Adverse drug events associated with the use of analgesics, sedatives, and antipsychotics in the intensive care unit

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As critically ill patients frequently receive analgesics, sedatives, and antipsychotics to optimize patient comfort and facilitate mechanical ventilation, adverse events associated with the use of these agents can affect all organ systems and result in substantial morbidity and mortality. Although many of these adverse effects are common pharmacologic manifestations of the agent, and therefore frequently reversible, others are idiosyncratic and thus unexpected. The critically ill are more susceptible to adverse drug events than nonintensive care unit patients due to the high doses and long periods for which each of these agents are often administered, the frequent use of intravenous formulations that contain adjuvants that may lead to toxicity in some instances, and the high prevalence of end-organ dysfunction that affects the pharmacokinetic and pharmacodynamic response to therapy. This paper will review the most common and serious adverse drug events reported to occur with the use of sedatives, analgesics, and antipsychotics in the intensive care unit; highlight the pharmacokinetic, pharmacodynamic, and pharmacogenetic factors that can influence analgesic, sedative, and antipsychotic response and safety in the critically ill; and identify strategies that can be used to minimize toxicity with these agents. (Crit Care Med 2010; 38[Suppl.]:S231–S243)

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Most critically ill patients undergoing mechanical ventilation require the administration of at least two different analgesic and sedative agents for an average of 3 days to optimize patient comfort and safety, facilitate patient-ventilator synchrony, and optimize oxygenation (1–3). Delirium occurs in up to 50% of patients admitted to the intensive care unit (ICU), and antipsychotics remain the pharmacologic mainstay for its treatment (4). With an ever-increasing number of safety concerns associated with the administration of analgesics, sedatives, and antipsychotics, the likelihood of patients experiencing an adverse drug event to one or more of these agents during their ICU admission is high (5–7). Although many adverse effects are common pharmacologic manifestations of an agent (e.g., dexmedetomidine-associated bradycardia), and therefore frequently reversible, others are idiosyncratic (e.g., propofol-related infusion syndrome), unexpected, and may be associated with substantial patient morbidity and mortality (8, 9).

Adverse events related to sedative, analgesic, and antipsychotic therapy are far more likely to occur in the ICU than non-ICU setting due to the fact that these agents are usually administered at far higher doses and for longer periods than outside the ICU and the fact that critically ill patients have a higher prevalence of end-organ dysfunction (e.g., renal, hepatic) that may result in higher drug concentrations than in patients on the floor (6, 7, 10–13). Factors, such as altered postreceptor binding, down-regulation of receptors, and brain dysfunction, may dramatically alter the response of ICU patients to these agents (6, 7). Cardiac dysfunction may increase the risk for dysrhythmias and hypotension (6). Adjuvants in the injectable formulations that are frequently used in the ICU may result in toxic effects (6, 7, 13).

This paper will review the most common and serious adverse drug events reported to occur with the use of sedatives, analgesics, and antipsychotics in the ICU; highlight the pharmacokinetic, pharmacodynamic, and pharmacogenetic factors that can influence analgesic and sedative response and safety in the critically ill; and identify strategies that can be used to minimize toxicity with these agents.

Neurologic events

Oversedation

Despite 2002 Society of Critical Care Medicine pain and sedation guideline recommendations (1) that sedation and analgesic therapy be titrated to maintain patients in a pain-free and arousable state, recent data suggested that these end points are frequently not obtained (10, 14–16). One large observational study (14) of sedation practices in 44 French ICUs found that 57% of patients on day 2 and 41% on day 6 were deeply sedated (i.e., Sedation Agitation Score of $\leq$2). Another study (15) at a large academic institution found that one third of ICU patients were unresponsive and that only 2.6% of the nursing assessments considered these patients to be oversedated. Patients who become oversedated are more difficult to liberate from mechanical ventilation, placing them at greater risk for complications, such as ventilator-associated pneumonia (10). In

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Table 1. Patient-specific factors associated with decreased recovery of neurologic function with use of common analgesics, sedatives, and antipsychotics

	Analgesics			Sedatives				Antipsychotics	
	Fentanyl	Hydromorphone	Morphine	Dexmedetomidine	Lorazepam	Midazolam	Propofol	Atypicals	Haloperidol
Moderate renal dysfunction, CLcreat 10–30 mL/min	+	0	+	0	0	+++	0	0	0
End-stage renal disease, CLcreat ≤10 mL/min	+	0	+++	0	0	+++	0	0	0
End-stage liver disease	+	+	+	+++	+++	+++	0	+	+
Obesity	+++	+	+	0	+	+++	0	0	0
Continuous IV infusion	+++	+	+	0	+++	+++	0	0	0
Genetic factors	+++	+	+	0	+	+++	+	+	+

0, no effect; +, minor effect; +++, major effect; CLcreat, creatinine clearance; IV, intravenous.

addition, they cannot be screened for delirium, are unable to interact with family and their environment, and have a decreased ability to form factual memories, increasing their risk for developing posttraumatic stress disorder (10). Finally, a drug-induced coma that develops during the ICU admission is associated with a higher mortality than the presence of delirium alone (17).

Although oversedation may be caused, in part, by ICU clinicians choosing not to use sedation strategies, such as protocolization and daily interruption, the failure to consider the numerous pharmacokinetic, pharmacodynamic, and pharmacogenetic factors that influence analgesic and sedative response, recovery, and safety in the critically ill is likely a far greater reason for the oversedation that is observed in practice (Table 1) (6–8, 11–13, 18–21). Excessive sedation from opioids is most often seen with the use of continuous infusions, particularly in patients with end-stage renal disease who receive fentanyl or morphine (13). In contrast, remifentanil, an intravenous opioid with an ultrashort half-life, when compared with morphine, allowed patients to spend more time in the desired sedation range and reduced the duration of mechanical ventilation (22). The high lipophilicity of fentanyl can lead to a prolonged duration of effect after repeated dosing or infusion, particularly in patients who are obese (13). Fentanyl patches should be avoided for acute analgesia because the time to reach peak effect is delayed by up to 24 hrs after patch application, and a prolonged drug effect is seen after patch removal (6, 13). Methadone may cause excessive sedation if the dose is not titrated downward after the first 5 days of therapy or if a CYP3A4 or CYP2D6 inhibitor is concomitantly administered.

The interaction between drug metabolism and organ dysfunction can contribute to unexpected prolongation of effect. The metabolite of morphine, morphine-6-glucuronide, which may accumulate in patients with decreased renal function, will lower the level of consciousness and induce hyperanesthesia (23). Although 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 that are excreted in the urine, the primary metabolite of midazolam, 1-hydroxymidazolam glucuronide, has central nervous system depressant effects and may accumulate in the critically ill patient, especially in the presence of kidney failure (23). Sedative clearance and metabolism decrease in an age-related fashion; thus, infusion rates should be reduced in the elderly, whenever possible (13). One recent study (24) that evaluated the pharmacokinetics and pharmacodynamics of propofol in critically ill patients found that patients who were sicker (based on the Sequential Organ Failure Assessment score) were more likely to experience a deeper level of sedation that was tied to a decrease in propofol clearance.

Genetic polymorphism is felt to account for up to half of the variability in drug response that is observed in practice and has been shown to affect the metabolism and response to fentanyl, methadone, and midazolam (13, 21, 30). For example, individuals who are homozygotic for the CYP3A5*1 allele will have increased hepatic CYP3A5 activity and will clear midazolam faster than patients who are homozygotic for the CYP3A5*3 and CYP3A5*6 allelic variants (30).

Estimating drug effect with analgesics and sedatives in the critically ill is challenging, given the large volume of distribution of most agents, the difficulty in estimating drug concentrations at the receptor site, and the lack of routine use of objective tools to measure pain and sedation needs (1, 10–13). Compared with benzodiazepines, where the time to awaken is similar between lorazepam and midazolam, propofol and dexmedetomide are associated with faster neurologic recovery after discontinuation (25–29). For example, lorazepam administered continuously led to a greater occurrence of coma and less time within the desired sedation range than continuously infused dexmedetomidine (28). Similarly, continuous midazolam infusions lead to a longer duration of mechanical ventilation than continuous dexmedetomidine (29). Even when administered intermittently, lorazepam leads to a longer duration of mechanical ventilation than propofol (27). With the cost for 1 ICU day for a mechanically ventilated patient exceeding $6,000, a prolonged duration of mechanical ventilation due to oversedation can lead to substantial increases in the cost of care (31). Evidence suggests that the acquisition cost of sedative therapy contributes only a small amount to the total cost associated with a particular sedation treatment regimen. For example, although both propofol and dexmedetomidine have acquisition costs that are greater than that of the benzodiazepines, recent pharmacoeconomic analyses (25, 32, 33) have demonstrated that total costs of care are cheaper with propofol and dexmedetomidine.

Delirium

Delirium, characterized by fluctuations in mental status, inattention, disorganized thinking, hallucinations, disorientation, and altered level of consciousness, occurs frequently in the ICU (4). Delirium is asso-

ciated with higher mortality, a longer duration of mechanical ventilation, increased ICU and hospital lengths of stay, and a number of adverse post-ICU sequelae (34, 35). Nonpharmacologic strategies focused on resolving or preventing delirium are frequently unsuccessful; thus, many patients are treated with psychoactive medications (4).

Opioids may cause hallucinations, agitation, euphoria, and sleep disturbances and have been associated with the development of delirium (36). Of the opioids, methadone may be the least deliriogenic due to its antagonistic activity at the N-methyl-D-aspartic acid receptor (13). There is emerging evidence that ICU delirium is related to the administration of benzodiazepines; thus, strategies that can avoid this class of agents may reduce delirium and associated sequelae (28, 29, 37). Although the mechanism by which benzodiazepine drugs predispose patients to delirium remains unclear, gamma-aminobutyric acid receptor activation alters levels of potentially deliriogenic neurotransmitters, such as dopamine, serotonin, acetylcholine, norepinephrine, and glutamate.

Dexmedetomidine is associated with a lower prevalence of delirium than the benzodiazepines, and possibly less than with propofol or the opioids, because it has no interaction with the gamma-aminobutyric acid receptor and lacks anticholinergic activity (8, 28, 29). One recent multicentered, double-blind, randomized, controlled study (28) evaluated dexmedetomidine vs. continuous lorazepam in 106 mechanically ventilated medical and surgical ICU patients and found that dexmedetomidine therapy resulted in more days alive without delirium or coma (median days, 7.0 vs. 3.0; $p = .01$). The SEDCOM study (29) found a reduction in the prevalence of delirium (54% vs. 76.6%, $p < .001$) as well as an increase in the mean number of delirium-free days (2.5 vs. 1.7 days, $p = .002$) compared with midazolam. One recent study (38) suggested that dexmedetomidine may be a useful treatment for delirium.

Other

Fentanyl, when administered at high doses, may cause muscle rigidity (13). The effects of opioids on intracranial pressure in patients with traumatic brain injury remains unclear (13). The use of meperidine as an analgesic should generally be avoided in the ICU, given its low potency, its propensity to cause nausea and vomiting, 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).

Paradoxic agitation has been described with lorazepam that may be the result of drug-induced amnesia or disorientation or may reflect the association between lorazepam and an increased occurrence of delirium (37). Controversy remains regarding the role of propofol in seizures, with evidence suggesting that propofol induces seizure activity, induces motor activity without seizures, and is an effective anticonvulsant (13). Propofol-associated hypertonicity and seizure-like movements have been reported and are felt to occur when cerebral concentrations of propofol rapidly change (39). Despite these reports, propofol is recommended for the treatment of refractory status epilepticus (40).

Intravenous haloperidol is associated with a lower prevalence of extrapyramidal effects than oral haloperidol due to the fact that the intravenous (IV) formulation does not undergo first-pass metabolism and, therefore, generates less hydroxyhaloperidol (41). Atypical antipsychotics, increasingly being used to treat delirium in the critically ill, have a lower prevalence of extrapyramidal effects than either oral or IV haloperidol (35, 42–44). Dystonia reported with dexmedetomidine may be related to its effect on acetylcholine release (44). Neuroleptic malignant syndrome (4) has been reported with all antipsychotic medications and is reviewed in the paper by McAllen and Schwartz in this supplement.

Cardiac events

The medications available to provide analgesia and sedation for ICU patients and to treat delirium or other behavioral conditions are commonly associated with adverse cardiac events, such as alterations in heart rate or blood pressure, arrhythmias, or changes in conduction. These cardiac events are common among patients in the ICU, even without administration of these drugs, related to comorbid conditions, electrolyte and metabolic abnormalities, and the nature of their underlying critical illness. We will review the prevalence of cardiac events associated with the analgesics, sedatives, and antipsychotics that are most commonly administered in the ICU; present the etiology for these effects; and discuss treatment strategies, where possible.

Hypotension

Hypotension is common to all medications used to provide sedation, including propofol, benzodiazepines (e.g., midazolam and lorazepam), and α_2 agonists (e.g., dexmedetomidine). The decline in blood pressure is likely multifactorial, related to decreased environmental stimulation as sedation occurs, decreased sympathetic tone, and vasodilation, and is more likely to occur in patients who are hypovolemic or already hemodynamically unstable. An additional mechanism linking sedative medications with hypotension is drug-induced adrenal insufficiency, which is discussed elsewhere in this supplement.

In studies comparing drug classes, no consistent difference in the prevalence or degree of hypotension among sedative drugs has emerged. A recent pilot study (45) showed no difference in the frequency of hypotension when comparing dexmedetomidine (4.9%) and standard care with midazolam or propofol (2.3%, $p = .5$). The MENDS study (28) identified a similar frequency of hypotension (systolic blood pressure <80 mm Hg) between lorazepam (20%) and dexmedetomidine (25%, $p = .5$). A similar pattern was seen in the SEDCOM study, with essentially identical rates of hypotension (56%) and hypotension requiring intervention (28%) occurring between the dexmedetomidine and midazolam treatment arms. The varying occurrence of hypotension in these studies reflects different definitions and surveillance designs (28, 29). Older studies (46, 47) comparing propofol and midazolam demonstrated a similar occurrence of hypotension.

Hypotension is more frequent with morphine compared with fentanyl and its analogs (sufentanil, alfentanil, remifentanil) due to the greater degree of histamine release that occurs after morphine administration (48). A recent open-label study (49) comparing the combination of remifentanil and propofol with standard therapy, including propofol, midazolam, or lorazepam combined with fentanyl or morphine, showed no difference in hypotension. In general, hypotension associated with sedative or opioid should be first treated with fluid administration. If the hypotension fails to resolve, then cli-

Table 2. Incidence of bradycardia in intensive care unit dexmedetomidine randomized studies

Author, yr (Reference)	Details	Dexmedetomidine (%)	Comparator	p
Triltsch, 2002 (54)	ICU after surgery, DBR, n = 30		Placebo (propofol rescue)	
	Bradycardia (not defined)	0	13%	.48
Martin, 2003 (55)	ICU after surgery, MC, DBR, n = 401		Placebo (propofol rescue)	
	Bradycardia (not defined)	9	2%	.003
Herr, 2003 (56)	ICU after CABG, MC, ROL, n = 295		Propofol	
	Bradycardia (not defined)	3	1%	.45
Pandharipande, 2007 (28)	Mixed ICU, 2 centers, DBR, n = 106		Lorazepam	
	HR <60 beats/min	17	4%	.03
	HR <40 beats/min	2	2%	.99
Ruokonen, 2008 (45)	Mixed ICU, MC, DBR, n = 85		Midazolam or propofol	
	Bradycardia (not defined)	7	0%	.07
Riker, 2009 (29)	Mixed ICU, MC, DBR, n = 375			
	HR <60 beats/min or 30% drop from baseline	42	19%	<.001
	Treatment for bradycardia	5	1%	.07

ICU, intensive care unit; DBR, double-blind, randomized; MC, multicenter; CABG, coronary artery bypass graft; ROL, randomized, open label; Mixed ICU, medical and surgical patients; HR, heart rate.

nicians should consider a dose reduction, a switch to an alternate agent, or use of vasopressor therapy. Haloperidol, when administered intravenously, may also cause hypotension, particularly in patients who are volume depleted (1, 4).

Hypertension

Hypertension is common during ICU care, but it is rarely due to sedating drugs. Although hypertension will occur as these medications are being administered, it is more likely a preexisting problem or related to inadequate blunting of sympathetic responses from pain, anxiety, or dyspnea. The exception to this statement is dexmedetomidine, which can increase blood pressure related to the activation of peripheral α_2-adrenergic receptors, leading to vasoconstriction (50). In healthy volunteers, Ebert et al (51) confirmed a biphasic response with dexmedetomidine, in which lower serum concentrations (0.7–1.2 ng/mL) decreased blood pressure from baseline, and higher serum concentrations (>8 ng/mL) increased it. Consistent with this association between higher-serum dexmedetomidine concentrations and hypertension, use of a loading dose or higher infusion rates has been reported to cause transient increases in blood pressure (38, 50, 52–54).

Bradycardia

Bradycardia is common with the α_2-agonist class of drugs (dexmedetomidine and clonidine) via reflex responses from vasoconstriction, direct sympatholytic effects, and augmentation of cardiac vagal activity (51). Unlike the biphasic response seen with blood pressure, healthy volunteers receiving high doses of dexmedetomidine experience a consistent drop in heart rate (51). Clinical trials comparing dexmedetomidine with benzodiazepines or propofol, while not using a standard definition for bradycardia, showed a greater prevalence of bradycardia with dexmedetomidine compared with lorazepam or midazolam (Table 2) (28, 29, 54–56). However, severe bradycardia or a requirement for intervention for bradycardia was rare in each group, although it tended to be slightly more common with dexmedetomidine than comparators.

This prevalence of bradycardia is increased when additional chronotropic inhibitors (such as β blockers, calcium-channel blockers, or digoxin) are administered simultaneously with dexmedetomidine (57). Propofol use can also cause bradycardia that may, in some instances, result in the propofol infusion syndrome (13, 58). Fentanyl and its analogs can produce bradycardia by a vagomimetic action, especially with the larger doses administered in anesthesia compared with the lower analgesic doses most frequently employed in the ICU (48).

Tachycardia

Like hypertension, tachycardia occurs frequently when administering sedatives and analgesics, but it is most often due to the underlying illness, comorbidities, or pain (1). Withdrawal from prolonged use of these medications may also lead to tachycardia (59). Meperidine is unusual among the opioids in that it may cause tachycardia directly (48).

QTc interval prolongation and arrhythmias

Drug-induced conduction changes and arrhythmias can be exacerbated by multiple factors, including electrolyte abnormalities, structural heart disease, genetic predisposition, and drug-drug interactions (60, 61). In addition to these risks, an increased pretreatment QTc interval has been a strong predictor of drug-induced arrhythmias (62–63). Despite this association, many controversies regarding QTc monitoring and drug-induced arrhythmias make firm guidelines difficult, including how best to measure the QTc, what threshold should prompt drug discontinuation, and how frequently to monitor it (50, 64, 65, 66).

Heightened concern for the impact of methadone on QTc prolongation and a possible association with increased mortality resulted in a Food and Drug Administration (FDA) black box warning in 2006 (67). Additional data have confirmed that the IV formulation of methadone also prolongs QTc, given the preservative chlorbutanol that is contained in the formulation (68). An observational study (69) expanded the association between QTc prolongation and opiates beyond methadone to oxycontin, but not morphine or tramadol. A recent review article (70) recommended searching for additional risk factors for QTc prologation (female gender, hypokalemia, high-dose methadone, underlying cardiac conditions, congenital long QT-interval syndrome, and predisposing deoxyribonucleic acid polymorphisms) and obtaining a baseline electrocardiogram, personal and family history of syncope, and a complete medication history before starting methadone treatment. Similar recommendations (61, 71) from an independent panel were not universally em-

braced. Although true practice guidelines for this issue remain undefined, caution should guide us regarding the risk of QTc prolongation and methadone or oxycontin use.

A similar concern for QTc-interval prolongation has long been observed for the antipsychotic medications, especially the first-generation medications haloperidol and thioridazine (66, 72, 73). Data (72, 73) suggested that the second-generation or "atypical" agents, other than ziprasidone, prolong the QTC to a lesser degree than older antipsychotic medications, with quetiapine and olanzapine seeming to alter cardiac conduction the least. Pending additional research to better define this issue, caution is suggested when using antipsychotic agents, correcting electrolyte abnormalities aggressively, and avoiding haloperidol, thioridazine, and ziprasidone when the QTc interval is already prolonged or when the risk factors noted above for arrhythmias are present.

Although prolongation of the QTc interval has not been an issue with most sedative medications with the exception of propofol, differences in the occurrence of arrhythmias have been reported. In a randomized study after cardiac surgery, Herr and colleagues (56) showed that dexmedetomidine reduced the prevalence of ventricular tachycardia (0% vs. 5%, $p = .007$) and β-blocker use (37% vs. 51%, $p = .01$) compared with patients sedated with propofol. Although the benefit of perioperative β blockade has recently been questioned, several meta-analyses (74, 75) have suggested that the sympatholytic effects of α_2 agonists may be cardioprotective, although additional research is needed to confirm this effect.

Infectious events

For many years, any connection between sedative or analgesic medications and infection was rarely considered, and seemed largely theoretical. However, observations over the last 10 yrs have shifted our focus and renewed interest in this area. The association between sedation and ventilator-associated pneumonia and sedation strategies that shorten duration of mechanical ventilation have become part of care bundles to reduce ventilator-associated pneumonia (76–78). Although some have questioned the role of ventilator bundles and their specific components, processes and protocols guiding our care in the ICU are generally accepted to reduce adverse outcomes, and incorporating what we have learned about the link between sedation and infection makes sense (79). This issue remains complex however, as strategies to lighten sedation and shorten duration of ventilatory support seem to reduce the prevalence of pneumonia, but unplanned extubation, a common sequelae of lighter sedation strategies, has also been shown to increase the prevalence of pneumonia (80). The link between specific drug classes and infection can be categorized into: a) direct effects of drugs on the infectious process or the body's response to it, and b) indirect effects, such as increased infection related to longer ventilator times or longer ICU lengths of stay.

The immune system can be separated into the innate immune system and the adaptive immune system. The innate system provides the initial response to a pathogen or injury, is nonspecific, and includes defenses, such as mucosal barriers, cytokine and complement responses, phagocytes, natural killer cells, and gamma-delta T cells. The adaptive system is more specific, has a memory component, and includes antigen-stimulated B lymphocytes, antibody-secreting plasma cells, and helper and cytotoxic T cells (81).

Propofol has been shown to impair multiple aspects of the innate immune response, including reducing macrophage chemotaxis and phagocytosis, suppressing nitric oxide production, and limiting production of interferon, tumor necrosis factor, and various interleukins and reactive oxygen species (81). In addition, at clinically relevant concentrations, propofol inhibited chemotaxis, phagocytosis, and reactive oxygen species production from neutrophils (82). In rat models of sepsis, propofol blunts the increase in tumor necrosis factor and interleukin-6 levels after endotoxin administration, whether given immediately or 1–2 hrs after endotoxin administration (83, 84). Furthermore, high-dose propofol impairs bacterial clearance from the lung and spleen of rabbits injected with *Escherichia coli* (85). In addition to immune-mediated effects, direct infection from propofol contamination has been reported. These events involved differing organisms, including *Staphylococcus aureus*, *Candida albicans*, *Moraxella osloensis*, *Enterobacter agglomerans*, *or Serratia marcescens*, and usually involved lapses in the strict aseptic technique required for this lipid moiety (86–88).

Regarding the benzodiazepines, *in vitro* testing of clinically relevant concentrations of midazolam have shown inhibition of neutrophil chemotaxis, phagocytosis, and reactive oxygen species production (89). Similarly, morphine inhibits macrophage phagocytosis and activation, chemotaxis, nitric oxide production, and superoxide formation; cytokine expression *in vitro* suppresses natural killer cell activity (81). In contrast, clinically relevant concentrations of clonidine and dexmedetomidine had no influence on chemotaxis, phagocytosis, and oxygen radical production by neutrophils (90). Even dexmedetomidine concentrations of 100 ng/mL (nearly 100 times greater than serum concentrations measured during ICU human clinical use) did not alter neutrophil function (90, 91). Translating these *in vitro* data to human clinical use of dexmedetomidine, the randomized and blinded SEDCOM study (29) showed a 50% reduction in new infections with dexmedetomidine compared with midazolam. Although some have expressed concern about the safety of using dexmedetomidine in the setting of sepsis, a secondary analysis (92, 93) of 39 septic patients in the MENDS trial also suggested the risk of death at 28 days was reduced 70% in patients treated with dexmedetomidine compared with lorazepam. Although these studies were not designed or powered to definitively answer these questions, they provide provocative information that supports additional study regarding the link between sedative analgesic medication and infection (94).

Gastrointestinal effects

Both opioids and sedatives have been associated with gastrointestinal (GI) complications in critically ill patients, such as constipation, postoperative ileus, acute acalculous cholecystitis, and pancreatitis (95, 96). The GI complications of these agents are important to avoid among ICU patients, given the fact that they may compromise adequate nutrition and enteral drug absorption, and they may increase morbidity and prolong the duration of critical illness (97).

Opioid agents reduce gastric motility by activating μ (mu_2) receptors in the enteric nervous system, leading to altered neurotransmitter release (95). Morphine administration impairs gastric function, leading to constipation and, in some instances, postoperative ileus—a condition

associated with significant morbidity and prolonged ICU lengths of stay (95). ICU administration of morphine plus midazolam showed a greater delay in gastric emptying than propofol alone (98). Impaired gastric emptying can result in inadequate nutritional support, as well as an increased risk for GI reflux and aspiration (98). Antipsychotics, such as quetiapine and clozapine, may also cause constipation, which is dose-related, and may lead to severe sequelae, including bowel obstruction and necrosis (99). Acute acalculous cholecystitis associated with critical illness can be devastating. Opiate agonists may contribute to acute acalculous cholecystitis by producing prolonged spasms of the sphincter of Oddi. Morphine increases biliary tract pressure and may produce biliary pain, even in patients without biliary tract disease (96). This process may also induce acute pancreatitis.

Several case reports (100) have described drug-induced pancreatitis secondary to propofol administration. Propofol's lipid formulation places patients at risk for hypertriglyceridemia, a known risk factor of pancreatitis. As a result, clinical practice guidelines (1) recommended monitoring serum triglyceride concentration if propofol therapy is continued >48 hrs. Although hypertriglyceridemia is the most common cause of propofol-induced pancreatitis, several cases (101) of propofol-induced pancreatitis in patients with normal serum triglyceride concentrations have been reported. One review (100) of 512 ICU patients prescribed propofol for >24 hrs found that 18% (29 of 159) of patients developed hypertriglyceridemia, of whom three (10%) progressed to pancreatitis. Acute pancreatitis has also been described with the use of atypical antipsychotic agents. Although the incidence seems to be rare, it is frequently associated with substantial morbidity and prolonged hospitalization (102). In most instances, pancreatitis usually resolves after drug discontinuation and the initiation of supportive care.

Although the use of opioids, sedatives, and antipsychotics can rarely be avoided in the critically ill, clinicians should know and recognize possible GI complications associated with their use, discontinue therapy when possible, and consider management strategies for these complications as outlined elsewhere in this supplement.

Endocrine effects

The stress of critical illness often results in an increased circulation of catecholamines, cortisol, glucagon and growth hormone, and decreased insulin secretion (103). Atypical antipsychotic agents, particularly olanzapine and risperidone, have been documented to induce hyperglycemia that can lead to diabetic ketoacidosis (104). The direct mechanism has yet to be determined but is likely multifactorial, related to weight gain leading to increased insulin resistance, direct effects on islet cell function, or tissue insulin sensitivity (102). Although hyperglycemia usually presents after a course of therapy that is far longer than that used in most ICU patients, clinicians should nonetheless monitor the blood glucose in patients treated with these agents.

Most analgesic and sedative agents do not interfere with endocrine function when administered at normal therapeutic doses. Morphine use in critically ill patients was shown to have minimal effects on cortisol levels and no effect on plasma concentration of epinephrine (103). Additionally, neither midazolam nor propofol has been shown to inhibit adrenocortical axis activity (103). Etomidate, on the other hand, has a potent effect on adrenal steroidogenesis that can result in the transient suppression of adrenocortical function for 12–24 hrs, even after a single bolus dose (105). This adrenal suppression may negatively affect patient outcome, including mortality, in some critically ill populations, particularly patients with trauma or sepsis (105, 106). This potential for increased mortality secondary to acute adrenal suppression has led to calls for the use of etomidate to be avoided in the ICU (106). A new etomidate analogue, methoxycarbonyl-etomidate, retains etomidate's favorable pharmacologic profile but does not result in adrenocortical suppression after bolus administration and, thus, may prove to be a safer alternative in the ICU (107). A full review of etomidate-induced adrenal suppression can be found in the endocrine disorders paper in this supplement.

Although dexmedetomidine is an imidazole compound that is similar to etomidiate, current evidence does not suggest that it results in adrenal suppression. One large, prospective, randomized trial (108) did not demonstrate inhibition of adrenal steroidogensis in ICU patients who received dexmedetomidine for up to 8 hrs postoperatively. Additional endocrine-related effects associated with α_2 agonists include stimulation of growth hormone, lower levels of C peptide and serum catecholamines, and decreased insulin secretion (103, 108, 109).

Multisystem effects

Excipients in IV formulations

Excipients in IV sedative preparations have been shown to lead to several different adverse events (Table 3). Propylene glycol (PG) is the diluent for several sedative agents (Table 3) and has been identified as the offending toxic agent in several cases (110–115). The U.S. FDA considers PG safe for use as a vehicle for IV administration and for oral administration, and the World Health Organization considers PG safe as long as doses do not exceed 25 mg/kg/day (116, 117).

Patients with hepatic and renal insufficiency are at increased risk for PG toxicity (117). Approximately 55% of an administered dose of PG is metabolized by hepatic alcohol dehydrogenase to DL-lactaldehyde or methylglyoxal, whereas the remainder is excreted unchanged by the kidneys (112). However, as the dose of PG increases, the renal elimination decreases by up to 63%, possibly secondary to saturation of proximal tubular secretion (117). One of PG's metabolites, D-lactate, has been associated with a prolonged half-life, which has been hypothesized to contribute to the central nervous system toxicity associated with PG accumulation (112).

Lorazepam, although advocated in the 2002 Society of Critical Care Medicine sedation guidelines (1) as the continuous sedative of choice in patients requiring prolonged mechanical ventilation, contains 830 mg/mL of PG and accounts for most of the cases of PG toxicity that occur in the ICU (112). Diazepam may also induce PG toxicity when large doses are administered for seizure control or alcohol withdrawal (110). Although not as widely used, a barbiturate coma for refractory seizure control or refractory intracranial hypertension with either phenobarbital or pentobarbital should be monitored for PG toxicity. Distinguishing PG toxicity from sepsis may be difficult due to similarity of their presentation (110–115). Up to 19% of medical ICU patients receiving benzodiazepines containing PG develop metabolic evidence of PG toxicity (112). In one prospective series of adult ICU patients receiving >1

Table 3. Adverse drug events associated with common sedative excipient formulations

Intravenous Excipient	Products Containing Excipients	Populations at Increased Risk for Sequelae	Clinical Signs of Toxicity	Laboratory Monitoring	Threshold Dose and/or Clinical Triggers of Toxicity
Benzyl alcohol	Midazolam Propofol	Children	Neonatal gasping syndrome • CNS depression • Severe metabolic acidosis • Gasping respirations Skin breakdown Renal failure Hepatic failure Thrombocytopenia Seizures Intracranial hemorrhage Hypotension Bradycardia Cardiovascular collapse Death	↑ Serum creatinine ↑ LFTs ↑ Lactate ↓ Serum pH	JECFA daily limit: 10 mg/kg/day or 0.6 g/day Repeat doses not recommended in neonates; greatest risk associated with doses ≥99 mg/kg/day
Disodium edetate (EDTA)	Midazolam Propofol	Unknown	Hypocalcemia	Decreased calcium	None
Egg phosphatide	Propofol	Egg allergy	Hypersensitivity	None	Documented egg allergy
Glycerol	Propofol	Unknown	Digestive	None	1 g/dose or 3 g/day
Liposomal emulsion	Propofol		Hypertriglyceridemia Pancreatitis Infection Venous irritation Fat emboli PRIS	Triglyceride levels >500 mg/dL	Hypertriglyceridemia/pancreatitis: doses ≥3 mg/kg/hr (50 μg/kg/min) or duration >48 hrs PRIS: dose >5 mg/kg/hr (83 μg/kg/min) for duration >48 hrs
Parabens	Haloperidol	Unknown	Contact dermatitis Hypersensitivity reactions	None	None
Propylene glycol	Etomidate	Renal insufficiency	Hyperosmolality	Serum osmol >320 mOsm/kg	PG dose >1.45 g/hr or 35 g/day for 48 hrs
	Phenobarbital	Hepatic insufficiency	Renal dysfunction	Increased lactate	Osmol gap >10
	Pentobarbital Diazepam Lorazepam		Cardiac arrhythmias/asystole Hemolysis Seizure/coma CNS depression Agitation Hypotension Metabolic acidosis Methemoglobinemia	Decreased serum pH Increased PG levels Increased serum creatinine	>1 mg/kg/day lorazepam
Soybean oil	Propofol	Soybean allergy	Hypersensitivity reactions	None	Known allergy to soybean
Sulfite	Propofol	Unknown	Hypersensitivity reactions • Bronchoconstriction • Pruritis • Urticaria • Chest pain • Angioedema • Hypotension	None	JECFA daily limit: 0.7 mg/kg/day or 42 mg/day

JECFA, Joint Expert Committee on Food Additives; PRIS, propofol-related infusion syndrome; CNS, central nervous system; LFTs, liver function tests; PG, propylene glycol.

mg/kg of lorazepam in a 24-hr period, 64% developed toxic PG concentrations, and 67% developed clinical signs of toxicity (i.e., metabolic acidosis or acute kidney injury) (115). Patients with an osmol gap of ≥10 were 4.4 more likely to have toxic PG concentrations (115).

A high anion gap metabolic acidosis with elevated osmol gap is often the initial presentation of PG toxicity. Metabolic abnormalities have been reported to occur when serum PG levels range between 58 and 127 mg/dL, although levels ranging from 104 mg/dL and 144 mg/dL have been associated with clinical deterioration (110). A study by Arroliga and colleagues (112) reported that high-dose lorazepam (≥10 mg/hr) had a significant correlation with serum PG (r^2 = .557, p = .021) and serum osmolality (r^2 = .804, p = .001) at 48 hrs, and they proposed a formula for predicting serum PG concentration based on the measured osmol gap (−82.1 + [osmolal gap × 6.5]). The correlation between osmol gap and predicted PG concentrations increases if the amount of PG administered in the preceding 36 hrs before time when the osmol gap is measured is known. At a minimum, an osmol gap should be determined when the total lorazepam dose exceeds 1 mg/kg/day (114, 118, 119). Lactate concentration and anion gap have

not been determined to correlate with serum PG concentrations (111, 117).

When PG toxicity is suspected, all potential offending agents should be discontinued, and supportive care should be initiated. In severe cases, intermittent hemodialysis is effective in rapidly decreasing PG levels (120). High-dose lorazepam should be substituted with a non-PG containing benzodiazepine, such as midazolam, to prevent benzodiazepine withdrawal. Practice guidelines (1) recommended lorazepam infusion doses of 0.01–0.1 mg/kg/hr. Extrapolation of PG dosing from these guidelines would translate to 0.29–2.9 g/hr or 6.9–69 g/day (119). Wilson and colleagues (110) reported a safe dose of PG of up to 1 g/kg/day, whereas Yahwak et al (115) identified frequent PG toxicity when 1 mg/kg/day of lorazepam was administered (roughly equivalent to 415 mg/kg/day of PG). Although initially suspected to occur only with high-dose administration (e.g., 5 mg/hr for >5 days or >10 mg/hr for ≥48 hrs), recent monitoring thresholds have been lowered to 1 mg/kg/day (111, 112, 115, 119).

The development of propofol-related adverse effects may partially depend on the particular formulation of propofol that is administered. The standard propofol formulation consists of an oil-in-water emulsion, containing propofol (10 mg/mL), soybean oil (100 mg/mL), egg phosphatide (12 mg/mL), and glycerol (22.5 mg/mL) (121). The original branded product by AstraZeneca (Wilmington, DE) includes disodium edetate (EDTA) for the preservative and has a pH range of 7–8.5. Three subsequent generic products marketed in the United States contain the same lipid emulsion and propofol concentration but contain different preservatives and have different pH ranges. The preservative and pH ranges are as follows: 1) Baxter (Deerfield, IL) formulation (sodium metabisulfite with pH range, 4.5–6.4); 2) Bedford Laboratories (Bedford, OH) formulation (benzyl alcohol with pH range, 7–8.5); and 3) Hospira formulation (combination of benzyl alcohol and sodium benzoate with a pH range, 7–8.5). Each of these preservatives has been associated with unique adverse effects (Table 3). It is unclear if the different preservatives or pH ranges that result are responsible for any specific effects in ICU patients.

Propofol's lipid vehicle introduces further risk for adverse drug events. The lipid formulation accounts for 1.1 kcal/mL, reported to induce hypertriglyceridemia (triglyceride concentration of ≥500 mg/dL) in up to 18% of ICU patients and associated with pancreatitis (1, 100). After the detection of postoperative infections in patients receiving the old formulation of Diprivan (AstraZeneca) that did not contain a preservative, the FDA mandated that all propofol formulations be reformulated with a preservative and that each bottle, once punctured, should not be used for >12 hrs (1, 121).

Emulsion degradation may reduce propofol release and increase the risk for fat emboli (121). Compared with EDTA-containing propofol emulsions, the sulfite-containing propofol emulsions contain larger oil droplets, are less stable, and undergo lipid aggregation (121). In one rat model, microscopically visible aggregates of oil were found in the brains of rats administered the sulfite-containing preparation but not after administration of the EDTA-containing product (121). The fat emulsion in propofol has also been implicated in the development of propofol-related infusion syndrome (PRIS) (58).

In December 2008, the FDA approved the propofol prodrug, fospropofol disodium (Lusedra; Esai Inc., Woodcliff Lake, NJ), a water-soluble alternative to propofol postulated to have a cleaner safety profile. Fospropofol is enzymatically converted to propofol, formaldehyde, and phosphate *via* alkaline phosphatase. Depending on the patient population, reported adverse events include pruritus (16% to 28%), paresthesias (52% to 85%), and hypertension (4% to 6%) (122). The paresthesias have been most prominent in the perineal region with reports of unpleasant burning, itching, or tingling lasting up to 2 mins (122). Development of hypoxemia is rare (4%) with the administration of standard doses but can occur in up to 27% of patients when high supplemental fospropofol doses (1.6 mg/kg) are used (122). Adverse reactions are greater in the elderly, when cardiovascular disease is present or in those patients who are receiving concomitant medications with respiratory depressant effects (122). Further evaluation of the utility and safety of fospropofol in critically ill patients is warranted, especially given the presence of formate, which can inhibit the cytochrome oxidase chain, a pathway linked with PRIS, resulting in increased lactate production, metabolic acidosis, and death (122, 123). Additionally, the phosphate byproduct can accumulate, causing seizure activity. Pharmacokinetic and pharmacodynamic differences between propofol and fospropofol disodium have been described (122), including prolonged onset of action, an increased volume of distribution, and a longer half-life; and one evaluation (123) found increased potency upon conversion of fospropofol disodium. Cyclodextrin formulations of propofol are being evaluated for safety and efficacy, but human data have not been reported.

Withdrawal effects

Prolonged administration of analgesic or sedative agents may result in withdrawal effects in the setting of rapid tapering or acute discontinuation. Identifying withdrawal can be difficult in the critically ill, given the challenges in differentiating withdrawal from delirium or worsening critical illness and the fact that multiple agents with the potential to cause withdrawal may be stopped at the same time. In general, the signs and symptoms of opioid and benzodiazepine withdrawal can be classified into three categories: central nervous system stimulation (e.g., agitation, anxiety, irritability, restlessness, pupillary dilation, sleep disturbances, tremors, movement disorders, hallucinations, and seizures); gastrointestinal disturbance (e.g., vomiting and diarrhea); and sympathetic nervous system activation (e.g., hypertension, tachycardia, tachypnea, sweating, and fever) (1, 59, 124). The prevalence of withdrawal ranges from 17% to 57% in pediatric patients and 13% to 33% in adult patients (59, 124). Opioid withdrawal generally occurs from central nervous system hyperstimulation related to rebound increases in neurotransmitter release, whereas benzodiazepine withdrawal is a product of disinhibition of the central nervous system due to decreased efficacy of available gamma-aminobutyric acid at the receptor (124). The intensity of withdrawal from combination sedative and opioid therapy has been reported to peak within the sixth hour after acute cessation of therapy, although this would likely change depending on the pharmacokinetics of the specific drug, the duration and dose of administration, and the metabolic milieu of the patient (e.g., adipose mass, liver and renal function, and presence of medications that may induce or inhibit metabolic pathways) (125).

The occurrence of withdrawal has been linked to high doses and longer duration of administration (>5 days) in both pediatric

and adult populations (59, 124). Recently, withdrawal was also reportedly associated with delirium in adult patients (124, 125). Several recommendations have been made to minimize the potential for withdrawal syndrome, including attention to the rate of medication weaning and recognition of the signs and symptoms of withdrawal. Practice guidelines (1) recommended tapering over several days or switching to alternative sedative with long-acting effects. Administration of lorazepam or diazepam via the GI tract should also be considered. No gold standard method for tapering currently exists. Weaning recommendations (1) ranged from a total daily reduction of 5% to 10% or initial dose reductions of 24% to 40% followed by subsequent reductions of 10% once or twice daily. Conversion to subcutaneous opioid and benzodiazepine continuous infusion has been a proposed weaning strategy (124). Recently, this tactic was successfully described for management of withdrawal syndrome, using the α2-agonist dexmedetomidine; subcutaneous dexmedetomidine infusions maintained efficacy with no apparent adverse events (127). There is a growing body of evidence in the literature (124, 127, 128) to support the use of dexmedetomidine in the treatment and prevention of withdrawal syndromes in both pediatric and adult patients. Clonidine has also been effectively utilized in opioid withdrawal and tolerance. Although limited data are published, clonidine may also provide a bridge in avoiding withdrawal syndromes in critically ill patients receiving high-dose continuous opioid infusions (129). Its utility in alcohol withdrawal has not been as significant; thus, its role in benzodiazepine withdrawal has been questioned (130). Importantly, clonidine itself can cause rebound hypertension, if discontinued abruptly. This phenomenon has not been described upon abrupt discontinuation of dexmedetomidine with prolonged infusion (44). In addition to α2 agonists, N-methyl-D-aspartic acid antagonists have demonstrated efficacy in the prevention and treatment of opioid tolerance. Methadone has been successful to treat withdrawal, given the fact that it inhibits rebound increases in neurotransmitter release (59, 124). Finally, antipsychotic agents have been found to be effective in delirium and alcohol withdrawal and may be considered as an adjunctive treatment option in opioid and benzodiazepine withdrawal syndromes (42, 43, 129). The effect of daily sedation interruption on the incidence of withdrawal syndrome remains unclear and may be dependent on the half-life of the agent that is being interrupted.

PRIS

PRIS is an increasingly recognized and often deadly consequence of propofol infusion. The original definition by Bray (130) included the sudden onset of marked, refractory bradycardia with progression to asystole plus one of the following—hyperlipidema, clinically enlarged or fatty infiltration of the liver, severe metabolic acidosis, or muscle involvement with evidence of rhabdomyolysis or myoglobinuria. Reviews of this syndrome have identified that metabolic acidosis, cardiac dysfunction, hyperkalemia, hyperlipidemia, elevated creatine kinase levels, rhabdomyolysis, myoglobinemia and/or myoglobinuria, and acute renal failure are the most prominent clinical characteristics of PRIS (58, 131, 132). Knowledge regarding the pathogenesis of PRIS is evolving. Impaired liver metabolism and delayed clearance of propofol's fat emulsion, resulting in the accumulation of ketone bodies and lactate, have been postulated to contribute to acidosis (58, 131). Numerous reports (132) supporting defects or disruptions in the mitochondrial respiratory chain due to propofol infusion have been identified, including inhibition of oxidative phosphorylation (Fig. 1). The potential consequence of these effects is myocytosis, particularly in critically ill patients, secondary to a mismatch of low-energy supply and high-energy demand and consumption (132). It is not clear whether the development of PRIS results from a disruption in the mitochondrial respiratory chain due to the propofol emulsion or a genetic predisposition, such as medium-chain acetyl coenzyme A dehydrogenase deficiency (131, 132). A low supply of carbohydrate has been implicated because of the associated increase in lipolysis, augmenting the risk for PRIS (131). This may be more of an issue in children due to decreased glycogen stores and a higher dependence on fat metabolism (1).

Propofol has direct cardiac depressive effects via antagonism of β-adrenergic binding and interaction with calcium-channel proteins (132). Electrocardiographic evaluations in patients with PRIS have identified a Brugada-like electrocardiographic pattern with a down-sloping ST-segment elevation in precordial leads V1 to V3 (131). The development of left- or right-bundle branch block, left ventricular dysfunction, brady- or tachyarrhythmias, and cardiac arrest have also been reported in many PRIS cases (58). Concomitant use of catecholamine infusions may decrease propofol serum concentrations, resulting in the need for higher propofol dosing (133). Additional risk factors for PRIS drawn from retrospective evaluation of confidential safety data and published cases include poor oxygen delivery, sepsis, serious cerebral injury, and the administration of high propofol doses (58). A threshold dose for risk of developing PRIS was initially described to be ≥5 mg/kg/hr (83 μg/kg/min) for >48 hrs (58, 131, 133). The combination of priming (sepsis) and triggering factors (propofol and catecholamines) may result in the clinical manifestations of PRIS (132, 133).

The mortality rate (83%) in Bray's initial report (130) is greater than that since reported in numerous published case reports of PRIS. A recent, large, retrospective analysis (134) of the FDA's MEDWATCH database identified a mortality rate of 30% and found that the following factors were independently associated with increased mortality: age ≤18 yrs, and the presence of cardiac symptoms, metabolic acidosis, renal failure, hypotension, and rhabdomyolysis. A PRIS mortality risk score of 0 to 4 was developed, based on the presence or absence of the six identified predictors of mortality. However, this PRIS mortality risk score on further investigation did not correlate with observed mortality (135). A recent large, prospective, observational study (136) of 1,017 ICU patients at 11 academic centers, who were prescribed propofol for >24 hrs, identified a prevalence of PRIS (based on a conservative and evidence-based definition) of 1.1% and a mortality rate of only 18%. This lower mortality rate may be a result of heightened awareness of the syndrome and the fact that institutions have implemented guidelines that limit propofol doses and recommend the prompt discontinuation of propofol when PRIS symptoms occur.

To minimize the potential for PRIS, mechanisms to optimize hemodynamic and oxygen delivery parameters in critically ill patients receiving propofol

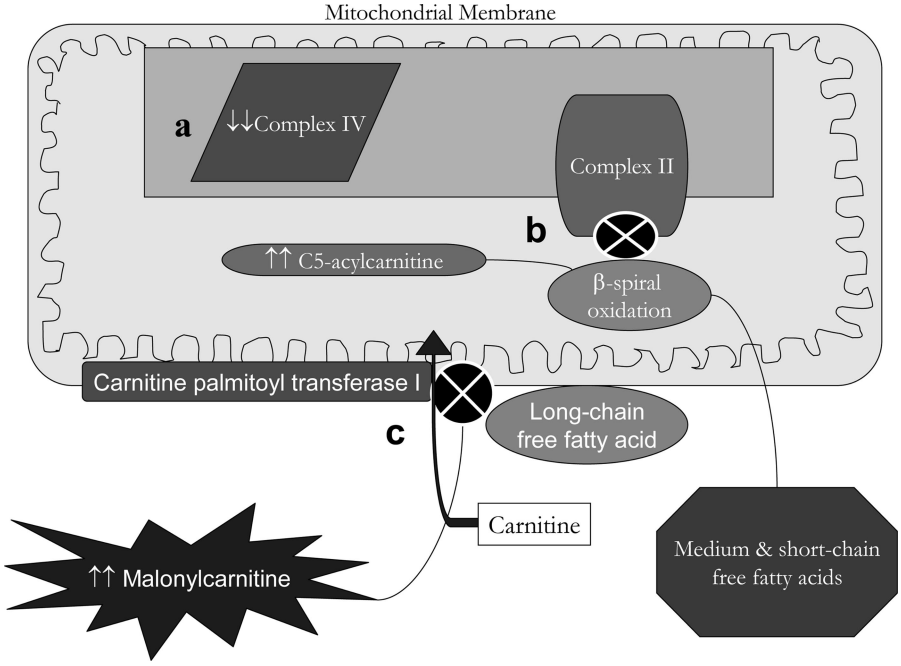

Figure 1. Proposed mechanism for the propofol-related infusion syndrome.

should be employed, and propofol doses for infusions of >48 hrs should not exceed 5 mg/kg/hr (58, 131, 132). Carbohydrate substitution at 6–8 mg/kg/min might prevent PRIS by suppressing fat metabolism. Recognizing the risk factors and clinical manifestations may be helpful in identifying patients developing PRIS. Monitoring parameters suggested by the FDA include blood pressure, electrocardiograph, and arterial blood gases to detect unexplained metabolic acidosis or arrhythmias. The American College of Critical Care Medicine suggested considering alternative sedative agents in patients with escalating vasopressor or inotropic requirements or in those with cardiac failure during high-dose propofol infusions (1, 58). The European Regulatory Authorities suggested monitoring for metabolic acidosis, hyperkalemia, rhabdomyolysis, or an elevated creatine kinase level, and/or the progression of heart failure during propofol use. If PRIS is suspected, propofol infusion should be discontinued immediately, and supportive care should be instituted to correct metabolic acidosis and other presenting symptoms. Hemodialysis or hemofiltration has reportedly been used successfully to help increase the elimination of propofol (131, 132). A number of unresolved questions surrounding PRIS remain that will require substantial research to answer (137).

Conclusion

Adverse drug events associated with the administration of sedatives, analgesics, and antipsychotics in the ICU are common and frequently serious. ICU clinicians should be aware of these adverse events, know the risk factors associated with their development, and be able to implement strategies that can be used to minimize or reverse toxicity.

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