Patients who are critically ill and on mechanical ventilation frequently require sedation and analgesic therapy to optimize patient comfort, facilitate patient-ventilator synchrony, and optimize oxygenation. Despite the 2002 Society of Critical Care Medicine (SCCM) pain and sedation guideline recommendations that sedation and analgesic therapy be titrated to maintain patients in a pain-free and slightly sleepy state, recent data suggests that these endpoints are frequently not obtained. For example, one large observational study of sedation practices in 44 French ICUs found that 57% of patients on day 2 and 41% on day 6 were found to be deeply sedated (ie, sedation agitation score ≤ 2). The etiology of oversedation in the ICU is complex and has many drug and nondrug causes. Clinicians in the ICU are often slow to incorporate into practice sedation strategies that have been shown to reduce the duration of mechanical ventilation, such as protocolization and daily interruption of sedative administration. Even more important is the failure by clinicians to consider the numerous pharmacokinetic, pharmacodynamic, and pharmacogenetic factors that influence analgesic and sedative response, recovery, and safety in patients who are critically ill.

Although newer sedatives and analgesics such as dexmedetomidine and remifentanil have been the focus of many recent studies and are discussed in other articles...
in this issue of the *Clinics*, at most centers analgesics and sedatives such as fentanyl, midazolam, lorazepam, and propofol remain the mainstay by which patient comfort is optimized.9–11 Over the past few years the understanding of the factors that affect the efficacy and safety of these sedatives and analgesics has changed substantially.1,12 The limited number of methodologically sound clinical trials that have evaluated the use of these agents in the ICU, coupled with the ever-changing dynamics of critical illnesses, requires clinicians to have a thorough knowledge regarding analgesic and sedative pharmacology to optimize patient outcome. The objective of this article is therefore to review the pharmacology of commonly used analgesic and sedative agents including the opioids, benzodiazepines, and propofol. Specifically, this article focuses on the important pharmacokinetic, pharmacodynamic, and pharmacogenetic factors that clinicians should consider when developing an analgesic and sedation regimen that optimizes patient outcomes, reduces oversedation, and prevents medication-related adverse events.

PHARMACOLOGIC PRINCIPLES GUIDING THE USE OF ANALGESICS AND SEDATIVES IN THE CRITICALLY ILL

Several important pharmacologic principles are crucial when formulating an analgesic and sedative regimen in patients who are critically ill. The two pharmacokinetic parameters that will affect the drug response and safety most are volume of distribution (Vd) and clearance. Vd describes the relationship between the amount of drug in the body and the concentration in the plasma after absorption and distribution are completed. Vd is affected by body size, tissue binding, plasma protein binding, regional blood flow, and various physiochemical properties of the drug. Agents that are hydrophilic (ie, do not penetrate the fat well) remain within the plasma (eg, morphine) and have a low Vd (0.5 L/kg), whereas drugs that are lipophilic and sequestered outside the circulation (eg, midazolam) have a much higher Vd.13,14 With hepatic dysfunction present in more than half of patients who are critically ill, drug clearance may be reduced because of decreased hepatic drug flow, decreased hepatocellular enzyme activity, and decreased bile flow.15,16 With shock resulting in a threefold decrease in liver blood flow, the clearance of medications that rely on flow-dependent hepatic clearance (eg, morphine) is reduced. Critical illness may compromise the cytochrome P-450 (CYP450) enzyme system, the primary metabolic pathway for midazolam, fentanyl, and methadone, by decreasing hepatic drug flow, intracellular oxygen tension, and cofactor availability.16

Much of the currently available pharmacokinetic data for the benzodiazepines and opioids are derived from single-dose studies completed in healthy volunteers.16,17 Single-dose studies fail to predict the pharmacokinetic parameters that are seen after long-term infusions of these agents because of the multicompartment behavior of the parent drug and its metabolites.17 Results of studies completed in healthy volunteers cannot be extrapolated to patients who are critically ill because the alterations in volume status, plasma protein binding, and end-organ function that occur in this population will affect drug bioavailability, volume of distribution, and clearance.16

The pharmacodynamic response describes the relationship between drug concentration in both the serum and at the site of action and the observed clinical response. Determining pharmacodynamic response with analgesics and sedatives in patients who are critically ill is challenging given the large Vd of most agents, the difficulty in estimating drug concentrations at the receptor site, and the lack of objective measures of pain and sedation.13 Many of the genes that encode the proteins dictating drug metabolism, transport, and pharmacodynamic action display genetic
This genetic variability may account for up to half of the variability in drug response that is observed in practice and has been shown to affect the metabolism of fentanyl, methadone, and midazolam.19–22

**ANALGESICS**

Opioid analgesic medications remain the mainstay of therapy for alleviating pain in the ICU patient.1,2 This class of agents is also frequently used because of its sedative properties and to facilitate mechanical ventilation given its potent respiratory depressant effects. Neither acetaminophen nor the nonsteroidal antiinflammatory agents are discussed in this article given their weak analgesic activity and their propensity to cause adverse effects in patients who are critically ill.2

**Opioids**

**Pharmacology**

Morphine, fentanyl, and hydromorphone are the opioids that are most frequently used in the ICU.10,11 Opioids elicit their action through stimulation of the μ-, κ-, and δ-opioid receptors, which are widely distributed within the central nervous system and throughout the peripheral tissues.23 The μ-receptor is the primary site of opioid activity and is subdivided into the μ1- and μ2-subreceptors. Stimulation of the μ1-subreceptor leads to inhibition of neuronal pain, thus altering the perception and response to pain (Table 1). Opioids are divided into three primary classes based on chemical structure: (1) Morphine-like agents that include morphine and hydromorphone; (2) Meperidine-like agents that include meperidine, fentanyl, and remifentanil; and (3) Diphenylheptanes that include methadone.23 Remifentanil is reviewed elsewhere. The use of meperidine should generally be avoided in the ICU given its low potency, its propensity to cause nausea and vomiting, the fact that its use is contraindicated in patients receiving monoamine oxidase inhibitors or serotonin reuptake inhibitors, and the risk for the accumulation of its active metabolite, normeperidine, in patients with renal insufficiency.2 Normeperidine accumulation is associated with neuroexcitatory effects including tremor, delirium, and seizures.24 Methadone has N-methyl-D-aspartate (NMDA) receptor antagonistic effects that may be useful in the treatment of neuropathic and opioid-tolerant states.25,26

**Pharmacokinetics**

Most of the currently available pharmacokinetic information regarding opioids is from single-dose studies conducted in either healthy volunteers or patients with chronic diseases.27 A paucity of data therefore exists surrounding the use of continuously infused opioids in patients who are critically ill—a population with numerous factors that could affect opioid distribution and clearance.28 The intravenous route of administration is preferred in patients who are critically ill given the fact that it facilitates a faster onset of activity, provides a high bioavailability, and affords better dose titratability. The oral, transdermal, and intramuscular routes of administration are generally not recommended in patients who are hemodynamically unstable given the decreases in drug absorption that will occur in low-perfusion states.2 Fentanyl patches should be avoided for acute analgesia because the time to reach peak effect is delayed by up to 24 hours after patch application and a prolonged drug effect is seen after patch removal.2

The high lipophilicity of fentanyl provides it with a faster onset of activity via the intravenous route (almost immediate) than either morphine or hydromorphone (5–10 minutes for both). However, this high lipophilicity can lead to a prolonged duration of effect after repeated dosing or infusion.1 The Vd of hydromorphone is similar to...
<table>
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<th>Drug</th>
<th>Mechanism of Action</th>
<th>Time to Onset (min)</th>
<th>Half-Life (h)</th>
<th>Lipophilicity</th>
<th>Primary Metabolic Pathway</th>
<th>Presence of Active Metabolites</th>
<th>Pharmacogenetic Implications</th>
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<tr>
<td>Fentanyl</td>
<td>μ-receptor agonist</td>
<td>&lt;1</td>
<td>2–4</td>
<td>+++</td>
<td>N-dealkylation CYP3A4/5 Substrate</td>
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<td>Yes</td>
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<td>Hydromorphone</td>
<td>μ-receptor agonist</td>
<td>5–10</td>
<td>2–3</td>
<td>++</td>
<td>Glucuronidation</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Morphine</td>
<td>μ-receptor agonist</td>
<td>5–10</td>
<td>3–4</td>
<td>+</td>
<td>Glucuronidation</td>
<td>Yes</td>
<td>Yes</td>
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<td>Oral: 30</td>
<td>9–59</td>
<td>+++</td>
<td>N-demethylation CYP3A4/5, 2D6, 2B6, 1A2 substrate</td>
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<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Weak δ-, κ-receptor agonist</td>
<td>IV: 10–20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meperidine</td>
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<td>5</td>
<td>3–4</td>
<td>+++</td>
<td>N-demethylation and hydroxylation CYP3A4/2B6 Substrate</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
that of morphine. Methadone is a unique long-acting synthetic opioid that can be used to treat chronic pain syndromes when patients experience tolerance with other opioids and may help facilitate the down-titration of opioid infusions in the ICU. Oral methadone, when administered in the acute care setting, has an onset of action of 30 minutes, reaches a peak effect in 2 to 4 hours, and has a duration of analgesia ranging from 3 to 12 hours—a period far shorter than its half-life.

Following metabolism in the liver, opioid metabolites are excreted via the kidneys. Morphine undergoes glucuronidation producing both a 6-glucuronide and 3-glucuronide metabolite. Morphine-6-glucuronide has significant analgesic activity and may accumulate in patients with decreased renal function. Fentanyl does not have an active metabolite but the parent compound may accumulate in patients with renal insufficiency and thus should be avoided in end-stage renal disease. Hydromorphone has a half-life of 2 to 3 hours and also undergoes glucuronidation similar to morphine. However, the hydromorphone-3-glucuronide metabolite that is produced is inactive, making hydromorphone the opioid of choice for use in patients with end-stage renal disease.

Both fentanyl and morphine are high hepatic extraction ratio drugs; therefore, clearance may be reduced in patients with decreased hepatic blood flow (eg, shock). During the first 3 to 5 days of methadone therapy, a more frequent dosing regimen (eg, every 6–8 hours) may be required secondary to its highly variable elimination half-life, and it may require more aggressive dosing (eg, every 6–8 hours). Drug interactions are possible with both fentanyl and methadone given that each are primarily metabolized by the CYP450 enzyme system. Fentanyl is a substrate CYP3A4 and is affected by CYP3A4 inhibitors (eg, fluconazole) and inducers (eg, phenytoin). Methadone is a substrate of CYP3A4, CYP2D6, and CYP2B6 and therefore is affected by the many inhibitors and inducers associated with these CYP450 isoenzymes.

Pharmacodynamics
A predictable relationship between opioid blood concentrations and analgesic and respiratory depressant effects has not been established. This is surprising given the increasing evidence that analgesia-based sedation regimens may be as effective as conventional hypnotic-based sedation care. Given this lack of pharmacodynamic data, clinicians in the ICU should therefore titrate opioid therapy using a validated pain assessment tool (either verbal or nonverbal) or other physiologic endpoints (eg, heart rate, blood pressure, or respiratory rate).

Dosing and costs for selected opioid analgesics are found in Table 2. It is important to note that the maximum dose of an opioid that should be used in the ICU is only limited by the presence of adverse effects. Scheduled intermittent dosing is recommended rather than a continuous infusion to avoid drug accumulation. Patients who may require additional opioid therapy while receiving an opioid infusion should initially receive additional intravenous bolus doses rather than an increase in the infusion rate given the prolonged time it will take to reach a new steady concentration with any increase in the infusion dose. Use of a protocol incorporating daily awakening has been shown to decrease the amount of opioid administered and to shorten both duration of mechanical ventilation and stay in the ICU. When converting from one opioid to another, or switching from the parenteral to oral route of administration, it is important to note that traditional opioid conversion charts are based on studies conducted in healthy volunteers after receiving a single dose of opioid therapy via the intramuscular route and are not reflective of the dosing requirements with continuous intravenous infusions.
Tolerance, a decrease in a drug’s effect over time despite constant plasma concentrations, is a characteristic of all opioid analgesics. Tolerance occurs most frequently when opioids are continuously infused. While tolerance likely accounts for substantial dosing increases that are required in the ICU, it is hard to characterize given that opioid dosing requirements may be elevated secondary to increased pain or numerous different pharmacokinetic factors. The changes that occur at the opioid receptor site over time that lead to tolerance may be related in part to genetic adaption that affects receptor transcription. Synthetic opioids (eg, fentanyl) may result in a greater degree of tolerance than nonsynthetic opioids (eg, morphine) given their increased affinity at the opioid receptor. Clinicians should consider the use of alternate opioid agents of a different class in those situations where opioid dosing requirements are escalating and adverse effects are observed. Given the role of NMDA receptor system in nociception and the development of tolerance, antagonism of central NMDA receptors through the use of methadone is another strategy that may slow the development of tolerance.

Exposure to more than one week of high-dose opioid therapy may lead to the development of neuroadaptation or physiologic dependence in patients who are critically ill. It is important to recognize that opioid therapy should be titrated to achieve adequate pain control while minimizing the risk of side effects. The use of nonopioid analgesics and nonpharmacologic strategies should be considered to complement opioid therapy and improve patient outcomes.
ill. In this situation, rapid discontinuation of opioid therapy, particularly if a short half-life opioid like fentanyl has been used, may lead to withdrawal symptoms that include agitation, hypertension, tachypnea, and sweating. These symptoms may mimic other problems encountered in patients who are critically ill such as delirium. Opioid infusion rates should generally not be decreased by more than 25% each day. Use of methadone may decrease the occurrence of withdrawal effects.\textsuperscript{2,29,42}

**Pharmacogenetics**

Genetic factors have been shown to regulate both opioid pharmacokinetics (ie, metabolizing enzymes and transporters) and pharmacodynamics (ie, target receptor sites and signal transduction elements) and could be a major contributor to the interpatient variability in response that is observed in clinical practice.\textsuperscript{19} More than 100 variants in the $\mu$-opioid receptor gene OPRM1 have been identified of which 20 have a prevalence >1%. The most common single-nucleotide polymorphism of the $\mu$-opioid receptor gene is A118G.\textsuperscript{19} It has been associated with greater dose requirements for patients receiving morphine and methadone.\textsuperscript{19–21}

The most highly polymorphic CYP450 gene is the CYP2D6 gene, which has been studied extensively and has been found to have large interethnic variations.\textsuperscript{21} For example, patients with the CYP2D6 poor metabolizer phenotype are unable to metabolize codeine into its more potent morphine metabolite.\textsuperscript{20} Genetic variability in the CYP2D6 gene has been reported to account for some of the interindividual variability associated with methadone.\textsuperscript{19} One study found treatment success to be lesser in patients who were ultrarapid metabolizers than in those who were poor metabolizers.\textsuperscript{43} Methadone concentrations are increased twofold in patients carrying the CYP2B6*6-variant allele and the risk for corrected QT (QTc) interval prolongation is greater in patients with the CYP2B6 slow metabolizer phenotype.\textsuperscript{44,45} Fentanyl clearance may be lower in Caucasians than in non-Caucasians given that CYP3A5, one of its primary metabolic pathways, is highly expressed in only 30% of Caucasians.

Glucuronidation of morphine into its metabolites is catalyzed by the UDP-glucuronosyltransferase (UGT) enzyme, UGT2B7. Allelic variations of this enzyme have been associated with variability in hepatic clearance.\textsuperscript{46} P-glycoprotein (P-gp), encoded at the MDR gene, is an efflux pump that is capable of pumping opioids out of the cell and therefore it affects both opioid absorption and elimination. Of the opioids discussed in this article, fentanyl, methadone, and morphine have all been confirmed as P-gp substrates and therefore may have their activity affected by genetic polymorphisms at the MDR1 gene.\textsuperscript{19,21}

**Safety**

Adverse effects related to opioid therapy occur commonly in the ICU.\textsuperscript{12,32,47} Opioid-induced respiratory depression is generally dose-related and is most deleterious for the patient in the ICU who is not intubated. Although opioids can cause nausea and vomiting because of their stimulatory effect at the chemoreceptor trigger zone, this is infrequent in the recumbent patient in the ICU. Fentanyl when administered at high doses may cause muscle rigidity. Opioid-induced hypotension occurs most commonly in patients who are hemodynamically unstable, are volume depleted, or have a high sympathetic tone. Compared with fentanyl and hydromorphone, morphine is associated with histamine release and so produces more hypotension, urticaria, pruritus, flushing, and bronchospasm. A synthetic opioid like fentanyl can safely be used in patients with a suspected allergy to morphine.

Excessive sedation from opioids is most often seen with the use of continuous infusions, particularly in patients with end-stage renal disease who are administered
fentanyl or morphine. Methadone may cause excessive sedation if the dose is not titrated downwards after the first 5 days of starting therapy or if a CYP3A4 or CYP2D6 inhibitor is concomitantly administered. QTc-interval prolongation can occur with methadone because of its effects on the hERG channel, particularly if the chlorbutanol-containing intravenous formulation is used. Opioids may cause hallucinations, agitation, euphoria, and sleep disturbances and have been associated with the development of delirium. Of the opioids, methadone may be the least deliriogenic because of its antagonistic activity at the NMDA receptor. The effects of opioids on intracranial pressure in patients with traumatic brain injury remain unclear.

Gastric retention and ileus are common in patients who are critically ill and receiving opioids, with prokinetic therapy and/or post-pyloric access required in patients prescribed enteral nutrition. Prophylactic use of a stimulant laxative will reduce the incidence of constipation. Methylnaltrexone, an opioid antagonist specific to peripheral receptors, may have a role in treating opioid-induced constipation that fails to respond to laxative therapy. Opioid-induced urinary retention is rarely a problem for patients in the ICU given the widespread use of urinary catheters.

SEDATIVES
Benzodiazepines
Benzodiazepines (eg, diazepam, lorazepam, midazolam) remain the most commonly administered class of sedatives for patients in the ICU given their potent anxiolytic, sedative, and hypnotic effects (Table 3). These observed pharmacologic effects depend on the degree to which the benzodiazepine binds to the GABA receptor, with 20% binding associated with anxiolysis, 30%–50% with sedation, and 60% with hypnosis. Although benzodiazepines induce anterograde amnesia, they do not cause retrograde amnesia. They have an opioid-sparing effect by their ability to modulate the anticipatory pain response. Benzodiazepines also have respiratory depressant effects, particularly when administered with an opioid.

Pharmacokinetics
Differences in the clinical response to benzodiazepines are related to both pharmacokinetic and pharmacodynamic factors and are most pronounced when these agents are administered as continuous infusions to patients who are critically ill. Midazolam is a short-acting, water-soluble benzodiazepine that undergoes extensive oxidation in the liver via the CYP450 enzyme system to form water-soluble hydroxylated metabolites, which are excreted in the urine. The primary metabolite of midazolam, 1-hydroxymidazolam glucuronide, has central nervous system (CNS) depressant effects and may accumulate in the patient who is critically ill, especially if kidney failure is present. In one series of patients on prolonged sedation >36 hours after cessation of a midazolam infusion, elevated levels of 1-hydroxymidazolam glucuronide were detected an average of 67 hours after the midazolam infusion was discontinued. Prolonged sedative effects with midazolam have also been observed in patients who are obese or have reduced serum albumin levels. Medications that interfere with CYP3A4 such as erythromycin, intraconazole, and diltiazem inhibit midazolam metabolism. Lorazepam is metabolized by hepatic glucuronidation to inactive metabolites that are cleared by the kidneys. In patients with liver failure, the metabolism of midazolam is more likely to be compromised than the metabolism of lorazepam. Although the greater lipid solubility of midazolam compared with lorazepam will result in a faster onset of action after a single intravenous bolus dose, it is also associated with a greater likelihood to result in a prolonged sedative effect when it is administered for a prolonged period. Patients who are obese are at particularly
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<th>Time to Onset (minutes)</th>
<th>Half-Life (hours)</th>
<th>Lipophilicity</th>
<th>Primary Metabolic Pathway</th>
<th>Presence of Active Metabolites</th>
<th>Pharmacogenetic Implications</th>
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<td>Diazepam</td>
<td>GABA&lt;sub&gt;a&lt;/sub&gt;/BZ receptor agonist</td>
<td>2–5</td>
<td>20–50</td>
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<td>Yes</td>
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<td>Lorazepam</td>
<td>GABA&lt;sub&gt;a&lt;/sub&gt;/BZ receptor agonist</td>
<td>5–20</td>
<td>10–20</td>
<td>++</td>
<td>Glucuronidation</td>
<td>No</td>
<td>Yes</td>
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<td>3–12</td>
<td>+++</td>
<td>Hydroxylation (CYP3A4/5 substrate)</td>
<td>Yes</td>
<td>Yes</td>
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<td>+++</td>
<td>Hydroxylation and glucuronidation (CYP2B6 substrate)</td>
<td>No</td>
<td>Yes</td>
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high risk for these effects. These differences lead to recommendations in the 2002 Society of Critical Care Medicine (SCCM) consensus guidelines that midazolam be used only for short-term (<48 hr) therapy and that lorazepam be used for patients in the ICU requiring long-term sedation. Though earlier randomized controlled trials have compared lorazepam with midazolam for long-term sedation and found no difference in the time to awakening between the groups, it should be noted that few of the patients in these comparative studies had renal, hepatic, or neurologic impairment at baseline.

**Pharmacodynamics**

The clinical effects of sedatives are usually measured in terms of time to effect, the ability to maintain sedation within a targeted range, the time to awaken, and the duration of mechanical ventilation. A limited number of studies have compared one or more of these outcomes to benzodiazepine serum drug concentrations. A recent study that compared clinical sedation scores with sedative exposure found only a moderate level of agreement to exist between the Richmond agitation sedation score and either the dose of lorazepam administered or the lorazepam plasma drug concentrations achieved. Another study of patients in the ICU that evaluated the pharmacodynamic response of lorazepam and midazolam after long-term continuous infusions concluded that variability in the sedative response to each agent that is observed in practice is an important reason for the oversedation that frequently occurs with the use of this class of agents.

Benzodiazepine dosing requirements are generally lesser in the elderly, given the greater Vd and reduced clearance seen in this population. Older patients require lesser benzodiazepine plasma concentrations to achieve levels of sedation comparable to those in younger patients. Patient-related factors that affect the benzodiazepine pharmacodynamic response are numerous and include age, concurrent pathology, prior alcohol use, and concurrent therapy with other sedative drugs. Benzodiazepine therapy should be initiated using a series of intravenous loading doses. Infusions should only be initiated when scheduled intermittent intravenous dosing does not reach the desired clinical end-point given the association between a prolonged duration of mechanical ventilation and the use of continuous infusions. Interruption of benzodiazepine sedation on a daily basis has been shown to shorten duration of mechanical ventilation without compromising the safety of the patient.

There is emerging evidence that delirium in the ICU is related to the administration of anxiolytic drugs, particularly lorazepam, thus strategies that can avoid this class of agents may help avoid delirium and the numerous negative sequelae associated with it. Delirium may be associated with alterations in level of consciousness, and the agitation that is sometimes present with delirium may lead to the administration of sedative agents, particularly if delirium is not recognized. Although the mechanism by which benzodiazepine drugs predispose patients to delirium remains unclear, the GABA receptor activation that this class of agents induces alters levels of potentially deliriogenic neurotransmitters such as dopamine, serotonin, acetylcholine, norepinephrine, and glutamate.

Posttraumatic stress disorder (PTSD) is frequent in ICU survivors. The amount of benzodiazepine administered during the ICU stay correlates with the severity of PTSD symptoms. In one study, every 10 mg increase in the dose of lorazepam administered was associated with a PTSD 10-Questions Inventory score increase of 0.39 (95% CI 0.17 to 0.61; \( P = .04 \)). Benzodiazepines remain the sedative drug of choice for patients admitted with substance disorders such as alcohol withdrawal. As with opioids, tolerance to benzodiazepines may occur after only a few hours of therapy,
and thus dosing requirements may increase. Benzodiazepines must be withdrawn with care, particularly after high-dose, long-term therapy. Administration of enteral lorazepam or diazepam may help prevent benzodiazepine withdrawal and help facilitate the down-titration of benzodiazepine infusions.

**Pharmacogenetics**

Increasing data suggested that the activity of CYP3A5, the primary isoenzyme that influences midazolam metabolism, is influenced by genetic polymorphism. It has been reported that individuals who are homozygotic for the CYP3A5*1 allele have increased hepatic levels of the protein CYP3A5 compared with individuals who are homozygotic for the CYP3A5*3 and CYP3A5*6 allelic variants. It is also important to note that critical illness itself has been associated with a substantial decrease in CYP450 isoenzyme 3A4 activity, which could also further influence the midazolam-related oversedation. Future research is required to focus the role of CYP3A5 genetic polymorphisms on the predisposition of patients for iatrogenic coma.

**Safety**

In patients who are not intubated, benzodiazepines must be used with caution because of their respiratory depressant effects. Paradoxic agitation has been described with lorazepam, which may be the result of drug-induced amnesia or disorientation. Lorazepam infusions should be diluted to a concentration of <1 mg/10 mL to prevent precipitation in the intravenous line.

Recent reports have alerted clinicians to the risks for toxicity related to propylene glycol (a diluent used to facilitate drug solubility) accumulation in patients receiving intravenous lorazepam. Toxocity from the direct effects of propylene glycol and its metabolites (ie, lactate, pyruvate) may result in hyperosmolar states, cellular toxicity, metabolic acidosis, and acute tubular necrosis. An infusion of 2 mg/h of lorazepam will lead to 19.9 g of propylene glycol per day—an amount that would be more than 11 times the World Health Organization’s recommended daily intake for a 70 kg adult. In addition to long-term and high-dose lorazepam therapy, other identified risk factors for propylene glycol toxicity include renal and hepatic derangement, pregnancy, age less than 4 years, and treatment with metronidazole. Monitoring propylene glycol serum concentrations is impractical in most institutions because these assays are rarely available. Instead, clinicians should monitor a daily serum osmol gap in patients who have received a daily lorazepam dose that exceeds 50 mg or 1 mg/kg based on a number of studies showing that an osmol gap greater than 10 to 15 reflects significant propylene glycol accumulation. Hemodialysis effectively removes propylene glycol and corrects hyperosmolar states, but generally discontinuing the parenteral lorazepam is all that is required.

**Propofol**

Propofol is an intravenous general anesthetic agent that has been widely used as a sedative in the ICU for nearly 20 years. It exhibits sedative and hypnotic properties at even low doses and has amnestic properties similar to that of the benzodiazepines. Its rapid onset and offset of action provides clinicians with a sedative option that is far more titratable than that of the benzodiazepines, and it is considered the preferred sedative for patients in whom rapid awakening is important. Controversy remains as to whether propofol acts as an effective anticonvulsant or in fact induces seizure activity. Propofol reduces intracranial pressure after traumatic brain injury more effectively than either morphine or fentanyl and also decreases cerebral blood flow and metabolism.
Pharmacokinetics
Propofol is hydrophobic and therefore is formulated in an oil-in-water emulsion. It provides 1.1 kcal/mL from fat and should be counted as a caloric source. A water-soluble prodrug of propofol, fospropofol, has recently been approved, although it is not well studied in the ICU setting. The lipophilic properties of propofol allow it to cross the blood-brain barrier rapidly. Metabolism of propofol occurs primarily by conjugation in the liver to inactive metabolites, which are eliminated through the kidneys. Clearance does not appear to be significantly altered by hepatic or renal disease, although in critical care populations, clearance is generally slower than in the general population because of decreases in hepatic blood flow. A slightly longer recovery from propofol therapy has been reported with long-term infusions. Elderly patients have decreased clearance and thus maintenance infusions should generally be reduced in an age-related fashion.

Pharmacodynamics
A recent study that evaluated the pharmacokinetics and pharmacodynamics of propofol in patients who are critically ill found that patients who were sicker (based on the sequential organ failure assessment [SOFA] score) were more likely to have a deeper level of sedation that may be related to decreased propofol clearance. In another study, Barr and colleagues showed that the offset of propofol activity can vary considerably and is a function of the depth of sedation, duration of the infusion, and patient size and body composition. For example, the emergence from a deep sedation (to decrease the Ramsey sedation score from 5 to 2) averaged 25 hours for a 24-hour infusion but increased to nearly 3 days for propofol infusions lasting 7 to 14 days.

In response to studies showing that continuous benzodiazepine infusions are associated with a longer duration of mechanical ventilation than propofol therapy, a recent prospective study compared scheduled intermittent lorazepam in conjunction with daily sedation interruption for patients admitted to the medical intensive care unit who required mechanical ventilation for at least 2 days. The authors concluded that sedation with propofol resulted in significantly fewer ventilator days than did scheduled intermittent lorazepam (median ventilator days 5.8 vs 8.4; P = .04).

The reasons that patients who receive propofol are on mechanical ventilation for a shorter period compared with patients who receive intermittent benzodiazepine therapy are unclear. One possible explanation may relate to differences in the pharmacokinetic and pharmacodynamic characteristics of each agent. With propofol’s shorter half-life, relative to lorazepam, its serum concentrations would be expected to decline more rapidly than lorazepam’s, even when lorazepam is administered on a scheduled, intermittent basis. The recent Awakening and Breathing Controlled study found that for those patients randomized to the spontaneous awakening trial arm, the benzodiazepine dose was lower, on average, compared with the dose in the control arm, but the average dose of propofol was not. This suggests that factors other than a reduction in the drug dose were responsible for the benefits observed with the spontaneous awakening trials.

Safety
Hypotension attributable to systemic vasodilation is a well-known adverse effect of propofol, particularly in hypovolemic patients. For this reason, and because of propofol’s rapid onset of activity, caution should be exercised when the use of a bolus is needed. Hypertriglyceridemia in ICU receiving propofol infusions occurs rarely and is typically associated with high propofol infusion rates, concurrent administration of parenteral lipids for nutrition or baseline hypertriglyceridemia. Propofol, like any
lipid-containing product, has been shown to have immunosuppressant effects, although the clinical importance of these effects remains unclear.86 Despite the presence of a preservative in all currently marketed formulations of propofol, both the propofol bottle along with the intravenous infusion set should be changed every 12 hours. Whether the preservatives used in commercially available propofol formulations (eg, ethylenediaminetetraacetic acid [EDTA] and sodium metabisulfite) have clinical effects other than their preservative effect remains to be established.

While propofol is generally considered a safe agent when prescribed based on product labeling recommendations, a troublesome syndrome known as the propofol related infusion syndrome (PRIS) has been reported with its use.87 PRIS was first described in 1992 in a case series of five pediatric patients in the ICU who developed metabolic acidosis with bradycardia and progressive myocardial failure resulting in death while receiving high dose propofol (>83 mcg/kg/min for >48 hours).88 Since this report, 38 cases of PRIS have subsequently been published in both adults and children with an associated mortality rate exceeding 80%. PRIS-associated clinical manifestations vary widely and have been reported to include: rhabdomyolysis, myocardial failure, acute renal failure, severe metabolic acidosis, bradycarrhythmias, cardiac arrest, dyslipidemias, and hypotension.89 Postulated risk factors for PRIS include propofol doses more than 83 mcg/kg/min, a duration of therapy more than 48 hours, concomitant use of catecholamine vasopressors or glucocorticoids, and an age more than 18 years.89–91 Other potential risk factors include having an inborn error of mitochondrial fatty acid oxidation or receiving a ketogenic diet.92,93 Recently, the product labeling of propofol has been changed to increase the prescriber’s awareness of PRIS. Current labeling advocates the optimization of hemodynamic and oxygen delivery parameters in all patients in the ICU treated with propofol in addition to the discontinuation of propofol if metabolic acidosis, rhabdomyolysis, hyperkalemia, and/or rapid progressive heart failure occur during therapy.94

Although PRIS is associated with a high mortality rate, the disparity between the high use of propofol in the ICU and the small number of published case reports of PRIS leaves the demographic and clinical factors associated with PRIS, particularly those factors associated with death, poorly characterized. One recent analysis of 1139 patients in the FDA MEDWATCH system with suspected PRIS (30% fatal) found that the presence of cardiac failure, rhabdomyolysis, hypotension, metabolic acidosis, and an age more than 18 years were each independently associated with death.95 Further study is needed to identify the incidence of PRIS and the exact mechanism(s) by which it occurs.

SUMMARY

The ideal sedative or analgesic agent should have a rapid onset of activity, a rapid recovery after drug discontinuation, a predictable dose response, a lack of drug accumulation, and no toxicity.96 Unfortunately, none of the earlier analgesics, the benzodiazepines, or propofol share all of these characteristics. Patients who are critically ill experience numerous physiologic derangements and commonly require high doses and long durations of analgesic and sedative therapy. There is a paucity of well-designed clinical trials evaluating the safety and efficacy of earlier sedative and analgesic agents in the ICU. In addition, the ever-changing dynamics of patients who are critically ill makes the use of sedation a continual challenge during the course of each patient’s admission. To optimize care, clinicians should be familiar with the many pharmacokinetic, pharmacodynamic, and pharmacogenetic variables that can affect the safety and efficacy of sedatives and analgesics.
REFERENCES


96. Diprivan for I.V. administration vol. 2007.