect (*eg*, the use of propofol, which has no analgesic properties, to sedate patients with pain). These unnecessarily high doses may lead to unwanted side effects. The use of different classes of drugs in a synergistic fashion to achieve each of the goals of sedation leads to lower doses of each individual drug and better sedation for the patient.

Dosing regimens

Drugs can be administered by either intermittent bolus dosing or continuous infusion. Bolus dosing may result in periods of oversedation and undersedation and may increase demands on nursing time. This may distract nursing attention away from other areas of patient care. Conceivably, continuous infusion may result in a more consistent level of sedation, but this approach is more likely to result in drug accumulation, which may delay recovery.

Assessing the adequacy of sedation

Assessing the adequacy of sedation can be difficult because of its subjective nature. Several objective sedation scales such as the Ramsay Sedation Score (Table 1) [8], and the Sedation Agitation Scale (Table 2) [9•] have been developed. The Ramsay scoring system has the benefit of simplicity but does not effectively measure quality or degree of sedation with regard to the goals outlined previously [10] and has never been objectively validated [11]. Recently, sedation scales designed specifically for use in critically ill patients have been reported and validated [9•,12].

Table 1. Ramsay Sedation Score levels

1	Patient anxious and agitated or restless or both
2	Patient cooperative, oriented, and tranquil
3	Patient responds to commands only
4	Patient asleep, shows brisk response to light glabellar tap or loud auditory stimulus
5	Patient asleep, shows sluggish response to light glabellar tap or loud auditory stimulus
6	Patient asleep, shows no response to light glabellar tap or loud auditory stimulus

Assessment of the adequacy of sedation is an individual bedside maneuver. The nurse's input is helpful, because he or she will often notice changes from an optimal level of sedation. Ideally, the clinician is able to achieve the goal for each indication for sedation, yet leave the patient fully communicative with bedside caregivers. This state of being fully awake yet adequately sedated can be attained in some patients. Others, however, must be sedated to a point where constant communication is not possible. We have previously reported a set of endpoints for assessing recovery from sedation. Asking the patient to (1) open eyes to verbal command, (2) follow the bedside observer with eyes, (3) hand grasp on command, and (4) stick out tongue on command was found to be simple, quick, objective, and reproducible between blinded and unblinded observers [13]. Recently, the bispectral index, a processed electroencephalography signal that reports a discreet scaled number, has been evaluated in the ICU setting. This device has been studied extensively in the operating room and has been found to reliably detect a patient's level of consciousness under general anesthesia. Although preliminary data suggest a good correlation between the bispectral index and the Sedation Agitation Scale [14], this instrument awaits more extensive validation in the ICU setting [1].

Complications related to sedative administration

The sedation of critically ill patients would be optimized if the pharmacokinetic and pharmacodynamic profiles of

Table 2. Sedation Agitation Scale

7	Dangerous agitation: pulling at endotracheal tube, trying to remove catheters, climbing over bed rail, striking at staff, thrashing side to side
6	Very agitated: does not calm, despite frequent reminding of limits; requires physical restraints, biting endotracheal tube
5	Agitated: anxious to mildly agitated, attempting to sit up, calms 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 dos not communicate or follow commands, may move spontaneously
1	Unarousable: minimal or no response to noxious stimuli, does not communicate or follow commands

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sedatives in such patients were well understood and described. Unfortunately, critically ill patients frequently exhibit unpredictable alterations in pharmacokinetic and pharmacodynamic profiles [15–17]. Drug–drug interactions, renal and hepatic dysfunction, altered protein binding, impaired gastrointestinal absorption, and circulatory instability are some of the variables leading to this unpredictability. Further unpredictability arises from the multicompartmental pharmacokinetics exhibited by many of the sedatives used in the ICU. This concept refers to the variable pharmacokinetics of drugs that undergo uptake by the peripheral tissues. For example, a lipophilic drug such as midazolam may have a short duration of action when administered by bolus, because the peripheral tissues rapidly remove the drug from the circulation. When administered continuously for a prolonged period, however, there is a tendency for drug accumulation in the peripheral compartment. Duration of action may then be prolonged, as the drug redistributes from the peripheral tissues back into the blood. As a result of these complexities, the extrapolation of experiences with these agents as used in the operating room or outpatient procedure area may result in serious errors and complications. Although drug accumulation may not occur with newer agents such as remifentanil, which is degraded rapidly by blood and tissue esterases, greater experience with these agents in the ICU is required before they can be recommended for use in this setting.

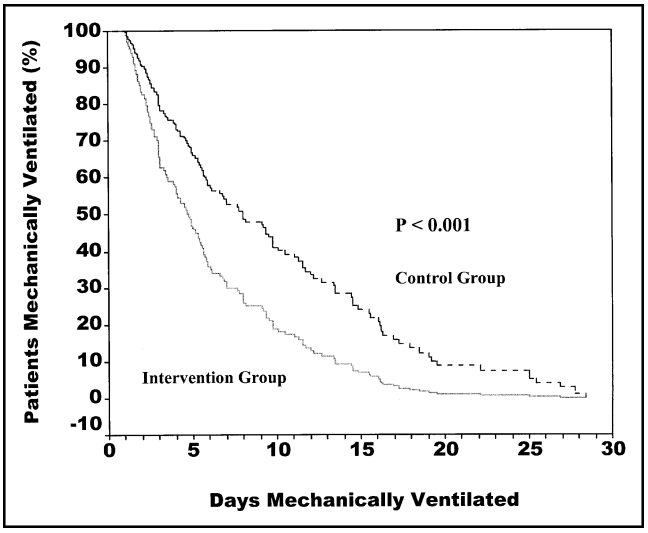
Patients with respiratory failure may require doses of sedatives that are much greater than those quoted in the literature and recommended by the drug manufacturer [18,19]. Respiratory failure itself may result in severe dyspnea and anxiety. Furthermore, contemporary approaches to the treatment of such patients, including permissive hypercapnia [20], low tidal volume ventilation [21], pressure-controlled ventilation, and prone positioning, are also inherently uncomfortable. For many of these patients, deep sedation, which leaves the patient poorly responsive if at all (*eg*, Ramsay score 5–6, Sedation Agitation Scale score 1–2), is necessary, and pharmacologic paralysis is sometimes required [22]. Attempting to minimize the amount of sedative initially administered often results in severe anxiety and agitation with acute cardiopulmonary instability, typically manifesting as extreme hypertension, tachycardia, tachypnea, ventilator dyssynchrony, hypoxemia, and even unplanned extubations [23]. As a result, deep sedation—at least initially—may be the only practical option for managing such patients.

Deep sedation may result in the accumulation of sedatives when they are administered by continuous infusions and/or for extended time periods [24]. Interestingly, most of the sedatives that are currently used in the ICU were originally reported to have a short duration of action, with rapid recovery of consciousness once stopped [25,26]. Unfortunately, this has not been the experience in critically ill patients [27–31]. Thus, clinicians caring for critically ill patients face a daily conflict between providing the deep level of sedation required for very sick patients and preventing the seemingly inevitable drug accumulation that accompanies such a level of sedation. Such drug accumulation as occurs with continuous sedative infusions may result in prolongation of mechanical ventilation and ICU length of stay [32•,33••].

Another complication of deep sedation is its ability to mask the development of intracranial, intrathoracic, or intra-abdominal catastrophes. It is important to be able to quickly and reliably awaken patients from sedation in order to perform daily assessments, including physical examination. Such assessments may detect complications early and thereby obviate the need to perform urgent imaging studies after a problem has advanced. We believe that mechanically ventilated patients receiving continuous sedative infusions should undergo a daily interruption of sedatives to allow patient communication and physical examination to take place. Exceptions to this recommendation are rare, but certainly include patients requiring muscle paralysis who should never be awakened from sedation until the paralytic agent has worn off. Besides allowing a thorough physical examination to occur, the "wake-up" period is also a time when the depth of sedation can be evaluated and adjusted to individual patient needs. After the wake-up test, it often becomes apparent that the depth of sedation can be decreased without compromising the specific goals of sedation.

We recently described how a strategy of daily interruption of continuous sedative infusions can reduce complications of sedation in critically ill patients receiving mechanical ventilation [33••]. We evaluated patients who received either midazolam and morphine or propofol and morphine by continuous infusion. Patients were randomized to a daily scheduled interruption of the sedative infusion or management of the sedative infusions by the primary ICU team without a mandatory daily interruption. After the wake-up assessment, patients in the interruption group had their sedative infusions restarted at half the previous dose. Daily discontinuation of sedative infusions reduced the duration of mechanical ventilation (Fig. 1) and intensive care (Fig. 2) by 2.5 days and 3.5 days, respectively. The number of diagnostic studies to investigate unexplained alterations in mental status was reduced from 27% to 9%, and the total amount of midazolam and morphine administered was decreased. This strategy allowed a focused downward titration of sedative infusion rates over time, streamlining administration of these drugs and minimizing the tendency for accumulation.

Figure 1. Kaplan-Meier analysis of the duration of mechanical ventilation in the intervention and control groups



After adjustment for baseline variables (age, sex, weight, APACHE II score, and type of respiratory failure), mechanical ventilation was discontinued more quickly in the intervention group compared with the control group (relative risk of extubation, 1.9; 95% CI, 1.3–2.7; $P < 0.001$).

Brook *et al.* [34] examined an alternative approach to the problems caused by deep sedation. In this study, the effect of a nurse-implemented sedation protocol on the duration of mechanical ventilation was analyzed by randomly assigning patients to either the protocol intervention or to a control group. Patients randomly selected to receive the sedation protocol had a significantly shorter duration of mechanical ventilation regardless of whether the sedatives were given continuously or intermittently. Taken together, our study [33••] and that of Brook *et al.* [34] suggest that a reduction in the duration of mechanical ventilation may be achieved through the use of sedation protocols that reassess the optimal dose of sedatives required for the patient on a daily basis. The effective sedation protocol also uses sedatives to their best advantage pharmacologically. For example, diazepam, with its active metabolites and tendency to accumulate in peripheral tissues, is a poor choice for administration by continuous infusion. The sedative propofol, however, has a short duration of clinical effect when discontinued, which makes it an ideal choice for continuous infusion when rapid emergence is desired.

Finally, patients receiving prolonged infusions of sedatives may experience withdrawal symptoms. Katz *et al.* [35] noted a high incidence of withdrawal in infants receiving fentanyl in high doses or for prolonged time periods. Similar findings have been reported in children sedated with midazolam [36]. Cammarano *et al.* [37] found a 32% incidence of withdrawal in adults receiving opioid and benzodiazepine infusions. This tended to be associated with higher doses of drugs and more rapid weaning off of drugs. Patients in these studies did not undergo daily interruption of sedative infusions.

Drugs for sedation of mechanically ventilated patients

Opioids

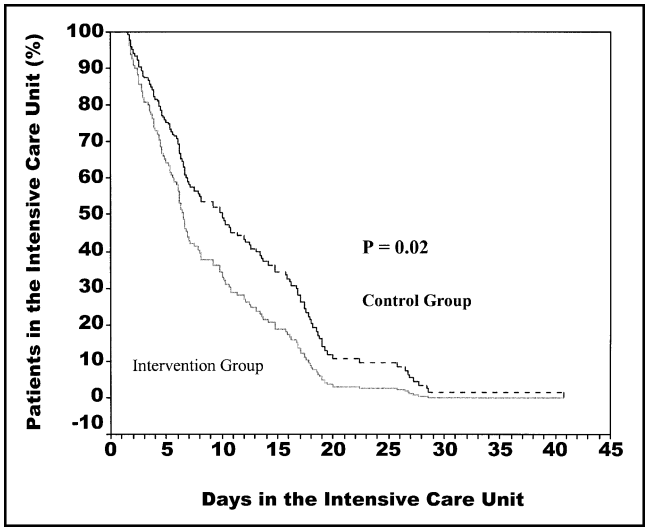
Opioids are endogenous or exogenous substances that bind to receptors found in the central nervous system and peripheral tissue. There are several classes of receptors, but the two most clinically important are μ and κ. The μ receptors have two subtypes, μ-1 and μ-2. μ-1 receptors are responsible for analgesia, whereas μ-2 receptors mediate respiratory depression, nausea, vomiting, constipation, and euphoria. The κ receptors are responsible for such effects as sedation, miosis, and spinal analgesia.

Pharmacokinetics

The following discussion applies to those intravenous opioids most commonly used in the ICU.

Morphine Morphine's onset of action is relatively slow (5–10 min) because of low lipid solubility. The duration of action is dose dependent but is approximately 4 hours after a single dose of 5 to 10 mg. Morphine undergoes conjugation to a glucuronide in the liver and has an active metabolite, morphine-6-glucuronide. Elimination occurs in the kidney, so effects may be prolonged in renal failure. As with benzodiazepines, prolonged sedation can be attenuated by daily interruption of continuous infusions and by decreasing the rate of the infusions as clinically indicated.

Figure 2. Kaplan-Meier analysis of the intensive care unit length of stay



After adjustment for baseline variables (age, sex, weight, APACHE II score, and type of respiratory failure), ICU discharge occurred sooner in the intervention group compared with the control group (relative risk of ICU discharge, 1.6; 95% CI, 1.1–2.3; $P = 0.02$).

Meperidine (pethidine) Relative to morphine, meperidine has a more rapid onset of action (3–5 min) because of greater lipid solubility. Because of redistribution to peripheral tissues, the duration of action is less than that of morphine (1–4 h). Meperidine undergoes hepatic metabolism and renal elimination. Normeperidine, a prominent metabolite, is a central nervous system stimulant that can precipitate seizures, especially in the setting of renal failure. Meperidine offers no real advantage over morphine and should probably not be used for analgesia in the ICU because of potential central nervous system toxicity.

Fentanyl Fentanyl exhibits very rapid onset of action (1 min) because of high lipid solubility, but the duration of action after a single dose is short (0.5–1 h) because of redistribution into peripheral tissues. Inactive products of hepatic metabolism are excreted by the kidney. Once again, the kinetics are altered with prolonged administration because of redistribution to peripheral tissues. When the infusion is stopped, the drug leaves peripheral tissues and re-enters the plasma where it can have a prolonged effect.

Hydromorphone The onset of action of hydromorphone is similar to that of morphine. Likewise, the duration of action is similar to that of morphine when given as a single dose. However, the absence of an active metabolite makes the duration of effect typically shorter than morphine when administered for extended time periods.

Pharmacodynamics

The opioids have similar effects and will be discussed without reference to individual drugs except in cases in which important differences are present.

Central nervous system The primary effect of opioids is analgesia, which is mediated primarily through the μ and κ receptors. Mild to moderate anxiolysis is also common, although less so with benzodiazepines. Opioids have no reliable amnestic properties.

Respiratory system Opioids lead to a dose-dependent, centrally mediated respiratory depression, which may be profound. This effect is mediated by the μ-2 receptors in the medulla. The initial pattern of respiratory depression is a decrease in respiratory rate with a preserved tidal volume. The carbon dioxide response curve is shifted to the right, and the ventilatory response to hypoxia is obliterated. Opioids are the best drugs to attenuate the subjective sense of dyspnea that is common in many critically ill patients.

Cardiovascular system Opioids, like benzodiazepines, have little hemodynamic effect on patients with euvolemia whose blood pressure is not sustained by the sympathetic nervous system. When opioids and benzodiazepines are administered concomitantly, they may exhibit a synergistic effect on hemodynamics. The reasons for this synergy are not entirely clear. Meperidine has a chemical structure similar to that of atropine and may elicit tachycardia. All other opioids usually decrease heart rate by decreasing sympathetic activity. Morphine and meperidine may cause histamine release, but this effect is usually not a factor with the doses typically administered in the ICU. Fentanyl does not cause histamine release [38].

Other effects Opiate side effects include nausea, vomiting, and decreased gastrointestinal motility. Methylnaltrexone, a specific antagonist of μ-2 receptors in the gut, has been recently reported to attenuate these side effects in humans [39]. The utility of methylnaltrexone in the ICU has not been tested. Other side effects include urinary retention and pruritus.

Benzodiazepines

Benzodiazepines are the most commonly used agents to sedate mechanically ventilated patients [40]. They act by potentiating gamma amino-butyric acid receptor complex–mediated inhibition of the central nervous system. The gamma amino-butyric acid receptor complex regulates a chloride channel on the cell membrane, and, by increasing the intracellular flow of chloride ions, neurons become hyperpolarized, with a higher threshold for excitability. Flumazenil is a synthetic antagonist of the benzodiazepine receptor that may reverse many of the clinical effects of benzodiazepines.

Pharmacokinetics

The following discussion applies to intravenous benzodiazepines because they are most commonly delivered by that route in the ICU.

Midazolam The onset of action of midazolam is rapid (0.5–5 min) and the duration of action following a single dose is short (2 h). All benzodiazepines are lipid soluble and are therefore widely distributed throughout body tissues (large volume of distribution). For all benzodiazepines, the duration of action after a single bolus is dependent primarily on the rate of redistribution to peripheral tissues, where the drugs have no effect. Midazolam undergoes hepatic metabolism and renal excretion. 1-hydroxy midazolam is an active metabolite but has a half-life of only 1 hour in the presence of normal renal function.

The kinetics of midazolam change considerably when it is administered by continuous infusion to critically ill patients. After continuous infusion for extended time periods (>1 d), this lipid-soluble drug accumulates in peripheral tissues as well as in the blood stream rather than being metabolized. When the drug is stopped, peripheral tissue stores release midazolam back into the

plasma, and the duration of clinical effect can be prolonged (clinical recovery may take hours to days) [30]. Obese patients with larger volumes of distribution and elderly patients with decreased hepatic and renal function may be even more prone to prolonged sedation.

As noted previously, this problem can be attenuated by daily sedative interruption with decreases in the infusion rates as clinically indicated. This daily recovery period tends to decrease the amount of drug redistributed to the peripheral tissues over time.

Lorazepam

Intravenous lorazepam has a slightly slower onset of action (5 min) than midazolam because of its lower lipid solubility, which increases the time required to cross the blood–brain barrier. The duration of action after a single dose is long (6–10 h) and is proportional to the dose given; however, most pharmacokinetic studies are conducted in healthy volunteers and may not apply to critically ill patients. A single dose of lorazepam will often be insufficient to keep mechanically ventilated patients adequately sedated for 6 hours. The longer duration of action of lorazepam is a result of lower lipid solubility with decreased peripheral tissue redistribution. The use of lorazepam in high doses has been associated with lactic acidosis from propylene glycol toxicity [41].

Diazepam

The onset of action of intravenous diazepam is short (1–3 min). The duration of action after a single dose is also short (30–60 min) because of high lipid solubility and peripheral redistribution. Diazepam is rarely administered by continuous infusion because it has a long termination half-life. Once the peripheral tissue compartment is saturated, recovery can take several days. Therefore, intermittent bolus dosing is the best method of diazepam administration. Even with this dosing method, peripheral tissue stores can accumulate, leading to prolonged effect. In addition, diazepam has several active metabolites that also have prolonged half-lives. The metabolism of diazepam is dependent on hepatic function and is prolonged in liver disease and in the elderly.

Pharmacodynamics

The benzodiazepines have similar effects and will be discussed without reference to individual drugs except in cases in which important differences are present.

Central nervous system All benzodiazepines cause a dose-dependent suppression of awareness along a spectrum from mild depression of responsiveness to obtundation. They are potent amnestic agents [42,43]; lorazepam appears to produce the longest duration of antegrade amnesia. All are potent anxiolytic agents, which is one of the reasons why they are frequently used in the ICU. If given in higher doses, they can induce hypnosis. A paradoxical state of agitation that worsens with escalating doses may occasionally occur, especially in elderly patients. Finally, all benzodiazepines are noted to have potent anticonvulsant properties [44].

Respiratory system Benzodiazepines cause a dose-dependent, centrally mediated respiratory depression. This ventilatory depression is less profound than that seen with opioids; however, it may be synergistic with opioid-induced respiratory depression. In contrast to opioids (as described previously), the respiratory pattern of a patient receiving benzodiazepines is characterized by a decrease in tidal volume and an increase in respiratory rate. Even low doses of benzodiazepines can obliterate the ventilatory response to hypoxia.

Cardiovascular system Benzodiazepines have minimal effects on the cardiovascular system in patients with euvolemia. They may cause a slight decrease in blood pressure without a significant change in heart rate. Clinically important hypotensive responses are usually only seen in patients who are hypovolemic and/or in those with increased endogenous sympathetic activity.

Propofol

Propofol is an alkylphenol intravenous anesthetic. Its exact mechanism of action is unclear, but it is thought to act at the gamma amino-butyric acid receptor. It is an oil at room temperature and is prepared as a lipid emulsion.

Pharmacokinetics

Propofol is highly lipid soluble and rapidly crosses the blood–brain barrier. Onset of sedation is rapid (1–5 min) and is dependent on whether a loading dose is given. The duration of action is dose dependent but is usually very short (2–8 min) because of rapid redistribution to peripheral tissues [45,46]. When continuous infusions are used, the duration of action may be increased, but it is rare for the effect to last longer than 60 minutes after the infusion is stopped. The drug is metabolized mainly in the liver, with an elimination half-life of 4 to 7 hours; again, the elimination half-life may be somewhat longer with prolonged infusions. There are no active metabolites. Because of its high lipid solubility and large volume of distribution, propofol can be given for prolonged periods without significant changes in its pharmacokinetic profile. The termination of its clinical effect is dependent solely on redistribution to peripheral fat tissue stores. When the infusion is discontinued, the fat tissue stores redistribute the drug back into the plasma but usually not to clinically significant levels.

Pharmacodynamics

Central nervous system Propofol is a hypnotic agent that, like benzodiazepines, provides a dose-dependent suppression of awareness from mild depression of respon-

siveness to obtundation. It is a potent anxiolytic as well as a potent amnestic agent [47]. The effect of propofol on seizure activity is controversial. Animal studies suggest that it is neither pro- nor anticonvulsant; however, there are case reports of propofol being used to treat seizures as well as being associated with seizure activity. Propofol has no analgesic properties and should be accompanied by a separate analgesic agent in most, if not all, patients.

Respiratory system Apnea often occurs after a loading dose of propofol (25% incidence). The carbon dioxide response curve is shifted to the right. The respiratory pattern is usually characterized by a decrease in tidal volume and an increase in respiratory rate.

Cardiovascular system Propofol can cause significant decreases in blood pressure, especially in hypovolemic patients. This is mainly a result of preload reduction from dilation of venous capacitance vessels. A lesser effect is mild myocardial depression [48,49]. Care must be taken when administering this drug to patients with marginal cardiac function; however, because myocardial oxygen consumption is decreased by propofol, and the myocardial oxygen supply–demand ratio is preserved, it may be useful in patients with ischemic heart disease.

Other effects Because it is delivered in a lipid carrier, hypertriglyceridemia is a possible side effect of propofol [50,51]. Triglyceride levels should be checked frequently, and the drug should be discontinued if levels reach 500 mg/dL. Lipid parenteral feedings should be adjusted according to the propofol infusion rate because there is a significant caloric load from propofol. Strict aseptic technique and frequent changing of infusion tubing is essential to prevent iatrogenic transmission of bacteria and fungi because propofol can support their growth [52]. Lactic acidosis has been associated with propofol use in the pediatric population [53]. Recent reports of dysrhythmia, heart failure, metabolic acidosis, hyperkalemia, and rhabdomyolysis have been described in adults treated with high doses of propofol (>80 μg/kg/min) [54•].

Butyrophenones (haloperidol and droperidol)

Butyrophenones such as haloperidol and droperidol are sometimes used in the ICU for sedation. These drugs result in a state of tranquility, and patients often demonstrate a detached affect. The exact site of action of these drugs is not known, but they appear to antagonize dopamine, especially in the basal ganglia.

Pharmacokinetics

Haloperidol After an intravenous dose of 1 to 10 mg of haloperidol, onset of sedation usually occurs after 2 to 5 minutes. The half-life is approximately 2 hours, but it is dose dependent. Dose requirements vary widely, starting at 1 to 10 mg and titrating to effect. Large doses (>100 mg) may sometimes be required. Haloperidol undergoes hepatic metabolism.

Droperidol The onset of action of droperidol is usually 2 to 5 minutes, with a typical starting dose of 0.625 to 2.5 mg. Half-life is approximately 2 hours, but it is longer when higher doses are used. Droperidol, like haloperidol, is metabolized in the liver.

Pharmacodynamics

Central nervous system Both haloperidol and droperidol produce central nervous system depression in patients who are agitated, resulting in a calm, often detached appearance. Patients demonstrate mental and psychiatric indifference to the environment [55]. Patients may also demonstrate a state of cataleptic immobility. There is no demonstrable amnesia with these drugs, and they have no effect on seizure activity. Analgesic effects are minimal with haloperidol; however, droperidol seems to have a significant potentiating analgesic effect when administered concomitantly with an opiate. The butyrophenones are the drugs of choice for patients thought to be demonstrating psychotic behavior or agitation resistant to other pharmacologic interventions.

Respiratory system Neither haloperidol nor droperidol have any significant effect on the respiratory system when used alone. There are reports of attenuation of respiratory depression in the presence of opioids, but this effect is mild. Droperidol has been shown to maintain the hypoxic pulmonary drive [56].

Cardiovascular system Haloperidol and droperidol may result in mild hypotension secondary to peripheral α-1 blocking effects. Haloperidol may also decrease the neurotransmitter function of dopamine and thereby lead to mild hypotension. Haloperidol may prolong the QT interval and has been reported to result in *torsade de pointes* [57]. This complication is rare.

Other effects Extrapyramidal effects are occasionally seen but are much less common with intravenous than with oral butyrophenones. When these complications occur, treatment with diphenhydramine or benztropine may be necessary. Neuroleptic malignant syndrome occurs rarely and is characterized by "lead pipe" muscle rigidity, fever, and mental status changes. The mechanism of neuroleptic malignant syndrome is controversial, but some investigators propose that central dopaminergic blockade leads to extrapyramidal side effects and muscle rigidity with excess heat generation. Bromocriptine, dantrolene, and pancuronium have all been used to successfully treat neuroleptic malignant syndrome [58]. Droperidol is a potent antiemetic and is sometimes used for nausea and vomiting associated with general anesthesia or chemotherapy.

Other drugs used for sedation in the intensive care unit

Dexmedetomidine

Dexmedetomidine [59,60,61•] is a selective α-2 agonist approved for short-term use (<24 h) in patients initially receiving mechanical ventilation. Although patients remain sedated when undisturbed, they arouse easily with stimulation. Dexmedetomidine has both analgesic and anxiolytic effects. Side effects include bradycardia and hypotension, especially with hypovolemia or high sympathetic tone. Further studies are needed to evaluate the role of dexmedetomidine in long-term sedation in the ICU.

Ketamine

Ketamine is a drug that is structurally related to phencyclidine, which results in a profound dissociative state. Patients may keep their eyes open and maintain a protective cough reflex but appear unaware of their surroundings. When administered slowly over a period of 60 seconds as recommended, there is minimal respiratory depression. There may be amnesia, but this is not a reliable property of the drug. Coordinated but seemingly purposeless movements are often seen. Administration of ketamine has been shown to result in profound analgesia. The common side effects of emergence delirium and severe hallucinations have limited its usefulness for sedation of adult patients in the ICU. Although ketamine administration is generally associated with increases in heart rate, cardiac output, and blood pressure, instances of hypotension, likely from direct myocardial depression, have been observed.

Barbiturates

Barbiturates such as thiopental and pentobarbital are potent agents that cause amnesia and unconsciousness. They have limited use in critically ill patients because they frequently lead to hemodynamic instability and accumulate in peripheral tissues after long-term infusions, leading to prolonged recovery from sedation.

Inhalational anesthetics

Inhalational anesthetics such as isoflurane have been studied in critically ill patients and have been shown to be safe and effective [62]. They have analgesic, amnestic, and hypnotic properties and may be useful as single agents to meet the criteria for sedation discussed previously. Isoflurane undergoes only 0.2% metabolism and is almost exclusively eliminated through the lungs. Technical problems delivering the drug safely through the ventilator at accurate concentrations and difficulty scavenging the exhaled gas have limited the use of inhalational anesthetics for sedation in the ICU in the United States.

Conclusions

Sedation is an important component of the treatment of mechanically ventilated, critically ill patients. There are currently a wide variety of pharmacologic agents available for the diverse needs of this heterogeneous group of patients. Directing treatment to specific and individualized goals will assure that patient needs are met. All currently available sedatives for use in the ICU have limitations. Rather than seeking an ideal drug, strategies of drug administration that focus attention on principles of sedative pharmacology in critical illness should be used.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • Of special interest
- •• Of outstanding interest

1 Puntillo KA: Pain experiences of intensive care unit patients. Heart Lung 1990, 19:526–533.

2 Anand KJ, Barton BA, McIntosh N, et al.: Analgesia and sedation in preterm neonates who require ventilatory support: results from the NOPAIN trial. Neonatal Outcome and Prolonged Analgesia in Neonates. Arch Pediatr Adolesc Med 1999, 153:331–338.

3 •• Jacobi J, Fraser GL, Coursin DB, et al.: Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. Crit Care Med 2002, 30:119–141.

This paper represents an important effort to provide evidence-based clinical practice guidelines for the use of sedatives and analgesics in the ICU.

4 • Ely EW, Inouye SK, Bernard GR, et al.: Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit [CAM-ICU]. JAMA 2001, 286:2703–2710.

This study validates an accurate and rapidly applicable method of identifying delirium in critically ill patients.

5 Griffiths RD, Jones C, MacMillan RR: Where is the harm in not knowing? Care after intensive care. Clin Intensive Care 1996, 7:144–145.

6 • Jones C, Griffiths RD, Humphris G, et al.: Memory, delusions, and the development of acute posttraumatic stress disorder-related symptoms after intensive care. Crit Care Med. 2001, 29:573–580.

This article suggests that the inability to recall factual memories from a period of critical illness may be associated with adverse psychological sequelae.

7 Stoltzfus DP: Advantages and disadvantages of combining sedative agents. Crit Care Clin 1995, 11:903–912.

8 Ramsey MAE, Savege TM, Simpson BRJ, et al.: Controlled sedation with alphalaxone-alphadolone. BMJ 1974, 2:256–259.

9 • Riker RR, Picard JT, Fraser GL: Prospective evaluation of the Sedation-Agitation Scale for adult critically ill patients. Crit Care Med 1999, 27:1325–1329.

This study validates a method of assessing adequacy of sedation designed specifically for use in critically ill patients.

10 Crippen DW: Neurologic monitoring in the intensive care unit. New Horiz 1994, 2:107–120.

11 Hansen-Flaschen J, Cowen J, Polomano RC: Beyond the Ramsay scale: need for a validated measure of sedating drug efficacy in the intensive care unit. Crit Care Med 1994, 22:732–733.

12 Sessler CN, Gosnell M, Grap MJ, et al.: A new agitation-sedation scale for critically ill patients: development and testing of validity and inter-rater reliability [abstract]. Am J Respir Crit Care Med 2000, 161:A506.

13 Kress JP, O'Connor MF, Pohlman AS, et al.: Sedation of critically ill patients during mechanical ventilation. A comparison of propofol and midazolam. Am J Respir Crit Care Med 1996, 153:1012–1018.

14 Simmons LE, Riker RR, Prato BS, et al.: Assessing sedation during intensive care unit mechanical ventilation with the Bispectral Index and the Sedation-Agitation Scale. Crit Care Med 1999, 27:1499–1504.

15 Bodenham A, Shelly MP, Park GR: The altered pharmacokinetics and pharmacodynamics of drugs commonly used in critically ill patients. Clin Pharmacokinet 1988, 14:347–373.

16 Wagner BKJ, O'Hara DA: Pharmacokinetics and pharmacodynamics of sedatives and analgesics in the treatment of agitated critically ill patients. Clin Pharmacokinet 1997, 33:426–453.

17 Bertz RJ, Granneman GR: Use of *in vitro* and *in vivo* data to estimate the likelihood of metabolic pharmacokinetic interactions. Clin Pharmacokinet 1997, 32:210–258.

18 Pohlman AS, Simpson K, Hall J: Continuous intravenous infusions of lorazepam versus midazolam for sedation during mechanical ventilatory support: a prospective, randomized study. Crit Care Med 1994, 22:1241–1247.

19 Oldenhof H, de Jong, M, Steenhoek A, et al.: Clinical pharmacokinetics of midazolam in intensive care patients, a wide interpatient variability? Clin Pharmacol Ther 1988, 43:263–269.

20 Tuxen DV, Williams T, Scheinkestel C: Limiting dynamic hyperinflation in mechanically ventilated patients with severe asthma reduces complications. Anaesth Intensive Care 1993, 21:718.

21 Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med 2000, 342:1301–1308.

22 Gottlieb JE, Park P, Girod A, et al.: Comparison of neuromuscular blocker and sedative use among patients with ARDS treated with low versus high tidal volume [abstract]. Am J Respir Crit Care Med 2000, 161:A506.

23 Boulain T: Unplanned extubations in the adult intensive care unit. Association des Reanimateurs du Centre-Ouest. Am J Respir Crit Care Med 1998, 157:1131–1137.

24 Hughes M, Glass P, Jacobs J: Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs. Anesthesiology 1992, 76:334–341.

25 Dundee JW, Samuel IO, Toner W, et al.: Midazolam: a water-soluble benzodiazepine. Studies in volunteers. Anaesthesia 1980, 35:454–458.

26 Michalk S, Moncorge C, Fichelle A, et al.: Midazolam infusion for basal sedation in intensive care: absence of accumulation. Intensive Care Med 1988, 15:37–41.

27 Shelly MP, Mendel L, Park GR: Failure of critically ill patients to metabolise midazolam. Anaesthesia 1987, 42:619–626.

28 Vree TB, Shimoda M, Driessen JJ, et al.: Decreased plasma albumin concentration results in increased volume of distribution and decreased elimination of midazolam in intensive care patients. Clin Pharmacol Ther 1989, 46:537–544.

29 Driessen JJ, Vree TB, Guelen PJ: The effects of acute changes in renal function on the pharmacokinetics of midazolam during long-term infusion in ICU patients. Acta Anaesthesiol Belg 1991, 42:149–155.

30 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, 289:799–800.

31 Malacrida R, Fritz ME, Suter PM, et al.: Pharmacokinetics of midazolam administered by continuous intravenous infusion to intensive care patients. Crit Care Med 1992, 20:1123–1126.

32 • Kollef MH, Levy NT, Ahrens TS, et al.: The use of continuous IV sedation is associated with prolongation of mechanical ventilation. Chest 1998, 114:541–548.

This prospective, nonrandomized, observational study suggests that the use of continuous intravenous sedation may prolong mechanical ventilation.

33 •• Kress JP, Pohlman A, O'Connor MF, et al.: Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med 2000, 342:1471–1477.

This study shows that the manner in which sedatives are used influences the duration of mechanical ventilation. Daily interruption of continuous sedative infusions reduced the duration of mechanical ventilation in critically ill adults.

34 Brook AD, Ahrens TS, Schaiff R, et al.: Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. Crit Care Med 1999, 27:2609–2615.

35 Katz R, Kelly HW, Hsi A: Prospective study on the occurrence of withdrawal in critically ill children who receive fentanyl by continuous infusion. Crit Care Med 1994, 22:763–767.

36 Fonsmark L, Rasmussen YH, Carl P: Occurrence of withdrawal in critically ill sedated children. Crit Care Med 1999, 27:196–199.

37 Cammarano WB, Pittet JF, Weitz S, et al.: Acute withdrawal syndrome related to the administration of analgesic and sedative medications in adult intensive care unit patients. Crit Care Med 1998, 26:676–684.

38 Rosow CE, Moss J, Philbin DM, et al.: Histamine release during morphine and fentanyl anesthesia. Anesthesiology 1982, 56:93–96.

39 Yuan CS, Foss JF, O'Connor MF, et al.: Methylnaltrexone for reversal of constipation due to chronic methadone use: a randomized controlled trial. JAMA 2000, 283:367–372.

40 Hansen-Flaschen JH, Bradzinsky S, Basile C, et al.: Use of sedating drugs and neuromuscular blocking agents in patients requiring mechanical ventilation for respiratory failure: a national survey. JAMA 1991, 266:2870–2875.

41 Tayar J, Jabbour G, Saggi SJ: Severe hyperosmolar metabolic acidosis due to a large dose of intravenous lorazepam. N Engl J Med 2002, 346:1253–1254.

42 Dundee JW, Wilson DB: Amnesic action of midazolam. Anaesthesia 1980, 35:459–461.

43 George KA, Dundee JW: Relative amnesiac actions of diazepam, flunitrazepam and lorazepam in man. Br J Clin Pharm 1977, 4:45–50.

44 Treiman DM: The role of benzodiazepines in the management of status epilepticus. Neurology 1990, 40:32–42.

45 Shafer SL: Advances in propofol pharmacokinetics and pharmacodynamics. J Clin Anesth 1993, 5(6 suppl):14S–21S.

46 Bailie GR, Cockshott ID, Douglas EJ, et al.: Pharmacokinetics of Propofol During and After Long term Continuous Infusion for Maintenance of Sedation on ICU Patients. Br J Anaesth 1992, 68:486–491.

47 Veselis RA, Reinsel RA, Marino P, et al.: Propofol in sedative doses is an amnestic agent [abstract]. Anesthesiology 1991, 75:A1023.

48 Goodchild CS: Cardiovascular effects of propofol and relevance to use in patients with compromised cardiovascular function. Semin Anesth 1992, 11:S37–S38.

49 Mouren S, Baron J, Albo C: Effects of propofol and thiopental on coronary blood flow and myocardial performance in an isolated rabbit heart. Anesthesiology 1994, 80:634–641.

50 Gottardis M, Khuenl-Brady KS, Koller W, et al.: Effect of prolonged sedation with propofol on serum triglyceride and cholesterol concentrations. Br J Anaesth 1989, 62:393–396.

51 Barrientos-Vega R, Mar Sanchez-Soria M, Morales-Garcia C, et al.: Prolonged sedation of critically ill patients with midazolam or propofol: impact on weaning and costs. Crit Care Med 1997, 25:33–40.

52 Bennett SN, McNeil MM, Bland LA, et al.: Postoperative infections traced to contamination of an intravenous anesthetic, propofol. N Engl J Med 1995, 333:147–154.

53 Cray SH, Robinson BH, Cox PN: Lactic acidemia and bradyarrhythmia in a child sedated with propofol. Crit Care Med 1998, 26:2087–2092.

54 • Cremer OL, Moons KGM, Bouman EAC, et al.: Long-term propofol infusion and cardiac failure in adult head-injured patients. Lancet 2001, 357:117–118.

This paper describes an increased risk of potentially serious complications in patients receiving high-dose propofol infusions.

55 Riker RR, Fraser GL, Cox PM: Continuous infusion of haloperidol controls agitation in critically ill patients. Crit Care Med 1994, 22:433–440.

56 Ward DS: Stimulation of the hypoxic pulmonary drive by droperidol. Anesth Analg 1984, 63:106–110.

57 Zee-Cheng CS, Mueller CE, Seifert CF, et al.: Haloperidol and torsades de pointes. Ann Intern Med 1985, 102:418.

58 Burke C, Fulda GJ, Castellano J: Neuroleptic malignant syndrome in a trauma patient. J Trauma 1995, 39:796–798.

59 Peden CJ, Cloote AH, Stratford N, et al.: The effect of intravenous dexmedetomidine premedication on the dose requirement of propofol to induce loss of consciousness in patients receiving alfentanil. Anaesthesia 2001, 56:408–413.

60 Ebert TJ, Hall JE, Barney JA, et al.: The effects of increasing plasma concentrations of dexmedetomidine in humans. Anesthesiology 2000, 93:382–394.

61 • Venn RM, Bradshaw CJ, Spencer R, et al.: Preliminary UK experience of dexmedetomidine, a novel agent for postoperative sedation in the intensive care unit. Anaesthesia 1999, 54:1136–1142.

This paper describes the initial clinical experience with dexmedetomidine, a novel sedative analgesic that does not significantly depress respiration.

62 Spencer EM, Willatts SM: Isoflurane for prolonged sedation in the intensive care unit: efficacy and safety. Intensive Care Med 1992, 18:415–421.