ABSTRACT

Because no single, ideal sedative exists, the clinician must take care to select the best agent to ensure effective sedation while minimizing side effects and maintaining a good cost-effectiveness profile. This article discusses the most commonly used sedatives and assesses their usefulness and effectiveness in the clinical setting, citing the latest guidelines provided the Society of Critical Care Medicine.

Since there is no ideal sedative, evidence-based medicine must be used to determine or choose a sedative regimen for patients; however, this can be difficult. Few randomized control studies have been conducted comparing different sedative agents. In some cases, the results of these studies have been unconvincing, as pharmacology of the drugs tends to change with duration of infusion, and studies may not reflect actual clinical use. Additionally, sedatives are frequently used in conjunction with analgesics; choice of analgesic agent is based on the patient’s individual needs and must be considered in the sedative selection. The recently revised guidelines by the American College of Critical Care Medicine (ACCM) provide parameters for the use of analgesics and sedatives in the ICU.

ANALGESICS

The ACCM guidelines define analgesia as “the blunting or absence of sensation of pain or noxious stimuli.” Inadequate pain relief can have a number of consequences, including agitation, and can evoke a stress response that is characterized by tachycardia, increased myocardial oxygen consumption, hypercoagulability, immunosuppression, and persistent catabolism. The concomitant use of analgesics and sedatives can relieve agitation and lessen the stress response. Opioid analgesics commonly used in the ICU include fentanyl, morphine, and hydromorphone.

OPIOIDS

Selection of an opioid is based upon its pharmacology and potential for adverse events. Characteristics of an ideal agent would include rapid onset, ease of titration, lack of accumulation, and low cost.
Adverse events as a result of the use of opioids occur frequently in the ICU and may include negative effects on respiratory rate, hemodynamic function, the central nervous system, and the gastrointestinal system. Hypotension may occur in patients who are hemodynamically unstable, hypovolemic, or those with elevated sympathetic tone. Myoclonus and muscle rigidity may occur with high-potency opioids and may affect ventilatory efforts.1,2

**Fentanyl**

Fentanyl is a synthetic opioid with a rapid onset and short duration of action. It may be delivered by intermittent intravenous administration, continuous infusion, or transdermal administration. It has no significant metabolites. Transdermal use is not recommended for acute relief due to a 12- to 24-hour delay to peak effect.

Repeated dosing of a drug may cause accumulation and prolonged effects.1,2 With prolonged infusion, the half-life increases dramatically from 30 to 60 minutes to 9 to 16 hours.1 Fentanyl also exhibits tachyphylaxis, with larger volumes of the drug necessary over time, which may result in an increased recovery period following prolonged infusions.4 Fentanyl is more hemodynamically stable than morphine; however, it still may result in hypotension due to suppression of endogenous catecholamines.5

**Morphine**

Morphine sulfate is a prototypical opioid with a longer duration of action than fentanyl. It is administered in intermittent doses. Significant metabolites include morphine-3 and morphine-6 glucuronides. Morphine has a half-life of 2 to 3 hours in healthy adults, but is increased in patients with severe cirrhosis or burns. Septic shock and renal disease decrease clearance, and end-organ disease significantly affects metabolism of the drug.1,2

Vasodilation may result in hypotension and the active metabolites may result in prolonged sedation in patients with renal insufficiency.1 A morphine-stimulated histamine release may result in allergic reactions and cardiovascular instability.2

**Hydromorphone**

Hydromorphone is a high-potency, semisynthetic opioid that may be administered in oral, rectal, and parenteral forms. It is inexpensive, has a half-life of approximately 2 to 3 hours, and is commonly used for patients with severe long-term pain. Hydromorphone-3-glucuronide is the active metabolite, but it is not clinically significant.1,2

While the duration of action is similar to morphine, it does not stimulate histamine release. Hydromorphone is a potent respiratory depressant

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Table 1. Characteristics of the Ideal Sedative

- Rapid onset of action
- Easily titratable level of adequate sedation
- Short acting, allowing patient assessment, rapid recovery following discontinuation, easy weaning from mechanical ventilation, and early extubation
- No or few adverse effects
- No anaphylaxis or allergic reaction
- No nausea, vomiting, or phlebitis
- No or minimal interaction with other drugs
- Minimal metabolism; not dependent on normal hepatic, renal, or pulmonary function
- Minimal respiratory depression
- Minimal effect on cardiovascular function
- No pain on injection
- No active or toxic metabolites
- No suppression of cortisol production by the adrenal cortex
- No or minimal interactions with other commonly prescribed ICU drugs
- Ease of administration
- Lack of accumulation with prolonged administration
- Does not promote growth of pathogens
- No tolerance and withdrawal symptoms
- Cost effective
- Easily prepared and long shelf life
- Safe for all ages with no age-related changes in pharmacokinetics
- Provides facilitation of ventilator synchrony and the performance of various procedures and nursing interventions
- Lack of abuse potential

Data from references 6-9.
and may accumulate in cases of renal failure, resulting in neuroexcitation and cognitive impairment. Literature states it is less effective and has greater toxicity than other opioids.1,2

**Sedative Hypnotics**

Efforts to reduce anxiety in the ICU may include frequent reorientation, maintenance of patient comfort, provision of adequate analgesia, and optimization of the environment.1 Sedative therapy often is used as an adjunct to these measures and frequently is essential as a part of the care plan in order to maintain patient safety and comfort. Sedation of mechanically ventilated patients frequently is medically necessary. Table 1 outlines characteristics of the ideal sedative.

Unfortunately, the ideal sedative does not exist, and therapeutic choice should be based upon individual patient needs.

**Propofol**

Propofol is ultra short acting following a bolus dose and short-term infusion. Its rapid onset and offset of action is particularly useful for the short-term sedation of 3 classes of patients:

- Short-term intubated patients, including:
  - Surgical patients
  - Asthmatics
  - Drug overdose patients
  - Any patient with an anticipated quick extubation
- Patients with changing neurologic status requiring frequent neurological evaluation
- The elderly

Propofol is a complex drug with 3 half-lives. The α half-life, or distribution of the drug from the blood to the tissues following administration, is 2 to 3 minutes. The β half-life, or the elimination half-life, ranges from 30 to 60 minutes (Figure). The γ half-life, or terminal half-life during which the drug is eliminated from tissue fat, ranges from 300 to 700 minutes.10 Wake-up time following short-term administration is approximately 15 minutes; however the duration of action is prolonged after infusion exceeding 72 hours,11 resulting in a wake-up time of 30 to 60 minutes. It has been found that daily wake-ups for neurological assessments can reduce wake-up time following prolonged propofol infusion.12

Propofol is a negative inotrope, a vasodilator that can cause dose-related hypotension and carries a risk of infection and hyperlipidemia. Long-term or high-dose infusions may result in hypertriglyceridemia. Other adverse effects may include bradycardia and pain upon injection.1

**Midazolam**

Midazolam has a rapid onset of action (generally 2 to 5 minutes) and a short duration of action following bolus dose (approximately 15 minutes). Its duration of action extends to 1 to 2 hours following short-term infusion. Studies have shown that duration following prolonged infusion (>72 hours) can range from 3 to 15 hours. Swart et al found an average elimination half-life of 8.9 hours, with a large interpatient variability (3 to 15 hours; standard deviation of 4.4 hours).13

Erratic recovery times after usage are common with benzodiazepines. Other possible adverse events include ventilatory depression, tolerance, and tachyphylaxis after prolonged therapy (≥3 days); a predisposition to chemical dependence has been associated with long-term use.10,14

**Lorazepam**

Lorazepam is a benzodiazepine with a slow onset of action (10-20 minutes), an intermediate half-life (6

Figure. Comparisons of Half-lives of Lorazepam, Midazolam, and Propofol
hours) following bolus dose, and a longer duration of action (12-32 hours) after 72 hours of infusion. Lorazepam is not easily titratable due to its longer half-life. It has a prolongation of effect, with severely decreased drug requirements in the elderly. Because it lacks active metabolites and has decreased lipophilicity, lorazepam may be a steady and predictable agent for long-term sedation, but some literature states it should not be used to treat seizures or acute anxiety.

Besides other adverse effects associated with benzodiazepines, the solvents used with lorazepam have been implicated in cases of reversible acute tubular necrosis, lactic acidosis, and hyperosmolar states after prolonged use.

Comparison Studies: Propofol, Midazolam, and Lorazepam

McCollam et al randomized 31 patients to receive lorazepam, propofol, or midazolam. Using the Ramsay scale, it was found that adequate sedation occurred most frequently with midazolam; oversedation was most common with lorazepam, and undersedation with propofol. Midazolam required the fewest number of titrations. Initial time to adequate sedation was shortest in the propofol group. Total drug cost was significantly higher for propofol than either midazolam or lorazepam, and 18% of the total cost for lorazepam was due to drug loss due to precipitation. Researchers considered only acquisition cost, however, and did not investigate cost effectiveness based upon cost of total care.

Several studies compared propofol with midazolam in patients following coronary artery bypass grafting (CABG).

- McMurray et al found treatment with propofol resulted in earlier extubation after discontinuation, decreased morphine requirements, and a lower PaCO₂ after extubation.
- Snellen et al demonstrated a longer recovery time with midazolam (66 minutes) versus propofol (24 minutes), and a longer time for weaning with midazolam (243 minutes) versus propofol (154 minutes) following post-CABG sedation. The quality of sedation between the 2 drugs was similar.
- Roekaerts et al found patients receiving midazolam required more adjustments and bolus doses; time from discontinuation to responsiveness was greater with midazolam (72 minutes) than propofol (11 minutes); time from discontinuation to extubation was greater with midazolam (391 minutes) than propofol (250 minutes). Propofol patients were found to be more hypotensive.

- In comparing the safety of the 2 drugs, Wahr et al found no difference in postoperative ischemia, non-Q-wave myocardial infarction (M1), Q-wave M1, or cardiac death. Patients receiving propofol were less tachycardic and hypertensive, but more hypotensive.

- Hall et al found time to extubation was greater with midazolam (24.7 hours) than propofol (6.7 hours), but length of stay in the ICU was shorter with midazolam (64 hours) than propofol (94 hours).

Ostermann et al conducted a review of 49 randomized controlled trials, reaching the following conclusions:

- Propofol is at least as effective as midazolam.
- Propofol exhibits a faster time to extubation than midazolam; it is not yet clear if this translates into shorter time on mechanical ventilation or length of stay in the ICU.
- Propofol results in a greater incidence of hypotension.
- Propofol may offer an advantage when rapid awakening is desired.
- Further study is necessary.

Table 2 summarizes the properties of propofol, midazolam, and lorazepam.

Pharmacoeconomics

The high cost of drug therapy in the ICU has led to pharmacoeconomic comparisons of commonly used sedatives. A true pharmacoeconomic study evaluates not only acquisition cost of drugs, but considers administration cost and impact of therapy on both positive and negative outcomes, such as length of stay and treatment of adverse events. Several studies have undertaken a pharmacoeconomic evaluation of propofol and midazolam and/or lorazepam.

A 1999 study by Swart et al concluded that lorazepam was a useful alternative to midazolam, with easier management of sedative level and a significant cost savings.

Barrientos-Vega et al compared propofol and midazolam, and demonstrated a significantly shorter time...
to waking and significantly shorter time to weaning among patients in the propofol group than the midazolam group. Total costs analyzed included acquisition cost, cost of ICU stay during sedation, and cost during weaning. Although the acquisition cost of propofol was higher, the total care cost for the group receiving propofol was $511,164, compared with $584,712 for the group receiving midazolam.21

Since the completion of each of these studies, both midazolam and propofol have had significant price reductions, effectively reducing acquisition differentials and possibly improving the cost effectiveness of propofol when compared with midazolam and lorazepam.

**Haloperidol**

Haloperidol is a neuroleptic agent used to treat delirium, and is not a sedative agent. It has a half-life of 18 to 54 hours, with loading regimens given to achieve a rapid response in acutely delirious patients. When used for the control of agitated patients following a traumatic brain injury, it may prolong the duration of posttraumatic amnesia.1

**Dexmedetomidine**

Dexmedetomidine is an alpha2-agonist that provides both sedation and analgesia. It causes no respiratory depression and induces a unique type of sedation that allows for easy arousal with preserved respiratory drive, and a quick return to sedated state is achieved without altering infusion rate. While the usual dose range is 0.2 to 0.7 mg/kg/h, doses over the maximum do not offer greater sedation. Currently, dexmedetomidine is only approved for short-term infusion, ≤ 24 hours. A common adverse effect is hypotension, particularly with volume depletion. Dexmedetomidine exhibits a ceiling on its sedative effect, which limits its effectiveness as a single agent.

**SCCM Guideline Recommendations**

The recently revised guidelines from the Society of Critical Care Medicine (SCCM) provide recommendations on choice of analgesics, sedatives, and sedation monitoring. Following are some of the recommendations:

**Analgesics**

If intravenous doses of an opioid analgesic are required, fentanyl, hydromorphone, and morphine are the recommended agents.

Scheduled opioid doses or a continuous infusion is preferred over an “as-needed” regimen to ensure consistent analgesia.

Fentanyl is preferred for a rapid onset of analgesia in acutely distressed patients.

Fentanyl or hydromorphone is preferred for patients with hemodynamic instability or renal insufficiency.

Morphine or hydromorphone is preferred for intermittent therapy because of its longer duration of effect.

<table>
<thead>
<tr>
<th>Sedative Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol is recommended when rapid wakening is important (eg, for neurosurgical assessment or extubation). Triglyceride concentrations should be monitored after 2 days of infusion, and total caloric intake from lipids should be included in the nutrition support prescription.</td>
</tr>
<tr>
<td>Midazolam or diazepam should be used for rapid sedation of acutely agitated patients. Midazolam is recommended for short-term use only, as it produces</td>
</tr>
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**Table 2. Properties of Intravenous (IV) Sedatives**

<table>
<thead>
<tr>
<th>Propofol</th>
<th>Midazolam</th>
<th>Lorazepam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bolus dose</td>
<td>2 mg/kg</td>
<td>1-5 mg</td>
</tr>
<tr>
<td>Elimination half-life</td>
<td>30-60 minutes</td>
<td>1-4 hours</td>
</tr>
<tr>
<td>Half-life of parent compound</td>
<td>26-32 hours</td>
<td>3-11 hours</td>
</tr>
<tr>
<td>Onset after IV dose</td>
<td>1-2 minutes</td>
<td>2-5 minutes</td>
</tr>
<tr>
<td>Lipophilicity</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Active metabolites</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Continuous IV</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Metabolic pathway</td>
<td>Oxidation</td>
<td>Oxidation</td>
</tr>
<tr>
<td>Unique adverse events</td>
<td>Elevated triglycerides; pain on injection</td>
<td>Benzodiazepine-related adverse events only</td>
</tr>
</tbody>
</table>

Data from references 1 and 10.
unpredictable awakening and time to extubation when infusions continue longer than 48 to 72 hours.

Lorazepam is recommended for the sedation of most patients via intermittent IV administration or continuous infusion.

The titration of the sedative dose to a defined endpoint is recommended with systematic tapering of the dose or daily interruption with retitration to maximize prolonged sedative effects.

The use of sedation guidelines, an algorithm, or a protocol is recommended.

SEDATION MONITORING

A sedation goal or endpoint should be established and regularly redefined for each patient. Regular assessment and response to therapy should be systematically documented.

The use of a validated sedation assessment scale is recommended. Objective measures of sedation, such as the Bispectral Index, have not been completely evaluated and are not yet proven useful in the ICU.

APPLYING THE GUIDELINES

At St. Luke's-Roosevelt Hospital Center, choice of sedative depends on individual patient needs and anticipated duration of intubation.

- Propofol is used for immediate postintubation and postoperative sedation. Use is generally limited to 72 hours, except in patients with head trauma or neurosurgical indications, and the elderly. Patients who have been sedated long term with another drug, but are moving toward extubation, may be switched to propofol.
- Morphine, lorazepam, and haloperidol are used for longer-term sedation.

CONCLUSIONS

Optimal care of the ICU patient consists of an individualized treatment plan based upon relief of pain, anxiety, and agitation. While there is no single ideal sedative, lorazepam, midazolam, and propofol each offer distinct benefits based upon individual patient needs. In determining an appropriate sedative, the SCCM guidelines recommend lorazepam for sedation of most patients, midazolam for short-term sedation, and propofol when rapid wakening for assessment or extubation is desired, or in the elderly. Because sedatives account for a high percentage of ICU drug resources, cost is a vital component of any decision-making process. As generics become available, acquisition cost is constantly changing and should not be the only factor considered. True cost effectiveness is based upon total cost of care, including both positive and negative outcomes.

Ultimately, a rational choice of sedative is a multifactorial decision, based upon individual patient needs, desired effect of sedation, and cost effectiveness.

REFERENCES


