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Journal of Pharmacy Practice 2010 23: 455 originally published online 4 August 2010
DOI: 10.1177/0897190010372339

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Sedation and Analgesia in Critically Ill Neurologic Patients

Jason M. Makii, PharmD, BCPS¹, Marek A. Mirski, MD, PhD², and John J. Lewin III, PharmD, BCPS³

Abstract
Critically ill neurologic patients can pose a challenge when it comes to providing sedation and analgesia, primarily with the balance of maintaining sedation to provide patient comfort while still allowing a neurological examination. Determination of the optimal agent requires assessment and understanding of the underlying requirement for sedation: provision of analgesia, anxiolysis, or treatment of delirium. Pharmacological options exist that can affect individual or multiple underlying sedation requirements. Numerous evaluation tools exist to monitor the efficacy of sedation as well as help clinicians titrate agents to predefined goals; these tools allow the safe administration of drugs that can otherwise have serious adverse effects. Sedation regimens must ultimately be individualized to each patient to account for differences in pharmacokinetics and dynamics of the various agents, and this is particularly true in sedating neurologically injured patients. The agents frequently used to provide sedation and analgesia in the critically ill neurologic patient will be reviewed.

Keywords
sedation, intensive care unit, neurologic, analgesia, delirium, anxiolysis

Introduction
In July 2000, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) introduced the mandate for the implementation of standards for pain assessment and treatment in hospitalized patients.¹ As a result, management of patients in the intensive care unit (ICU) has evolved significantly with recent standards for ventilator weaning and reducing ventilator-associated pneumonia. There has also been an emphasis on the use of sedation and analgesia guidelines and efforts to decrease the use of neuromuscular paralysis. Further spurring the interest in ICU sedation are clinical studies documenting that routine assessment of nonparalyzed patients and reduced or discontinued periods of sedation are instrumental in reducing ventilator time, shortening ICU length of stay, and in prevention and early intervention of evolving neurologic deterioration.²,³

The reexamination of analgesia and sedation for critically ill patients has been helpful in the evaluation and care of the neurological patient. Patients are likely to be more awake and responsive than in previous eras of critical care and are less likely to develop adverse effects of neuroactive agents, many of which can cause cognitive and motor dysfunction beyond their intended actions. This paradigm shift has also forced a pharmacological reassessment of the medications selected, dosing intervals, routes and modes of administration, and the monitoring of their effects. Guidelines emphasize minimizing the depth and duration of sedation, advocating intermittent periods of arousal, and a titration scheme to provide the least amount of medication necessary to achieve a comfortable and controlled behavioral state.

Need for Sedation and/or Analgesia in the Neurocritical Care Unit
Neurologically injured patients may be the most difficult ICU population to manage with respect to preservation and frequent assessment of the neurological examination. Cognitive dysfunction can lead to increased fear, restlessness, and agitation. However, even modest sedation can mask subtle neurological deterioration. Thus, there is a need for an interdisciplinary approach to observation and titrating medications while minimizing the impact on the neurological evaluation. Sedation

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regimens in neuroscience-specific ICUs have been designed to enable repeated achievement of a high-quality neurological examination as the principle means of assessing patient status. Several triggers guide clinicians to provide sedation. Yet, “sedation” often includes the provision of analgesia, anxioly sis, antipsychosis, or a combination thereof. Correct diagnosis of a single or overlapping disturbance becomes the starting point as there are pharmacological options that can be guided toward multiple or individual pathologies. To minimize toxicity and side effects, it is best to select agents appropriate for the indication.

Management of Pain

The importance of pain assessment and management has been reinforced by the development of standards by JCAHO. Patient reports of pain/discomfort are the prerequisite for treatment with analgesic therapy. The ICU itself is a stimulus for patient discomfort whether from therapeutic means (mechanical ventilation, catheters, and drains) or routine nursing care (therapeutic suctioning, dressing changes, patient turning and repositioning). Critically ill neurologic patients can have primary physiological reasons to experience pain/discomfort (headache-migraine, elevated intracranial pressure (ICP), subarachnoid hemorrhage, neuropathy, etc). These patients are often not able to verbalize pain/discomfort and physiological signs (heart rate and blood pressure) are often used by medical staff during their assessment of patient analgesia, yet these methods may be inadequate to assess the level of pain/discomfort in the critically ill brain-injured patients.

The ideal analgesic agent would strictly address the pain/discomfort and possess no deleterious effects; unfortunately no such agent exists. Most pharmacological agents utilized for analgesia can decrease the patients overall level of arousal when administered to eradicate the perception of pain/discomfort. Therefore, in neurologically compromised patients, analgesia is often titrated to reduce pain/discomfort to less than 3 on a 0 to 10 ordinal scale in order to preserve patient responsiveness. The balance between preservation of the neurological examination and adequate analgesia in neurologically injured/postoperative neurosurgical patients is often difficult to manage. A study by Morad et al showed that a patient-controlled analgesia (PCA) regimen was more effective in terms of pain control, with no major adverse events as compared to a traditional as needed (pro re nata [PRN]) dosing strategy in postoperative neurosurgical patients. Common medications used for analgesia include nonsteroidal anti-inflammatory drugs, narcotics, alpha-2 agonists, steroids, and local anesthetics.

Management of Anxiolysis

Anxiety is a psychological state that can present as apprehension, general nervous tension, or in its most severe state as agitation. The resulting physiological response can manifest as changes in blood pressure, heart rate, respiratory rate, or an overall excitatory state (the fight or flight response). The ICU environment can have numerous psychological stressors that accompany a patient’s critical illness including an unfamiliar environment, constant noise and activity, and disturbed sleep—wake cycles. Treatments and conditions that can contribute to a stress can include intubation and mechanical ventilation, sepsis, traumatic head injury, medication side effects, and encephalopathy. Pain and anxiety often occur simultaneously, and uncontrolled pain can further contribute to feelings of anxiety. It is important to discern if pain is the cause of anxiety and to appropriately treat a patient’s pain, or if the feelings of anxiety are separate in origin. Treatment options for anxiety include benzodiazepines or sedative/hypnotic agents such as barbiturates and propofol. Some agents can provide anxiolysis and analgesia including alpha-2 agonists, ketamine, and some low-dose narcotics (morphine and meperidine).

Management of Delirium

Delirium, an acute disturbance of consciousness and cognition, has been a topic of increasing interest in recent years. It has been shown that delirium in the ICU has been associated with adverse patient outcomes including prolonged hospital stay, long-term cognitive impairment, and increased mortality. Delirium is categorized into subtypes according to psychomotor behavior which can range from hypoactive (decreased responsiveness, withdrawn, and apathetic) to hyperactive (agitation, restlessness, and emotional lability), with many patients presenting in its hypoactive or mixed forms. The ICU environment has several inciting causes of delirium including disrupted sleep—wake cycles, electrolyte abnormalities, metabolic disturbances, and infections. Some medications have been shown to have a “deliriogenic” potential; benzodiazepines, narcotics, and anticholinergic agents can exacerbate delirium symptoms. Strategies to prevent the occurrence of delirium include removing/reducing “deliriogenic” agents, establishing consistent sleep—wake cycles, appropriate pain management, timely removal of catheters and restraints, and early mobilization and exercise. Although no current medications have an Food and Drug Administration- (FDA) approved indication for delirium, the Society of Critical Care Medicine (SCCM) recommends the use of haloperidol. Newer atypical antipsychotics (quetiapine and olanzapine) have been used to treat delirium, but data are preliminary in the ICU population.

Monitoring of Sedation/Analgesia/Delirium

Sedation monitoring in the neuro-ICU is a unique challenge because subtle changes in consciousness can be a result of worsening neurological injury. Unfortunately, many of the pain, sedation, and delirium monitoring scales utilized have not been validated in the neuro-ICU patient populations. Other markers in the neuro-ICU that have been used to monitor the level of sedation include ICP and cerebral oxygen consumption; but again, these methods have not been validated for routine use outside of traumatic brain injury (TBI). The following scales
are suggested as part of routine ICU monitoring of sedation/analgesia/delirium, with the caveat that many lack specific validation to the neuro-ICU patient population.

**Pain**

There are numerous means by which to quantify patient pain/discomfort in the ICU setting. For patients that are awake and interactive the Numerical Rating Scale (1-10) and/or Visual Analog Scale (VAS, 1-100)\textsuperscript{16} may be used. Physiologically based scales exist for sedated, mechanically ventilated patients who cannot self-report their level of pain/discomfort. Examples include the Behavioral Pain Rating Scale (BPRS),\textsuperscript{17} Behavioral Pain Scale (BPS),\textsuperscript{6} Nonverbal pain Scale (NVPS),\textsuperscript{18} and the Pain Assessment and Intervention Notation (PAIN) algorithm.\textsuperscript{19}

**Anxiety/Sedation**

Sedation scales in the ICU environment have been around since the 1970s with the Ramsay scale for use in sedation of cardiac surgery patients.\textsuperscript{20} At the time, the clinical focus was to produce a deeper level of sedation. Since then numerous evaluation tools have been developed focusing on a lighter level of sedation with delineations between various levels of arousal, agitation, and levels of patient interaction. Some of the scales that have been developed include the Riker Sedation—Agitation Scale (SAS),\textsuperscript{21} Motor Activity Assessment Scale (MAAS),\textsuperscript{22} Richmond Agitation-Sedation Scale (RASS),\textsuperscript{23} Adaptation to the Intensive Care Environment Scale (ATICE),\textsuperscript{24} AVRIPAS (a 4-component scale: agitation, alertness, heart rate, and respiration rate),\textsuperscript{25} Vancouver Interaction and Calmness Scale (VICS),\textsuperscript{26} and Minnesota Sedation Assessment Tool (MSAT).\textsuperscript{27} Regardless of the type of scale used, all can be used as an objective measure to routinely monitor the depth of sedation. Sedation scales can minimize the amount of drug a patient receives to reach a sedation goal, they have been shown to decrease days of mechanical ventilation and cost of hospital stay, and more importantly they can facilitate communication between care providers.\textsuperscript{28} Of the aforementioned sedation scales, the phase I validation of the RASS contained patients from the neuroscience ICU at the study institution and may be the most applicable for use in monitoring sedation in neuro-ICU patients at the time of writing this review.

**Delirium**

The delirium assessment gold standard is a patient’s clinical history and examination as guided by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*. This can be difficult due to the inability of many ICU patients to verbally communicate. Various delirium assessment scales have been developed and validated in the ICU patients and include the Cognitive Test for Delirium (CTD),\textsuperscript{29} abbreviated CTD,\textsuperscript{30} Confusion Assessment Method–Intensive Care Unit (CAM-ICU),\textsuperscript{31} Intensive Care Delirium Screening Checklist (ICDSC),\textsuperscript{32} NEECHAM,\textsuperscript{33} and Delirium Detection Score (DDS).\textsuperscript{34} Each scale is different, but some form of assessment should be applied as part of routine ICU patient monitoring. Unfortunately, neuro-ICU patients were largely excluded from these validation studies.

**Choice of Sedative Agents**

Pharmacologic choices for sedation are many and each has advantages and disadvantages to use in the ICU patient population. Options include opioids, benzodiazepines, barbiturates, propofol, neuroleptics, alpha-2 agonists, ketamine, and many others. Concerns in the ICU patient for these agents include routes of administration, pharmacokinetics, ability to titrate easily, and adverse effect profiles with emphasis on effects on the neurologic examination, respiratory drive, systemic, and cerebral hemodynamics. Short-acting agents are typically preferred in the neurological intensive care environment due to the frequency of the neurologic examination.\textsuperscript{8} Ultimately, an individualized approach should be utilized, with specific aspects of drug selection requiring consideration, such as drug–drug interactions, drug–disease state interaction, drug reversibility, and cost-effectiveness. Agents commonly used in the ICU will be discussed in the following sections and are summarized in Tables 1 and 2.

**Narcotics (Opioids)**

Opioids primarily provide analgesia but can have a sedative effect at low doses. The common adverse effects associated with opioid use in the ICU are respiratory depression and decreased gastric motility. Opioids offer advantages over other sedative agents due to their ease of titration, ability to provide patient comfort, and their reversibility. There are a large number of options within the opioid drug class from natural opioids (eg, codeine, morphine), synthetic opioids (eg, fentanyl, meperidine), and semisynthetic opioids (eg, hydromorphone, oxycodone,). Within the ICU setting morphine, fentanyl, and remifentanil are used more commonly and will be discussed further in the following sections.

**Mechanism of Action.** All opioids exert their effect through interactions with the opioid receptors (mu $\mu$, delta $\delta$, kappa $\kappa$). The various opioids can have central and peripheral effects as agonists, partial agonists, and mixed agonist–antagonist. The pharmacologic effects (eg, analgesia) and side effects (eg, respiratory depression, gastrointestinal (GI) hypomotility, and euphoria) are exhibited via the drugs interaction with various receptor subtypes.\textsuperscript{35}

**Rationale for ICU Use and Adverse Reactions.** Analgesia is a common patient requirement in the intensive care unit, and opioids are the cornerstone for analgesia-based sedation regimens. Opioids are for the most part well tolerated with minimal adverse physiological effects. Modest bradycardia can occur with high-dose narcotic administration, but typically...
narcotics have little to no effect on chronotropy or systemic pressure. Opioids do not have a direct effect on ICP or cerebral blood flow, but any hypercarbia related to depressed respiratory drive by opiates may lead to cerebral vasodilatation and its sequelae.\textsuperscript{35} Elevations in ICP have been documented in patients with TBI receiving morphine, although the mechanism is thought to be secondary to hypercarbia from the respiratory depressant effect. Another proposed hypothesis is the autoregulatory compensation of the mean arterial pressure (MAP) decrease that results from bolus administration of opioids.\textsuperscript{36} Caution should be used in patients with TBI or with preexisting elevated ICP receiving opioids due to the potential for miosis that could mask other causes of neurological deterioration. High doses of morphine and fentanyl have induced seizure-

### Table 1. Pharmacological Profile of Common Sedatives in the Neuroscience Intensive Care Unit

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Sedation/ Analgesia</th>
<th>Mechanism of Action</th>
<th>Advantages</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>Opioid</td>
<td>++++/−</td>
<td>Mu receptor agonist</td>
<td>Rapid onset, short duration, reversible</td>
<td>Gastric dysmotility, respiratory depression, chest wall rigidity, hypotension</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>Opioid</td>
<td>++++/−</td>
<td>Mu receptor agonist</td>
<td>Rapid onset, short duration, reversible</td>
<td>Gastric dysmotility, respiratory depression, chest wall rigidity, hypotension</td>
</tr>
<tr>
<td>Morphine sulfate</td>
<td>Opioid</td>
<td>++++/−</td>
<td>Mu receptor agonist</td>
<td>Reversible</td>
<td>Gastric dysmotility, respiratory depression, chest wall rigidity, hypotension, hallucinations, Respiratory depression, hypotension, confusion, long-acting active metabolite</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Benzodiazepine</td>
<td>++++/−</td>
<td>GABA\textsubscript{A} receptor agonist</td>
<td>Reversible, short duration</td>
<td>Rapid onset</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Benzodiazepine</td>
<td>++++/−</td>
<td>GABA\textsubscript{A} receptor agonist</td>
<td>Reversible, rapid onset, longer duration</td>
<td>Respiratory depression, hypotension, confusion, long-acting active metabolite</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Benzodiazepine</td>
<td>++++/−</td>
<td>GABA\textsubscript{A} receptor agonist</td>
<td>Reversible, rapid onset, short duration, titratable</td>
<td>Respiratory depression, hypotension, confusion, long-acting active metabolite</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Neuroleptic</td>
<td>+/−</td>
<td>Blocks dopamine, adrenergic, serotonin, acetylcholine, and histamine receptors</td>
<td>Preserves level of arousal, no respiratory depression, treats delirium</td>
<td>EPS, may lower seizure threshold</td>
</tr>
<tr>
<td>Droperidol</td>
<td>Neuroleptic</td>
<td>+/−</td>
<td>Blocks dopamine, adrenergic, serotonin, acetylcholine, and histamine receptors</td>
<td>Combination sedation, antipsychotic, antiepileptic, and anxiolytic</td>
<td>EPS, may lower seizure threshold, QT prolongation</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Atypical</td>
<td>+++−</td>
<td>Blocks dopamine, adrenergic, serotonin, acetylcholine, and histamine receptors</td>
<td>Low incidence of EPS, oral disintegrating dosage form</td>
<td>Anticholinergic effects</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Atypical</td>
<td>+++−</td>
<td>Blocks dopamine, adrenergic, serotonin, acetylcholine, and histamine receptors</td>
<td>Shortest acting atypical antipsychotic, low incidence of EPS</td>
<td>Anticholinergic effects</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Atypical</td>
<td>+++−</td>
<td>Blocks dopamine, adrenergic, serotonin, acetylcholine, and histamine receptors</td>
<td>Oral disintegrating dosage form</td>
<td>Anticholinergic effects</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>Alpha-2 agonist</td>
<td>++++/−</td>
<td>Alpha-2 receptor agonist (pre- and postsynaptic)</td>
<td>More potent than clonidine, short acting, titratable</td>
<td>Dry mouth, bradycardia, hypotension</td>
</tr>
<tr>
<td>Thiopental</td>
<td>Barbiturate</td>
<td>++++/−</td>
<td>GABA\textsubscript{A} receptor agonist</td>
<td>Rapid onset, short duration</td>
<td>Respiratory depression, hepatic enzyme induction</td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>Barbiturate</td>
<td>++++/−</td>
<td>GABA\textsubscript{A} receptor agonist</td>
<td>Rapid onset, short duration</td>
<td>Respiratory depression, hepatic enzyme induction</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Barbiturate</td>
<td>++++/−</td>
<td>GABA\textsubscript{A} receptor agonist</td>
<td>Potent GABA agonist</td>
<td>Respiratory depression, hepatic enzyme induction</td>
</tr>
<tr>
<td>Fospropofol</td>
<td>Hypnotic</td>
<td>+++−</td>
<td>Unclear/GABAergic (proposed)</td>
<td>Rapid onset, short duration</td>
<td>Respiratory depression, hypoxia, pruritus, paresthesia</td>
</tr>
<tr>
<td>Propofol</td>
<td>Hypnotic</td>
<td>++++/−</td>
<td>Unclear/GABAergic (proposed)</td>
<td>Very rapid onset, short duration, titratable</td>
<td>Hypotension, respiratory depression, metabolic acidosis, rhabdomyolysis, pain at injection site</td>
</tr>
</tbody>
</table>

Abbreviations: +, mild; ++, moderate; ++++, high; GABA, gamma-aminobutyric acid; EPS, extrapyramidal side effect.
like activity in patients undergoing general anesthesia.\textsuperscript{37} The cases involved documented absence of electrographic seizure activity, which suggests that this activity was a manifestation of narcotic-induced muscle rigidity or myoclonus. Nonepileptic myoclonus has been documented in patients receiving high-dose intravenous (IV) or intrathecal (IT) morphine.\textsuperscript{38} Nor meperidine, the renally eliminated active metabolite of meperidine, has been associated with an excitatory syndrome that includes seizures. Patients with renal dysfunction are primarily at risk.

Common adverse reactions to narcotics include pruritis, somnolence, respiratory depression, chest wall and other muscle rigidity (primarily with fentanyl and remifentanil), dysphoria or hallucinations (primarily with morphine), nausea and vomiting, GI dysmotility, hypotension, histamine release causing urticaria and flushing (primarily with morphine and meperidine), anaphylaxis (rare), and immune suppression after repeated dosing.\textsuperscript{35,39} Morphine may induce hypotension even at low therapeutic doses (partly due to the histamine release); fentanyl and remifentanil tend to have little effect on blood pressure at sedative doses. Fentanyl can reduce the heart rate, which is often favorable in patients with cardiovascular disease. It is recommended that all patients receiving narcotic sedation undergo frequent, if not continuous, monitoring of respiratory rate and pulse oximetry, due to the potential decrease in respiratory drive from these agents.

### Table 2. Pharmacokinetic Profile of Common Sedatives in the Neuroscience Intensive Care Unit

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half-Life</th>
<th>Starting Dose</th>
<th>Titration</th>
<th>Protein Binding</th>
<th>Metabolism/Active Metabolite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>30-60 min (single IV dose); hrs in repeated dosing</td>
<td>25-50 mcg IV every 5-10 min</td>
<td>0.5-2.5 mcg/kg/hr every 15-30 min, up to 50-100 mcg/hr</td>
<td>80%-86%</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>3-10 min after single dose</td>
<td>0.5-1 mcg/kg IV bolus</td>
<td>Infusion: 0.05-0.2 mcg/kg/min</td>
<td>70%</td>
<td>Plasma esterases</td>
</tr>
<tr>
<td>Morphine sulfate</td>
<td>1.5-4.5 hrs IV, IM, SQ</td>
<td>5-20 mg IM every 4 hrs 2-10 mg IV every 4 hrs</td>
<td>Caution: metabolites may accumulate; For postoperative pain (PCA): 0.2-3.0 mg and 5-20 min lockout intervals</td>
<td>20%-30%</td>
<td>Hepatic/Morphine-3-glucuronide, Morphine-6-glucuronide</td>
</tr>
<tr>
<td>Diazepam</td>
<td>30-60 hrs</td>
<td>2 mg IV every 30-60 min</td>
<td>—</td>
<td>99%</td>
<td>Hepatic/ N-Desmethyldiazepam, N-methyloxazepam, oxazepam</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>10-20 hrs</td>
<td>0.25 mg-1 mg IV every 5-30 min</td>
<td>Infusion: 0.01-0.1 mg/kg/hr</td>
<td>91%-93%</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Midazolam</td>
<td>1-2.5 hrs</td>
<td>0.5-1 mcg IV every 5-30 min</td>
<td>Infusion: 0.25-1 mcg/kg/min</td>
<td>97%</td>
<td>Hepatic/1-hydroxymethylmidazolam</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>12-36 hrs</td>
<td>0.5-5 mg IV</td>
<td>—</td>
<td>92%</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Droperidol</td>
<td>4-12 hrs</td>
<td>0.625-2.5 mg IV</td>
<td>—</td>
<td>92%</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>21-54 hrs</td>
<td>2.5-5 mg PO daily</td>
<td>—</td>
<td>93%</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>6 hrs</td>
<td>25-50 mg PO twice daily</td>
<td>—</td>
<td>83%</td>
<td>Hepatic/N-desalkyl quetiapine</td>
</tr>
<tr>
<td>Risperidone</td>
<td>20-30 hrs</td>
<td>0.5 mg PO</td>
<td>—</td>
<td>90%</td>
<td>Hepatic/9-hydroxyrisperidone</td>
</tr>
<tr>
<td>Dexametomidine</td>
<td>2 hrs</td>
<td>1 mcg/kg IV bolus over 10 min</td>
<td>Infusion 0.2-1.0 mcg/kg/hr</td>
<td>94%</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Thiopental</td>
<td>3-18 hrs</td>
<td>1-2 mg/kg IV</td>
<td>1.5-5 mg/kg/hr</td>
<td>97%</td>
<td>Hepatic/pentobarbital</td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>15-50 hrs</td>
<td>10-20 mg/kg IV</td>
<td>0.5-3 mg/kg/hr</td>
<td>35%-55%</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>36-117 hrs</td>
<td>10 mg/kg IV at 100 mg/min until seizures are controlled</td>
<td>50 mg/min until seizures are controlled</td>
<td>20%-60%</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Fospropofol</td>
<td>1-2 hrs</td>
<td>6.5 mg/kg</td>
<td>1.6 mg/kg every 4 minutes Increase infusion 5-10 mcg/kg/min every 5-10 mcg/kg/min to maintenance of 25-80 mcg/kg/min up to 100-300 mcg/kg/min</td>
<td>98%</td>
<td>Hepatic/propofol</td>
</tr>
<tr>
<td>Propofol</td>
<td>4-10 min</td>
<td>1.0-2.5 mg/kg IV (anesthesia induction); 5 mcg/kg/min (sedation)</td>
<td>Increase infusion 5-10 mcg/kg/min every 5-10 mcg/kg/min to maintenance of 25-80 mcg/kg/min up to 100-300 mcg/kg/min</td>
<td>&gt;90%</td>
<td>Hepatic and extrahepatic</td>
</tr>
</tbody>
</table>

Abbreviations: IM, intramuscular; IV, intravenous; PCA, patient-controlled analgesia; SQ, subcutaneous; PO, oral.
An advantage with the use of opioid analgesics is the ability to quickly reverse their activity with the opioid antagonist naloxone. With recommended dosing (>0.4 mg), respiratory depression and sedation effects can be reversed in 1 to 2 minutes following administration. Lower doses are recommended in ICU patients to avoid the “overshoot” phenomenon which can result in a catecholamine surge leading to hypertension, tachycardia, and emergence agitation which can exacerbate myocardial ischemia, pulmonary edema, and intracranial hypertension. While this is not advocated for reversal of sedation to facilitate a routine neurological assessment, a conservative approach to avoid overshooting reversal in nonemergent situations would be to dilute 400 mcg in 10 mL of saline (final concentration 40 mcg/mL) and administer 40 to 80 mcg titrating to the desired level of arousal and/or reversal of sedation or respiratory depression.7

Drug–Drug Interactions. When morphine is combined with other neuroleptics, greater decreases in blood pressure may be observed. Drug interactions with narcotics tend to reflect the respiratory depression and level of consciousness exaggerated and prolonged with concomitant use of phenothiazines, monoamine oxidase (MAO) inhibitors, and tricyclic antidepressants.35

Pharmacokinetics and Dosing

Morphine. Opioids are readily absorbed through the GI mucosa or through subcutaneous, intramuscular (IM), IT, epidural, or IV routes of administration. Morphine readily distributes to the central nervous system (CNS) and has a peak effect in 10 to 15 minutes following IV administration. Following enteral administration, morphine undergoes significant first-pass hepatic metabolism resulting in an oral bioavailability of ~20% to 40%. Morphine is metabolized in the liver via N-demethylation, N-dealkylation, O-dealkylation, conjugation, and hydrolysis. The majority of clearance is by glucuronidation to the 2 major metabolites morphine-3-glucuronide (~50%, inactive) and morphine-6-glucuronide (5%-15%, active) which are renally excreted; the latter is a more potent analgesic than morphine and can accumulate in patients with renal insufficiency. The half-life of morphine can vary greatly depending on the route of administration, with ranges from 90 to 240 minutes for immediate release products upward of 15 hours for extended release formulations. Morphine is 20 to 36% bound to plasma protein, and has a volume of distribution (Vd) of 1 to 6 L/kg, depending on route/formulation of administration. Morphine sulfate is a longer acting narcotic compared to fentanyl and remifentanil. The time to peak is 20 to 30 minutes, with a duration of action of ~4 hours, which makes intermittent dosing a reasonable administration option. Recommendations are reflective of opiate-naive patients. For analgesia dosing, 5 to 20 mg IM every 4 to 6 hours or 2 to 10 mg IV at a rate of 2 mg/minute is recommended. Preference should be given to IV dosing in the ICU to minimize patient discomfort. Oral dosing when appropriate can reasonably start at 15 to 30 mg of immediate release formulations every 4 hours.

Fentanyl. Fentanyl is more lipophilic than morphine, leading to a shorter time to peak effect following IV administration of ~5 minutes. Buccal administration of fentanyl results in ~50% to 70% bioavailability depending on the product selected. Onset of action is within 5 to 15 minutes via transmucosal routes with a peak effect within 15 to 30 minutes. IM administration results in an onset of 7 to 8 minutes and a duration of 1 to 2 hours. Transdermal fentanyl has a much slower onset of action of 12 to 24 hours, but this rate can be faster in febrile patients. Steady state is reached in 36 to 48 hours, and duration of action can be up to 72 hours following removal of the transdermal fentanyl. IV administration has immediate onset, with a peak effect occurring in ~5 minutes, and a duration of effect of 30 to 60 minutes. Repeated doses or continuous infusions may accumulate in adipose tissue and skeletal muscle, with release from these storage sites after discontinuation, accounting for its longer elimination half-life (3-8 hours) in this setting.40 Fentanyl is metabolized by N-dealkylation via the cytochrome P450 system to norfentanyl and other inactive metabolites that are renally excreted. Elimination half-life ranges from ~200 minutes for the IV formulation up to 17 hours for the transdermal dosage forms. Fentanyl is 80% to 86% bound to plasma proteins and has a Vd of 3 to 6 L/kg. Fentanyl given IV is the preferred route in the ICU patient population. As a general rule of thumb, fentanyl and remifentanil are roughly 100 times more potent than morphine. Starting doses of 25 to 50 mcg IV every 5 to 10 minutes for mild sedation and analgesia are recommended, keeping in mind the time to peak is ~3 minutes following each dose. Thus, as the previous dose effects are wearing off, the next dose is being administered. Alternatively a continuous infusion of 0.5 to 2.5 mcg/kg/hr may be given titrating to effect every 15 to 30 minutes. It is not recommended that opiate-naive patients receive doses greater than 2 mcg/kg/hr, unless they have a protected airway and mechanical ventilation is available.41 In narcotic-tolerant patients, as an adjuvant to anesthesia or other sedatives, or if deeper sedation is required, continuous infusion doses greater than described may be necessary. It is quite common for patients admitted to the ICU to have narcotic tolerance to large doses of oral opioids at baseline. It is not unreasonable to begin initial opioid titration with IV fentanyl until the acute discomfort is relieved.41 Doses upward of 1000 mcg of fentanyl over 30 minutes in highly opioid-tolerant patients are not uncommon. Once pain is controlled in stable patients, it is reasonable to substitute longer acting agents such as morphine or oxycodone if the neurological examination allows. Lower doses should be considered in patients with hepatic or renal insufficiency and those patients with advanced age.

Remifentanil. Remifentanil is even more lipophilic than fentanyl and morphine leading to the shortest onset, 1 to 2 minutes, to peak effect following IV administration of the opioids discussed. This also contributes to the shortest duration of action of 3 to 10 minutes, which can increase with a prolonged infusion. It is ~70% bound to plasma proteins (primarily alpha-1-acid glycoprotein) and has a Vd of 100 mL/kg.
Remifentanil is rapidly metabolized via plasma and tissue esterases to the inactive carboxylic acid metabolite which is 90% renally excreted. The rapid onset and short duration of action, which are independent of hepatic and/or renal clearance, make remifentanil the easiest opioid to titrate. Initial use as a sedative in the ICU environment has shown promising results, but use in TBI may not garner the same benefit. Moderate dosing showed preserved cerebral autoregulation with intracranial hypertension associated with agitation, coughing, and tracheal suctioning. Large doses were required to blunt the cough response and were associated with a reduction in MAP and elevations in ICP due to preserved autoregulation. Although remifentanil possesses ideal pharmacokinetics to provide a true “on–off” agent, its cost relative to fentanyl or morphine is much higher, and this agent may not be the most cost-effective choice in the majority of patients. However, this agent may be more preferable in patients requiring frequent neurologic assessments. Due to its short duration of action, when titrating a patient off remifentanil, it is imperative to have a plan in place for longer acting opioids and pain control with implementation prior to remifentanil discontinuation, as abrupt discontinuation may precipitate withdrawal. Remifentanil can be titrated quickly to effect when given as a continuous infusion due to its short duration of action. Dosing ranges for sedation and analgesia start at 0.02 to 0.05 mcg/kg/min and upward to a typical maximum of 0.1 mcg/kg/min. Larger doses rapidly lead to apnea and subsequently anesthetic doses. No adjustment is needed for patients with renal or hepatic insufficiency, but a 50% dose reduction is recommended in patients older than 65 years of age.

**Benzodiazepines**

Benzodiazepines are one of the most common sedative agents used in the ICU, and they exert their effect via an anxiolytic action. The three most common agents used are diazepam, lorazepam, and midazolam.

**Mechanism of Action.** The effects of benzodiazepines on the CNS are through the potentiation of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). The effects include sedation, anxiolysis, muscle relaxation, anterograde amnesia, analgesia (with diazepam), and anticonvulsant activity (not all benzodiazepines). Benzodiazepines lack respiratory depression in most patients, but caution should be used in pediatrics, those with hepatic impairment, patients with preexisting pulmonary disease, or when used with other sedatives. High doses of several benzodiazepines can lead to vasodilatation and neuromuscular blockade through the interaction with peripheral sites.

**Rationale for ICU Use and Adverse Reactions.** The provision of anxiolysis and amnesia make benzodiazepines an option for use in the relief from the stressors of the ICU environment. In addition, this class is considered the treatment of choice for patients with concomitant alcohol withdrawal, and the anticonvulsant property makes it ideal for the acute management of seizures and status epilepticus. It should be noted that in treating seizure disorders tolerance can rapidly develop and efficacy can diminish with time. Small doses titrated carefully can usually be given to provide therapeutic comfort without overt compromise of cognitive function. The anterograde amnesia can be useful during discomforting procedures, although analgesia should also be provided. Like opioids, benzodiazepines typically provide their therapeutic effects without significant changes to heart rate, blood pressure, and respiratory drive (unless high doses are provided). Low oral (hypnotic) doses of benzodiazepines have little effect on blood pressure, but higher IV doses (sedative or anesthetic) doses may cause hypotension and increased heart rate. On their own, benzodiazepines have little to no effect on ICP. However, cerebral perfusion can be impaired by the mean arterial pressure decreases associated with high-dose benzodiazepine infusions. Similar to opioids, high doses of benzodiazepines may incite respiratory depression and apnea; the hypercarbia associated with this effect may stimulate elevation in ICP.

Oversedation is the most common unintended effect of benzodiazepines, but it is dose dependent and oftentimes avoidable. Another unintended adverse effect of benzodiazepines is the precipitation of an altered cognitive state that in definition can be classified as delirium. Pandharipande et al discuss the use of lorazepam, increased age, and APACHE II score as independent risk factors for delirium in their ICU patients. The potentiation of delirium is an adverse effect that must be considered when this drug class is administered.

Similar to other sedative agents, benzodiazepines effects can be additive or synergistic when given concomitantly with other agents that decrease the level of consciousness, suppress respiratory drive, or decrease blood pressure. Apnea can be precipitated when benzodiazepines are used in combination with opioids, and caution should be used when these agents are administered together. As with the opioids, the potential for decreased respiratory drive and hypotension associated with high-dose benzodiazepine administration requires careful monitoring of pulse oximetry and blood pressure. This is especially important in patients maintained on continuous infusions and those who are not mechanically ventilated.

High doses of several benzodiazepines can lead to vasodilation and neuromuscular blockade through the interaction with peripheral sites. Caution should be used with continuous infusions of lorazepam due to the propylene glycol diluent, which can lead to toxicity when infused at high doses (≥1 mg/kg/day). Propylene glycol toxicity can result in an anion gap metabolic acidosis and acute renal failure, as well as CNS toxicities such as CNS depression and seizures. An osmol gap can be an indicator of propylene glycol accumulation and should be monitored in patients on higher doses, along with renal function, and acid–base status. Midazolam, while highly lipophilic, is an aqueous preparation as the hydrochloride salt, and therefore not diluted in propylene glycol. At lower pH (as is the commercially available product), a higher percentage of midazolam molecules are in the “open-ring” configuration, rendering it more water soluble, allowing for an
aqueous preparation. On injection and exposure to physiologic pH, all molecules rapidly revert to the “closed-ring” highly lipophilic configuration.\textsuperscript{49} Other common adverse effects of benzodiazepines include weakness, headache, vertigo, nausea, and vomiting. Somnolence, respiratory depression, and effects on the cardiovascular system have previously been discussed.

The GABA\textsubscript{A}-receptor antagonist flumazenil can reverse the effects of benzodiazepine overdose. Caution should be used with flumazenil as it may precipitate rises in ICP, systemic hypertension, and lowering of the seizure threshold, primarily in patients with TBI, neurosurgical patients, and those who have been taking long-term benzodiazepines. Flumazenil has a duration of action of \~30 to 60 minutes, and patients who have received longer acting benzodiazepines become resedated once flumazenil has been metabolized.

\textbf{Drug—Drug Interactions.} Diazepam and midazolam are susceptible to drug interactions due to their metabolism via the cytochrome P450 enzymes. Inducers of the P450 enzymes (eg, rifampin, carbamazepine, phenytoin, and phenobarbital) may enhance the clearance of these drugs, while inhibitors (eg, macrolides, azole antifungals, and protease inhibitors) may decrease clearance and cause prolonged sedation. Lorazepam is prone to very few drug interactions due to its metabolism via glucuronidation.

\textbf{Pharmacokinetics and Dosing}

\textbf{Diazepam.} The lipophilicity of each benzodiazepine determines the time of onset and offset following single IV doses. They rapidly distribute to the brain, followed by redistribution to muscle and adipose tissue, the rate of which is dependent on lipophilicity. Of the 3 agents, diazepam is the most rapid in onset and offset, followed by midazolam and lorazepam. With multiple dosing or continuous infusions, the time to offset is determined by the agent’s half-life and presence of active metabolites. Diazepam has the shortest onset time and initial duration, but it has the longest half-life of more than 50 hours. The primary active metabolite, \textit{N}-desmethyldiazepam, has an elimination half-life upward of 100 hours and can prolong the recovery of repeated dosing or lengthy infusions.\textsuperscript{34} For sedation, initial doses of 1 to 2 mg IV every 10 to 20 minutes are recommended (incrementally increasing by 5 mg per dose). The short duration of action limits its use to brief sedation (for procedural sedation) or to help induce sleep. When large doses or continuous IV infusions are used, the possibility of prolonged sedation must be considered due to the long duration of active metabolites.

\textbf{Midazolam.} Midazolam has a short duration of action and half-life (1-4 hours), making it the most appropriate benzodiazepine to use as a continuous infusion. Midazolam does possess an active metabolite, alpha-hydroxy-midazolam, that is renally eliminated and may prolong sedation in patients with renal impairment. Initial doses of 0.5 to 2 mg IV every 5 to 10 minutes for acute sedation are recommended. Midazolam can be given IM in doses of 0.07 mg/kg to 0.1 mg/kg if IV access is an issue, in contrast to diazepam where the propylene glycol solvent can cause myonecrosis. Maintenance infusions can be initiated at 0.02 to 0.1 mcg/kg/hr (1 to 7 mg/hr) and titrated to the target sedation score.

\textbf{Lorazepam.} Lorazepam is the most water-soluble benzodiazepine with the smallest redistribution effect, leading to its longer duration of effect. The duration of 4 to 6 hours for lorazepam compared to \~30 minutes following administration of diazepam or midazolam is attributed to the low redistribution effect. Lorazepam does not possess any active metabolites. All benzodiazepines are highly bound to plasma proteins, have large Vds, and are hepatically metabolized. For sedation, 0.25 mg to 0.5 mg IV every 2 to 4 hours is usually sufficient. Doses of 1 to 2 mg can provide moderately deep sedation for 4 to 8 hours. In patients exhibiting acute withdrawal symptoms where higher doses may be required, the provision of respiratory support must be available, particularly if other sedative agents are also being used.

\textbf{Alpha-2 Agonists}

Clonidine and dexmedetomidine are the 2 agents used in the ICU for management of sedation, anxiolysis, and analgesia. Clonidine has long been used as an adjuvant to general, neuraxial,\textsuperscript{50} and regional anesthesia\textsuperscript{51} due to its sedative and analgesia properties, but the depressant effect on the cardiovascular system has limited its utility when combined with other agents and thus the remainder of this class review will primarily focus on dexmedetomidine. Dexmedetomidine has shown promise for use in the ICU as an alternative and adjunct to traditional sedatives for its ability to relieve discomfort of mechanical ventilation while still allowing rapid patient arousability for neurological examinations.\textsuperscript{52,53} Neither agent alone is capable of producing general anesthesia, but both agents can markedly enhance the efficacy of anesthetics as well as opioids, decreasing the requirements for these other agents.\textsuperscript{54}

\textbf{Mechanism of Action.} Both clonidine and dexmedetomidine are selective alpha-2 adrenergic receptor agonists. Dexmedetomidine has roughly 8 to10 times the affinity for the alpha-2 receptors than clonidine. The sedative and analgesic properties are a result from the presynaptic inhibition of descending noradrenergic activation of spinal neurons and activation of postsynaptic alpha-2 adrenergic receptors coupled to potassium-channel activating G-proteins.\textsuperscript{55} The end result of these effects is a decrease in sympathetic outflow from the locus caeruleus, a decrease in tonic activity in spinal motor neurons and spinothalamic pain pathways, and subsequent decreases in heart rate and blood pressure. At recommended doses the respiratory drive is not compromised.

\textbf{Rationale for ICU Use and Adverse Reactions.} An advantage of dexmedetomidine, as compared with other classes of sedatives, is the mild reduction in the level of arousal. Consistent with lighter levels of sedation goals, these agents can provide
effective sedation without the loss of attentive behavior and cognition with low levels of auditory or tactile stimulation. Thus, the neurological assessment can be preserved while still maintaining a nonanxious and nonagitated patient. Additional benefits of dexmedetomidine are the ability to lower the shivering threshold, which can pose a benefit in therapeutic hypothermia protocols, and its ability to blunt the autonomic response. The combination effects of sedation/anxiolysis and analgesia provided by dexmedetomidine may permit single drug therapy for both sedation and mild analgesia during the postoperative and ICU period in some patients. The unique mechanism of action can allow for lower doses of traditional sedatives in patients requiring deeper levels of sedation.

Recently in the ICU, dexmedetomidine has demonstrated to possess advantageous characteristics for sedation in the critically ill, primarily due to a lower incidence of delirium and preservation of patient cognition. In the SEDCOM study specifically, patients receiving dexmedetomidine (as compared to midazolam) spent less time on the ventilator, experienced less delirium, and experienced less tachycardia and hypertension compared to patient receiving midazolam. There was no difference in ICU length of stay between the 2 populations and the dexmedetomidine group did experience less infection, but more bradycardia. There was no difference in the primary end point of percentage of time at target sedation level, but dexmedetomidine appeared advantageous in the aforementioned secondary end points. It should be noted that the subset of patients excluded from the study were those with serious CNS pathology, making it difficult to extrapolate these results to this patient population.

The most common adverse effects of dexmedetomidine include dry mouth, bradycardia, hypotension, light-headedness, and anxiety. Dexmedetomidine can cause bradycardia and hypotension that is frequently observed during the initial loading dose. Treatment is supportive and decreased or discontinuation of the infusion often alleviates the effect, rarely IV fluids, pressors, or vagolytics may be required. For the management of patients with TBI, clonidine had no significant effect on ICP but did decrease cerebral perfusion pressure due to a reduction in systemic arterial pressure. The same effect was noted in a study of 39 neurosurgical patients receiving dexmedetomidine. The mean cerebral perfusion pressure (CPP) increased while the ICP decreased during sedation. Agitation was noted as primary adverse reaction, whereas hypotension occurred in 10 of 39 patients. This drug class appears safe in neurosurgical patients. Other reported adverse effects of dexmedetomidine include nausea, vomiting, fever, dry mouth, anxiety, and atrial fibrillation, although the incidence of these side effects were not significant compared to placebo. Rare elevations in hepatic enzymes have also been reported.

Drug–Drug Interactions. Because of its sedating properties, dexmedetomidine can potentiate the effects of other centrally acting depressants. Hypotension and bradycardia can be exacerbated by concomitant administration of antihypertensive and antidysrhythmic medications. Conversely, tricyclic antidepressants combined with clonidine may produce a paradoxical increase in blood pressure. Similarly to the previously mentioned sedatives, caution should be used when combining alpha-2 agonists with multiple medications, especially in hypovolemic or otherwise hemodynamically unstable patients. In vitro studies show inhibition of the cytochrome P450 enzymes by dexmedetomidine. However, this does not appear to have clinically significant effects on the metabolism of other agents metabolized via this pathway.

Pharmacokinetics and Dosing

Dexmedetomidine. Dexmedetomidine is only given as an IV infusion, which rapidly distributes to the brain with an equilibrium half-life of 6 to 9 minutes. The elimination half-life in healthy volunteers is ~2 hours, but due to extensive hepatic metabolism may increase up to 7.5 hours in individuals with hepatic insufficiency. Its relatively short half-life allows for easy titration of dexmedetomidine. Excretion is primarily via the kidneys as inactive methyl and glucuronide conjugates. Dexmedetomidine is 94% bound to plasma proteins and has a Vd of between 100 and 120 L. When used for procedural sedation in nonintubated patients or in the ICU for sedation of mechanically ventilated patients, a bolus dose of 1 mcg/kg over 10 minutes (which is optional) followed by a continuous infusion of 0.2 to 1.0 mcg/kg/hr is recommended for up to 24 hours. Recent data suggesting infusion doses up to 1.4 mcg/kg/hr for durations up to 30 days have been shown to be safe. Dosage adjustments may be necessary in patients with hepatic insufficiency.

Neuroleptics/Antipsychotics

Neuroleptics are considered the drug of choice for patients diagnosed with delirium. The lack of respiratory depression makes them potentially attractive alternatives to more conventional sedatives for nonintubated patients. The 2 most common agents used in the ICU and anesthesia realms are the butyrophenones, haloperidol, and droperidol. Recently, the atypical antipsychotics have been studied for their role in sedation in the ICU environment.

Mechanism of Action. Neuroleptics produce both therapeutic and adverse effects by blocking cerebral and peripheral (but not spinal) dopamine, adrenergic, serotonin, acetylcholine, and histamine receptors, with variable selectivity depending on the agent. These effects include sedation (tolerance develops with repeated dosing), anxiolysis, restlessness, suppression of aggression and emotional outbursts, a reduction in delusions, hallucinations, and disorganized thoughts (following repeated doses), antiemetic properties, hypotension (variable by agent), and extrapyramidal side effects. Haloperidol and droperidol have limited anticholinergic properties compared to other neuroleptics, reducing the occurrence of blurred vision, urinary retention, and GI hypomotility.
Rationale for ICU Use and Adverse Reactions. The utility of neuroleptics is in the treatment of acute agitation secondary to psychosis or delirium. Their adverse effects negate the use of these agents for mild sedation. However, when appropriate, the anxiolytic effects can be dramatic and provide the necessary conditions to enhance ICU management. Studies have documented the adverse effect of ICU delirium on patient ICU length of stay and mortality.11

Unfortunately, the use of these agents has many potential physiological and neurological complications that limit their use in the ICU. Extrapyramidal side effects (eg, parkinsonism, acute and tardive dystonia, tardive dyskinesia, akathisia, and perioral tremor) can occur frequently with use. Although less common with butyrophenones than with phenothiazines, such motor disturbances may occur with either haloperidol or droperidol. Droperidol has little effect on ICP, although cerebral perfusion pressure was decreased due to moderate systemic hypotension.55

The lowering of the seizure threshold has been a longstanding concern for the phenothiazines. Neuroleptics can induce slowing and synchronization (with associated increased voltage) of the electroencephalograph (EEG).64 Effects on the seizure threshold are highly variable depending on the agent. The newer atypical agents (ie, aripiprazole, quetiapine, risperidone, and ziprasidone), haloperidol, and related butyrophenones (including droperidol) have unpredictable effects on seizure threshold, and although most studies suggest a low risk, caution should be used in patients with known seizure disorders.

The butyrophenones have significant effects on the cardiovascular system. Both droperidol and haloperidol can induce QT prolongation and tordades de pointes, and warnings have been issued regarding this effect even with low doses of droperidol, greatly limiting its use for perioperative sedation and as an antiemetic.65 As a result, droperidol is contraindicated in patients with QT prolongation and should be used with caution in those at risk of cardiac dysrhythmias or with concurrent medications that can prolong the QT interval (eg, antihistamines, some antibiotics, class I or III antiarrhythmics, and many antidepressants). The effects on the QT interval are less pronounced with the atypical agents, but caution should still be taken when starting these agents in patients at risk of cardiac dysrhythmias. Hypomagnesemia and hypokalemia should be avoided and treated, and it is recommended to have continuous electrocardiographic (EKG) monitoring for several hours following administration. The butyrophenones can cause hypotension, via peripheral vasodilatation, when given IV and frequent blood pressure monitoring should be performed during the administration and use of these agents.

Other potential side effects including anticholinergic effects, increased prolactin secretion, neuroleptic malignant syndrome, and jaundice (rare with butyrophenones) have been reported for neuroleptics in general.64 As with all medications, nonspecific adverse effects have been reported, which include anaphylaxis, laryngospasm, and bronchospasm.

Drug–Drug Interactions. As previously mentioned caution should be used when given concomitantly with drugs that prolong the QT interval. Also, due to their sedative and potential autonomic effects, the effects of other sedatives agents (including anticonvulsants) may be enhanced when neuroleptics are given. Medications that induce the hepatic microsomal enzymes may increase the rate at which these agents are metabolized. Selective serotonin reuptake inhibitors can compete with neuroleptics for hepatic oxidative enzymes and therefore may elevate circulating levels of haloperidol or droperidol.

Pharmacokinetics and Dosing

Haloperidol. Haloperidol is lipophilic and highly bound to plasma protein (greater than 90%) with a Vd of 9.5 to 21.7 L/kg. Sedative effects can be seen within minutes following IV administration. Plasma half-life varies from 10 to 36 hours, but the effective half-life may be much longer (a week or more) due to accumulation in brain and other tissues with a high blood supply. Haloperidol is available as IM, IV, or oral dosage forms. IV dosing allows for rapid onset and easy titration, but caution should be used with repeated dosing due to highly variable metabolism and elimination that can lead to systemic accumulation. Initial IV doses of 0.5 to 5 mg have been used for sedation. Dosages should be decreased in the elderly and those with hemodynamic instability or at high risk of seizures. The half-life is 12 to 36 hours, but active metabolites may remain for a much longer period.

Droperidol is only available IV and is extensively bound to plasma protein and has a Vd of 2 L/kg. When administered IV, droperidol has a rapid onset (1-3 minutes), although peak effects may take up to 30 minutes. Duration of action varies from 2 to 12 hours, and elimination appears to follow first-order kinetics even at high doses. Systemic elimination mirrors hepatic blood flow, and thus metabolism is presumably similar to that of haloperidol. Therefore, caution should be used with repeated dosing due to highly variable metabolism and elimination that could lead to systemic accumulation. For sedation in the setting of agitation, starting doses of 0.625 mg to a maximum of 2.5 mg IV are recommended. Additional doses should not exceed 0.625 to 1.25 mg IV every 2 to 4 hours.

Atypical agents. Olanzapine, quetiapine, and risperidone are the atypical agents that have been studied in the ICU patient populations for the treatment of delirium. All the listed agents have been studied with the oral dosage form, as IV forms are currently not available. All the atypicals are highly protein bound to plasma proteins (93%, 83%, and 90% for olanzapine, quetiapine, and risperidone, respectively) and metabolized extensively via cytochrome P450 enzymes in the liver. Following oral administration peak plasma levels are reached in 6, 1.5, and 1 hour for olanzapine, quetiapine, and risperidone, respectively. The respective plasma half-lives for each of the agents are ~30, 6, and 25 hours. Recommended dosing for olanzapine is 2.5 to 5 mg daily initially titrating up based on clinical judgment and use of rescue therapy.67 Quetiapine dosing is typically initiated at 25 to 50 mg twice daily and can be titrated up to 200 mg twice daily68,69; and in 1 pilot study, quetiapine in addition to PRN haloperidol resulted in faster time to
delirium resolution compared to haloperidol plus placebo (1 vs 4.5 days, \( P = .001 \)). Of note, patients with neurologic injury were excluded from this study. Risperidone dosing should be initiated at 0.5 mg twice daily, increasing to a maximum of 2.5 mg/day. Duration of treatment of delirium with the atypical agents ranges from 7 to 14 days.

### Propofol

Propofol is the most commonly used anesthetic for sedation in critically ill patients as well as for general anesthesia in the United States. It is an ultra-short-acting alkylphenol; although structurally distinct, its clinical effects, effects on cerebral activity, and intracranial dynamics are similar to short-acting barbiturates such as thiopental. It has an extremely high rate of clearance that is exhibited in its even shorter duration of action, especially following prolonged infusions, as compared with barbiturates. The advantages over older agents include less emetic properties, it is mood stabilizing, and easily titratable. Unfortunately, reports describing a syndrome of fatal metabolic acidosis and myocardial failure following high dose (>5 mg/kg/day), long-term administration (>48 hours) of propofol in serious neurological injury and/or sepsis has tempered enthusiasm for this agent.

#### Mechanism of Action

The specific mechanism of action for propofol remains unclear. Propofol is a phenolic compound with general anesthetic properties whose mechanism is unlike any other agents currently in use. It is hypothesized that a GABAergic mechanism is based on in vivo and in vitro binding studies, with evidence that propofol may directly bind to GABA\(_A\) receptors and activate inhibitory chloride channels in the absence of GABA. Other studies suggest a nonspecific, but structurally dependent effect on neuronal plasma membrane fluidity.

#### Rationale for ICU Use and Adverse Reactions

The ultra-short duration of action allowing for rapid titrations and rapid elimination are the advantages of this agent in the ICU. It can suppress EEG activity similar to the barbiturates, from increasing theta and delta to a flat EEG pattern during deep general anesthesia. Thus, this drug can be used to suppress seizure activity at high doses. As a sedative—hypnotic, propofol provides sedation devoid of any analgesia. Due to a dose-dependent effect on cerebral metabolism, propofol also has a role in the control of intracranial hypertension.

Propofol is by no means an ideal drug especially in the ICU. As previously mentioned, since there is no analgesic action this agent should not be used alone during sedation for painful maneuvers/procedures. It can cause hypotension due to both vasodilatation and a negative inotropic effect, and it impairs the cardio-accelerator response to decreased blood pressure. This hypotension may be pronounced in patients with reduced cardiac outputs, hypovolemia, on other cardiodepressant medications, or in the elderly. As a result, when used to sedate patients with severe TBI, propofol may diminish cerebral perfusion pressure even as it induces a decrease in ICP. Propofol has a dose-dependent respiratory depression and should be used in the setting of a protected airway or in the presence of experienced critical care or anesthesia staff. During bolus or continuous infusions of propofol, frequent or continuous monitoring of pulse oximetry, respiratory rate and depth of respiration, and blood pressure are recommended. Invasive blood pressure and cardiac output monitoring may be necessary for high-dose propofol (eg, burst suppression EEG) due to the cardiac-related adverse effects.

Due to its insolubility in water, propofol is suspended in an emulsion of soy, glycerol, and egg phospholipids leaving it susceptible to bacterial contamination. Some emulsions contain disodium edentate or EDTA as bacteriostatic agents but vials should still be handled in an aseptic manner. The infusion tubing and any unused solutions should be discarded within 12 hours once the sterile seal is broken. Injection site pain is a common adverse effect due to the carrier solution, which can be lessened by administration through a central or larger vein, or by pretreatment with IV lidocaine (0.5-1 mg/kg). Anaphylactoid reactions with propofol are rare, and most immunologic reactions are due to the emulsion carrier that contains egg and soy proteins. Thus, its use is contraindicated in patients with severe allergic reactions to these food substances. Hypertriglyceridemia may also occur, particularly at higher doses or with prolonged infusions, due to the lipid vehicle. Additionally, the lipid vehicle provides 1.1 kcal/mL due to the fat content, and nutritional requirements should be adjusted for this consideration.

Fospropofol, the water-soluble prodrug of propofol, was recently approved by the FDA for use in instances of procedural sedation (bronchoscopy and colonoscopy). By eliminating the lipid-emulsion carrier solution, some of the disadvantages of propofol could be reduced (eg, injection site pain, hypertriglyceridemia, infections from bacterial contamination). As one would expect for a prodrug, the onset of action is increased for fospropofol and as is the duration of action, 4 to 12 minute (onset) and 5 to 18 minute (duration), following bolus administration. Liberated propofol from the prodrug also exhibits a lower peak concentration than that of the lipid-emulsion propofol, theoretically minimizing the risk of oversedation. Fospropofol is administered via bolus injection with intermittent supplemental doses every 4 minutes during the procedure. Fospropofol has been studied in mechanical ventilation in the ICU, but at the time of writing there have been no published clinical results from these studies.

Although the side effect profile is more favorable than that of barbiturates, “propofol-related infusion syndrome” (PRIS) has been described in pediatric and adult patients receiving doses greater than 80 mcg/kg/min for prolonged periods of time. While the exact mechanism of PRIS is still unclear, the clinical signs include metabolic acidosis, hyperkalemia, rhabdomyolysis, hypoxia, and progressive myocardial failure. Many of the case reports describing this syndrome have been in critically ill patients receiving multiple other medications that may have initiated the metabolic disorder. Monitoring for
electrolytes derangements or increases in lactic acid, creatinine kinase, and/or triglycerides is recommended in patients receiving higher doses (>80 mcg/kg/min) for greater than 48 hours. We recommend these laboratory parameters be checked at least once daily for patients at risk.

**Drug—Drug Interactions.** Propofol may potentiate the sedating or cardio depressant effects of concomitant alcohol, opioids, benzodiazepines, barbiturates, and other general anesthetics, anti-hypertensives, and antiarrhythmics. Propofol does not appear to alter metabolism, elimination, or plasma protein binding of other drugs. Due to the reports of PRIS, caution should be used combined with agents that can cause rhabdomyolysis, metabolic acidosis, or myocardial failure.

**Pharmacokinetics and Dosing.** Propofol is rapidly distributed to the brain following IV administration due to its similarity in lipophilicity to thiopental. The distribution half-life ranges from 1 to 8 minutes, with an equally rapid recovery following redistribution to other less perfused tissues. Propofol has a high total body clearance (1.5-1 L/min), which is greater than that of hepatic blood flow; this is suggestive that there are extrahepatic sites of metabolism. The short elimination time allows for more rapid recovery following cessation of a continuous infusion. Propofol has a Vd of ~60 L/kg and is also extensively bound to plasma protein (97%–99%), with elevated free circulating levels in hypoalbuminemic states. Propofol is administered IV at a premixed concentration of 10 mg/mL (1%). For ICU sedation, it is given as a continuous infusion, doses range from 5 to 80 mcg/kg/min, but it may be given as boluses in other indications (eg, burst suppression EEG for refractory status epilepticus or refractory intracranial hypertension) as general anesthesia doses from 100 to 300 mcg/kg/min may be required. Due to its insolubility in water, propofol is suspended in an emulsion of soy, glycerol, and egg phospholipids, leaving it susceptible to bacterial contamination. The emulsion contains disodium edetate as a bacteriostatic agent but should still be handled in an aseptic condition. The infusion tubing and any unused solutions should be discarded within 12 hours once the sterile seal is broken.

**Barbiturates**

The barbiturates were extensively used sedative–hypnotics which have largely been replaced by safer alternatives. They can provide CNS depression, ranging from mild sedation to general anesthesia. They reversibly depress activity within all excitatory tissue, via action on the GABA receptor, which owns to the appeal for use as a general anesthetic. To narrow the drug class, pentobarbital, phenobarbital, and thiopental and their use in the ICU will be discussed.

**Mechanism of Action.** Barbiturates act throughout the CNS (both pre- and postsynaptically). The inhibitory effects occur primarily at synapses where GABA mediates neurotransmission. Barbiturates are distinct from other GABAergic agents in that they enhance the binding of GABA to the GABA\(_A\) receptor and also by promoting the duration that the receptor is open rather than increasing the frequency of the firing like benzodiazepines. The anti-anxiety properties of barbiturates are inferior to those provided by benzodiazepines.

**Rationale for ICU Use and Adverse Reactions.** Within the neuro-ICU patient population, barbiturate therapy still has a role in sedating patients who are refractory to other therapies (eg, benzodiazepines and/or propofol). Sedation with barbiturates is recommended for refractory intracranial hypertension management in patients with TBI. Barbiturates are also recommended for treatment of refractory status epilepticus in the most recent guidelines issued by the European Federation of Neurological Societies (EFNS). Barbiturates depress the neurogenic respiratory drive at hypnotic doses but can eliminate the neurogenic respiratory drive and depress the protective reflexes at anesthetic doses. When given orally in sedative or hypnotic doses, barbiturates do not significantly decrease blood pressure or heart rate anymore than what would occur during normal sleep. In cases of barbiturate toxicity hypotension, bradycardia and depressed cardiac contractility can occur. The best-known effects with barbiturates are those on the hepatic microsomal drug metabolism pathway, which will be discussed in the next section.

**Drug—Drug Interactions.** As discussed with previous sedatives—hypnotics, barbiturates can potentiate the sedative effects of other CNS-depressant agents. Barbiturates can competitively displace other drugs at metabolism sites, but the class is best known for inducing cytochrome P450 drug metabolism.

**Pharmacokinetics and Dosing**

**Thiopental.** The sulfur substitution on the barbituric acid ring owns to IV thiopental being the most lipophilic barbiturate discussed. The high lipid solubility allows for wide tissue distribution resulting in a short onset of action (<1 minute) and a short duration relative to the other barbiturates discussed (5-30 minutes with single doses). Thiopental varies in protein binding ranging from 60% in children to 97% in adults. Thiopental is primarily metabolized in the liver to pentobarbital and other inactive metabolites. The elimination half-life ranges from 3 to 18 hours, with longer half-lives due to redistribution into adipose tissue from repeated dosing.

For elevated ICP, it is recommended to dose thiopental at 1.5 to 5 mg/kg/dose and repeat as needed for ICP elevations. In refractory status epilepticus, the initial doses of thiopental range from 75 to 250 mg/dose, with repeated 50-mg doses every 2 to 3 minutes until seizures are controlled. Maintenance infusions of 3 to 5 mg/kg/hr may be needed in some cases. Dosage should be reduced by 25% in patients with impaired renal function (CrCl < 10 mL/min).

**Pentobarbital.** The primary metabolite of thiopental, pentobarbital, is a shorter acting barbiturate which is 35% to 55%
bound to plasma proteins and has a Vd of ~1 L/kg. Pentobarbital is primarily metabolized by hydroxylation and oxidation pathways in the liver. The elimination half-life of pentobarbital ranges from 15 to 50 hours, which can be prolonged in patients with hepatic insufficiency. The onset of action is ~1 minute with a duration of ~15 minutes following individual doses. For elevated ICP in TBI, pentobarbital should be loaded 10 mg/kg over 30 minutes followed by 5 mg/kg every hour for 3 hours. A maintenance infusion of 1 to 3 mg/kg/hr titrated to a burst-suppression EEG can then be given every hour for 3 hours. A maintenance infusion of 1 to 20 mg/kg loading dose over 1 to 2 hours followed by a 0.5 to 3 mg/kg/hr maintenance infusion titrated to a burst-suppression EEG are recommended.\textsuperscript{77}

**Phenobarbital.** When given orally, phenobarbital has good oral bioavailability of 80% to 100%. It is 20% to 60% bound to plasma proteins and has a similar Vd to that of pentobarbital (1 L/kg). Phenobarbital is metabolized via hydroxylation and glucuronide conjugation in the liver, with the inactive metabolites excreted in the urine. The elimination half-life is the longest of the barbiturates discussed, ranging from 40 to 140 hours. When given IV, the onset of action is ~5 minutes with a duration of action ranging from 4 to 10 hours.

For the control of status epilepticus, a 10 mg/kg loading dose (at a rate of 100 mg/min) can be administered followed by 50 mg/min until seizures are controlled. Therapeutic drug levels for seizures range from 10 to 40 mcg/mL. Dosage interval should be increased to 12 to 16 hours in patients with severe renal insufficiency (<10 mL/min). Phenobarbital is contraindicated in severe hepatic impairment.

**Summary**

Appropriate analgesia and sedation are key components to the management of any critically ill patient. Neurological patients can represent a challenging subset, given the need to balance both patient comfort and a high-quality neurological examination. Knowledge of the available agents and patient-specific variables is needed to achieve this balance, necessitating the need for an interdisciplinary approach. The appropriate agent should be chosen to address the underlying need for sedation: analgesia, anxiolysis, or treatment of delirium. Appropriate sedation scales should be utilized to define the depth of sedation, assure optimal dose titrations, and to assist in communication of the goals of therapy. The choice of sedative agent must be individualized for patient needs, cardiovascular and respiratory status, and presence of underlying cerebral pathology and other comorbidities to optimize patient comfort and safety.

**Declaration of Conflicting Interests**

The author(s) declared no conflicts of interest with respect to the authorship and/or publication of this article.

**Funding**

The author(s) received no financial support for the research and/or authorship of this article.

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