A 52 year old man with a past medical history of depression presented to the emergency department with severe headaches, a right facial droop and right arm weakness. Soon after hospital admission, his mental status quickly deteriorated. A head CT revealed a left cerebellar intracerebral hemorrhage (approximately 20 cc); he was taken immediately to the operating room for a suboccipital decompressive craniectomy. His post-operative course was complicated by hydrocephalus, for which an extraventricular drain was placed, and ventilator-associated pneumonia. His neurological exam progressively improved over the course of a week, to the point where he was following simple commands and answering yes/no questions with gestures. On intensive care unit (ICU) day 6, he developed bilateral opacities on chest x-ray and severe hypoxemia and was diagnosed with acute respiratory distress syndrome. He was placed on a lung-protective low tidal volume ventilator strategy. He soon became acutely agitated with a Richmond Agitation Sedation Scale (RASS) score of +3, hypertensive, and was biting on the endotracheal tube. He had been receiving a fentanyl infusion at 200 mcg/hr. Propofol infusion was added at 20 mcg/kg/min and titrated up to 60 mcg/kg/min to further treat his agitation and facilitate ventilator synchrony. After initiation of propofol, he was no longer following commands (RASS -4). Intermittent interruptions of propofol were attempted to facilitate neurological assessment, but he would quickly become agitated (RASS +2) and hypertensive with associated ventilator dysynchrony and hypoxemia. Dexmedetomidine infusion was initiated, and titrated up to 0.6 mcg/kg/hr, with simultaneous weaning of propofol. Fentanyl was also weaned down to 100 mcg/hr, and a RASS of 0 to -1 was able to be maintained. His neurological examination returned to the state prior to propofol initiation.

**INTRODUCTION**

Common indications for sedation in the ICU may include the following: patient comfort, management of agitation, pain, ventilator dysynchrony, or intracranial hypertension. Neurologically injured patients may be the most difficult ICU population to manage in regards to sedation and analgesia because of the need for frequent and reliable assessment of the neurological examination unconfounded by sedatives. Cognitive dysfunction itself can lead to increased fear, restlessness, and agitation. However even modest sedation can mask subtle neurological deterioration. Thus, there is a need for an interdisciplinary approach to observation and titration of medications while minimizing the impact on the neurological evaluation. Sedation regimens in neuroscience ICU’s should ideally be designed to enable repeated achievement of a high-quality neurological examination as the principle means of assessing patient status [1].

Several triggers guide clinicians to provide sedation. Yet, “sedation” often includes the provision of analgesia, anxiolysis, antipsychosis, or a combination thereof. Correct diagnosis of the etiology of agitation becomes the starting point, as there are pharmacological options that can be guided towards differing pathologies.
GENERAL MANAGEMENT PRINCIPLES AND MONITORING

Pain

The importance of pain assessment and management has been reinforced by the development of standards by The Joint Commission as well as recent guidelines [2]. Patient reports of pain are the usual prerequisite for treatment with analgesic therapy. In addition to the stressors of the ICU, critically ill neurologic patients can have primary physiological reasons to experience pain (headache-migraine, elevated intracranial pressure, subarachnoid hemorrhage, neuropathy, etc.). These patients are often not able to verbalize pain; therefore, physiological signs (heart rate and blood pressure) are often used by clinicians during their assessment. Yet these methods may be inadequate to assess the level of pain or discomfort [3].

The ideal analgesic agent would strictly address pain and possess no deleterious effects; unfortunately no such agent exists. The balance between preservation of the neurological exam and adequate analgesia in neurologically injured or post-operative neurosurgical patients is often difficult to manage. The best method for establishing this balance has not been determined. However, a study by Morad et al. showed that a patient controlled analgesia regimen was more effective in terms of pain control with no major adverse events as compared to a traditional as needed (PRN) dosing strategy in post-operative neurosurgical patients [4,5].

Anxiety

Anxiety is a psychological state that can present as apprehension, general nervous tension, or agitation. The resulting physiological response may manifest as changes in blood pressure, heart rate, respiratory rate, or an overall excitatory state. The ICU environment can be anxiety-inducing, as it is unfamiliar, has constant noise and activity, and can produce disturbed sleep-wake cycles. Treatments and conditions that can contribute to anxiety include intubation and mechanical ventilation, sepsis, traumatic brain injury, stroke, medication side effects, and encephalopathy. Pain and anxiety often occur simultaneously, and uncontrolled pain can further contribute to feelings of anxiety. It is important to discern if pain is the cause of anxiety and to appropriately treat a patient’s pain, or if the feelings of anxiety are separate in origin, thus requiring targeted treatment for anxiolysis. Treatment options for anxiety include benzodiazepines or sedative/hypnotic agents such as barbiturates and propofol. Some agents that can provide both anxiolysis and analgesia include alpha-2 agonists, ketamine, and some opioids at low dose (e.g. morphine).

Delirium

Delirium is an acute disturbance of consciousness and cognition that has been a topic of increasing interest and research in recent years. Delirium in the ICU has been associated with adverse patient outcomes, including prolonged hospital stay, long-term cognitive impairment and increased mortality [2,6]. Delirium is categorized into subtypes according to psychomotor behavior which ranging from hypoactive (e.g. decreased responsiveness, withdrawn, and apathetic) to hyperactive (e.g. agitation, restlessness, and emotional lability), with many patients presenting with hypoactive or mixed forms [7]. Some medications have been shown to have a “deleriogenic” potential; benzodiazepines, opioids, and anticholinergic agents can potentially induce or exacerbate delirium symptoms. Delirium in the ICU...
setting is an area of active research. While evidence suggests that patients with ICU delirium have worse outcomes [2,8-11] (such as long term cognitive impairment), it is unknown as to whether delirium is the cause of these worse outcomes as opposed to a marker of underlying brain injury. Strategies to prevent the occurrence of delirium include removing or reducing “deleriogenic” agents, establishing consistent sleep-wake cycles, appropriate pain management, removal of catheters and restraints, and early mobilization and exercise. Although no current medications have an FDA approved indication for delirium, haloperidol or atypical antipsychotics have been used to treat delirium.

**Monitoring of sedation/analgesia/delirium**

Monitoring in the neurocritical care environment is a unique challenge, as subtle changes in consciousness may indicate worsening neurological injury. Unfortunately, many of the pain, sedation, and delirium monitoring scales utilized have not been validated in the neuro-ICU patient populations. The following scales are suggested as part of routine ICU monitoring and communication in relation to sedation, analgesia, and delirium, with this caveat.

**Pain**

There are numerous means by which to quantify patient pain in the ICU setting. For patients that are awake and interactive the Numerical Rating Scale (1 to 10) and/or Visual Analog Scale (1 to 100) may be employed [12]. Physiologically-based scales exist for sedated, mechanically ventilated patients who cannot self-report their level of pain/discomfort. Examples include the Behavioral Pain Rating Scale [13], Behavioral Pain Scale [3], Nonverbal pain Scale [14], the Pain Assessment and Intervention Notation algorithm [15], and the Nociception Coma Scale [16].

**Sedation**

Sedation scales in the ICU environment have been around since the 1970s when the Ramsay scale was introduced for use in sedation of cardiac surgery patients [17]. Since then numerous evaluation tools have been developed that focus on a lighter level of sedation with delineations between various levels of arousal, agitation, and levels of patient interaction. Some of the scales that have been developed include the Riker Sedation-Agitation Scale (SAS) [18], Motor Activity Assessment Scale (MAAS) [19], the RASS [20], AVRIPAS (a four-component: agitation, alertness, heart and respiration rate) [21], and the Nursing Instrument for the Communication of Sedation (NICS) [22]. Sedation scales can help clinicians minimize the amount of drug a patient receives to reach a sedation goal, have been shown to decrease days of mechanical ventilation and cost of hospital stay, and can facilitate communication between care providers [23]. Of the aforementioned sedation scales, the RASS and the NICS have included critically ill neurologic patients in their validity and reliability assessments.

**Delirium**

Of the various delirium assessment scales that have been developed, the Confusion Assessment Method – Intensive Care Unit [24] and the Intensive Care Delirium Screening and ICDSC [25] are the most valid and reliable scales in the ICU population [2]. It is clear that these validated scales are of value in identifying delirium in the ICU. However, it is unclear if delirium in the neurologically impaired patient can be definitely diagnosed and differentiated from other neurologic pathology with currently available instruments. To this
end, it is debatable as to whether they add additional value over serial detailed neurologic assessments that are routinely performed in a neurocritical care unit [26], and this represents an area of needed research.

CHOOSING SEDATIVE AGENTS

Pharmacologic choices for sedation are many and each has advantages and disadvantages in critically ill patients, especially with primary neurological conditions. Options include opioids, benzodiazepines, barbiturates, propofol, neuroleptics, alpha-2 agonists, ketamine, and many others. Considerations in the ICU patient include routes of administration, pharmacokinetics, ability to titrate easily, and adverse effect profiles with emphasis on effects on the neurological exam, respiratory drive, and systemic or cerebral hemodynamics. Short acting agents are typically preferred in the neurological intensive care environment due to the frequent need for repeated neurological examination. Ultimately, an individualized approach should be utilized, with specific aspects of drug selection requiring consideration, such as drug-drug interactions, drug-disease state interactions, drug reversibility, and cost-effectiveness. Selected agents and selected salient pharmacologic parameters will be discussed in the following sections and are summarized in Tables 16-1, 16-2, and 16-3.

Opioids

Opioids primarily provide analgesia, but can also have a sedative effect. Opioids offer advantages over other sedative agents due to their ease of titration, ability to provide patient comfort, and their reversibility. Within the ICU setting morphine, fentanyl, and remifentanil are used more commonly and will be discussed further.

Mechanism of Action

All opioids exert their effect through interactions with opioid receptors (mu (μ), delta (δ), kappa (κ)). The various opioids can have central and peripheral effects as agonists, partial agonists, and mixed agonist-antagonists. The pharmacologic effects (e.g., analgesia) and side effects (e.g., respiratory depression, gastrointestinal hypomotility, and euphoria) are exhibited via the drug’s interaction with various receptor subtypes.

Rationale for ICU use and adverse reactions

Opioids are typically well-tolerated with minimal adverse effects. Opioids do not have a direct effect on intracranial pressure (ICP) or cerebral blood flow, but any hypercarbia related to depressed respiratory drive from opiates may lead to cerebral vasodilatation and its sequelae. Elevations in ICP have been documented in patients with traumatic brain injury (TBI) receiving morphine, although the mechanism is thought to be secondary to hypercarbia from the respiratory depressant effect. Another proposed hypothesis is the auto-regulatory compensation of the mean arterial pressure (MAP) decrease that results from bolus administration of opioids [27]. In patients with neurological injury, the potential for opioid-induced miosis (a known side-effect of opioids), should be taken into account when performing the neurological exam. High doses of morphine and fentanyl have induced seizure-like activity in patients undergoing general anesthesia [28]. The cases involved documented absence of electrographic seizure activity, which suggests that this activity was a manifestation of opioid-induced muscle rigidity or myoclonus. Nonepileptic myoclonus has been documented in patients receiving high dose IV or intrathecal morphine [29]. Normeperidine, the renally eliminated active
metabolite of meperidine, has been associated with an excitatory syndrome that includes seizures and patients with renal dysfunction are primarily at risk.

Other adverse reactions of opioids include pruritus, somnolence, respiratory depression, chest wall and other muscle rigidity (primarily with fentanyl and remifentanil), dysphoria or hallucinations (primarily with morphine), nausea and vomiting, gastrointestinal dysmotility, hypotension, histamine release causing urticaria and flushing (primarily with morphine and meperidine), anaphylaxis (rare), and immune suppression after repeated dosing. Bradycardia can occur with high-dose opioid administration, but typically opioids have little to no effect on chronotropy or systemic blood pressure. Morphine may induce hypotension even at low therapeutic doses (partly due to histamine release); fentanyl and remifentanil tend to have little effect on blood pressure at sedative doses. It is recommended that all patients receiving opioid sedation undergo frequent, if not continuous, monitoring of respiratory rate and pulse oximetry, due to the potential decrease in respiratory drive from these agents.

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

Table 16-1. Pharmacological Profile of Common Medications used for Pain, Agitation, and Delirium in the Neuroscience Intensive Care Unit

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Sedation/ Analgesia</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>Opioid</td>
<td>+/+/-</td>
<td>Mu receptor agonist</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>Opioid</td>
<td>+/+/-</td>
<td>Mu receptor agonist</td>
</tr>
<tr>
<td>Morphine sulfate</td>
<td>Opioid</td>
<td>+/+/-</td>
<td>Mu receptor agonist</td>
</tr>
<tr>
<td>Ketamine</td>
<td>Dissociative anesthetics</td>
<td>+++/+</td>
<td>Noncompetitive antagonist of the NMDA receptor.</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Benzodiazepine</td>
<td>+++/+</td>
<td>GABA_A receptor agonist</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Benzodiazepine</td>
<td>+++/-</td>
<td>GABA_A receptor agonist</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Benzodiazepine</td>
<td>+++/-</td>
<td>GABA_A receptor agonist</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Neuroleptic (butyrophenone)</td>
<td>+/-</td>
<td>Blocks dopamine, adrenergic, serotonin, acetylcholine, and histamine receptors</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Atypical Antipsychotic</td>
<td>++/-</td>
<td>Blocks dopamine, adrenergic, serotonin, acetylcholine, and histamine receptors</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Atypical Antipsychotic</td>
<td>++/-</td>
<td>Blocks dopamine, adrenergic, serotonin, acetylcholine, and histamine receptors</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Atypical Antipsychotic</td>
<td>++/-</td>
<td>Blocks dopamine, adrenergic, serotonin, acetylcholine, and histamine receptors</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>Alpha-2 agonist</td>
<td>+++/+</td>
<td>Alpha-2 receptor agonist (pre- and postsynaptic)</td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>Barbiturate</td>
<td>+++/-</td>
<td>GABA_A receptor agonist</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Barbiturate</td>
<td>+++/-</td>
<td>GABA_A receptor agonist</td>
</tr>
<tr>
<td>Propofol</td>
<td>Hypnotic</td>
<td>+++/-</td>
<td>Unclear/GABAergic (proposed)</td>
</tr>
</tbody>
</table>

+, mild; ++, moderate; ++++, high; GABA, gamma aminobutyric acid
Drug-drug interactions

When morphine is combined with other neuroleptics, greater decreases in blood pressure may be observed. Concomitant use of opioids with other agents with similar adverse effects (e.g., phenothiazines, monoamine oxidase inhibitors, and tricyclic antidepressants) can result in additive respiratory depression and depressed level of consciousness.

Pharmacokinetics

Morphine readily distributes to the central nervous system (CNS) and has its peak effect in 10 to 15 minutes following IV administration. Morphine is metabolized in the liver via N-demethylation, N-dealkylation, O-dealkylation, conjugation, and hydrolysis. The majority of clearance is by glucuronidation to its two major metabolites morphine-3-glucuronide (~50%, inactive) and morphine-6-glucuronide (5 to 15%, active) which are then renally excreted; the latter is a more potent analgesic than morphine and can accumulate in patients with renal insufficiency. With a 4 hour duration of action, morphine is a longer acting opioid than fentanyl and remifentanil and this makes intermittent dosing of morphine a reasonable administration option.

Fentanyl is more lipophilic than morphine, leading to a shorter time to peak effect. IV administration has essentially immediate onset of action, peak effect in approximately 5 minutes, and a duration of effect of 30 to 60 minutes. Repeated doses or continuous infusions may lead to accumulation in adipose tissue and skeletal muscle, with release from these storage sites after discontinuation accounting for its longer elimination half-life (3 to 8 hours) in this setting. Fentanyl is metabolized by N-dealkylation via the cytochrome P450 system to norfentanyl and other inactive metabolites that are renally excreted. Fentanyl given IV is the preferred route in the ICU patient population. As a general rule of thumb, fentanyl and remifentanil are roughly 100 times more potent than morphine.

Remifentanil also possesses a short onset time of 1 to 2 minutes, and a short duration of action of 3 to 10 minutes. Remifentanil is rapidly metabolized via plasma and tissue esterases to an inactive carboxylic acid metabolite which is 90% renally excreted. Its rapid onset and short duration of action, which are independent of hepatic and renal clearance, coupled with its lower volume of distribution as compared to fentanyl make remifentanil easy to titrate and unlikely to accumulate, even with prolonged infusions. In larger doses remifentanil can blunt the cough response from endotracheal suctioning, however is associated with a reduction of MAP and subsequent elevations in ICP assuming autoregulation is preserved[30]. Although remifentanil possesses ideal pharmacokinetics to provide a true “on-off” agent, it has a higher cost than fentanyl or morphine and therefore may not be the most cost-effective choice for most patients. However, it may be more preferable in patients requiring frequent neurological assessments. Due to its short duration of action, when titrating a patient off of remifentanil, it is imperative to have a plan in place for use of longer acting opioids and pain control and this plan should be implemented prior to remifentanil discontinuation, as abrupt discontinuation may precipitate symptoms of opiate withdrawal. Remifentanil can be titrated quickly to effect when given as a continuous infusion due to its short duration of action. Larger doses may lead to apnea. No dose adjustment is needed for patients with renal or hepatic insufficiency, but a 50% dose reduction is recommended in patients older than 65 years of age.
Sufentanil, the most potent synthetic opioid, has also been used for ICU sedation. Like fentanyl, it is highly lipophilic, has a fast onset of action (1-3 minutes) and offset (due to rapid redistribution) with a single dose, and is hepatically metabolized. In one comparative trial including over 1500 mechanically ventilated ICU patients, substitution of continuous infusion remifentanil in place of sufentanil in an “analgesia-based” sedation regimen was associated with a reduction in ventilator days (10 vs. 14 days, p<0.01) and ICU days (16 vs. 19, p<0.01) [31]. This is presumably due to sufentanil’s large volume of distribution and accumulation in tissues with prolonged infusions.

**Benzodiazepines**

Benzodiazepines are one of the most commonly used sedative agents used in the ICU, and they exert their effect via an anxiolytic action. They are by and large devoid of analgesic activity. The most commonly used agents used are lorazepam and midazolam.

**Mechanism of action**

The effects of benzodiazepines on the CNS are through the potentiation of the inhibitory neurotransmitter γ-aminobutyric acid (GABA). Effects include sedation, anxiolysis, muscle relaxation, anterograde amnesia, analgesia (with diazepam), and anticonvulsant activity (not all benzodiazepines).

**Rationale for ICU use and adverse reactions**

The provision of anxiolysis and amnesia make benzodiazepines an option for use in the relief from the stressors of the ICU environment. Small doses titrated carefully can usually be given to provide therapeutic comfort without overt compromise of cognitive function. The induction of anterograde amnesia can be useful during discomforting procedures, although analgesia should also be provided. Like opioids, benzodiazepines typically provide their therapeutic effects without significant changes to heart rate, blood pressure, and respiratory drive, unless high doses are administered. Low oral (hypnotic) doses of benzodiazepines have little effect on blood pressure, but higher IV doses (sedative or anesthetic) doses may cause hypotension and increased heart rate. In and of themselves, benzodiazepines have little to no effect on ICP. However, cerebral perfusion pressure (CPP) can be impaired by decreases in MAP associated with high dose benzodiazepine infusions. Similar to opioids, high doses of benzodiazepines may incite respiratory depression and apnea; the hypercarbia associated with this effect may result in elevation of the ICP [32].

Over-sedation is the most common unintended effect of benzodiazepines, but this is dose dependent and often times avoidable. It is important to note that benzodiazepines, being lipophilic in nature, can accumulate in soft tissues with prolonged use leading to prolonged effect even after weaning or discontinuation. Another unintended adverse effect of benzodiazepines is the precipitation of an altered cognitive state that by definition can be classified as delirium. Pandharipande et al. identified the use of lorazepam, increased age, and APACHE II score as independent risk factors for delirium in their ICU patients [33]. The potentiation of delirium is an adverse effect that must be considered when this drug class is administered.

Similar to other sedative agents, benzodiazepines effects can be additive or synergistic when given
concomitantly with other agents that decrease the level of consciousness, suppress respiratory drive, or decrease blood pressure. Apnea can be precipitated when benzodiazepines are used in combination with opioids, and caution should be used when these agents are administered together. As with the opioids, the potential for decreased respiratory drive and hypotension associated with high dose benzodiazepine administration requires careful monitoring of pulse oximetry and blood pressure. Caution should be used with continuous infusions of lorazepam due to the propylene glycol diluent, which can lead to toxicity when infused at high doses (>1 mg/kg/day). Propylene glycol toxicity can result in a high anion gap metabolic acidosis and acute renal failure, as well as CNS toxicities such as depressed level of consciousness and seizures. An osmolar gap can be an indicator of propylene glycol accumulation and should be monitored along with renal function, and acid-base status in patients on higher doses[34]. Midazolam, while highly lipophilic, is an aqueous preparation as the hydrochloride salt, and therefore not diluted in propylene glycol. At lower pH, a higher proportion of midazolam molecules are in the “open-ring” configuration rendering it more water-soluble and allowing for an aqueous preparation. On injection and exposure to physiologic pH, all molecules rapidly revert to the “closed-ring” highly lipophilic configuration.

The GABA<sub>3</sub>-receptor antagonist flumazenil can reverse the effects of benzodiazepine overdose. Caution should be used with flumazenil as it may precipitate rises in ICP, systemic hypertension, and lowering of the seizure threshold, primarily in patients with TBI, neurosurgical patients, and those who have been taking benzodiazepines long-term. Flumazenil has a duration of action of roughly 30 to 60 minutes, and patients who have received longer acting benzodiazepines become re-sedated once flumazenil has been metabolized.

Drug-drug interactions

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

Pharmacokinetics

Midazolam has a short duration of action and half-life (1 to 4 hours). It does possess an active metabolite, alpha-hydroxy-midazolam, that is renally eliminated and may prolong sedation in patients with renal impairment. Midazolam can be given intramuscularly (IM), in contrast to diazepam and lorazepam where the propylene glycol solvent can cause myonecrosis.

Lorazepam is the least lipophilic benzodiazepine with the smallest redistribution effect, leading to its longer duration of effect. The duration of 4 to 6 hours for lorazepam compared to about 30 minutes following administration of diazepam or midazolam is attributable to this low redistribution effect. Lorazepam does not possess any active metabolites.
Clonidine and dexmedetomidine are the two agents used in the ICU for management of sedation, anxiolyis, and analgesia. Clonidine has long been used as an adjuvant to general, neuraxial, and regional anesthesia due to its sedative and analgesic properties, but a depressant effect on the cardiovascular system has limited its utility when combined with other agents. Thus, the remainder of this drug class review will focus on dexmedetomidine. Dexmedetomidine has shown promise for use in the ICU as an alternative and adjunct to traditional sedatives for its ability to relieve discomfort while still allowing rapid patient arousability for neurological examinations [35,36].

**Mechanism of action**

Dexmedetomidine is a selective alpha-2 adrenergic receptor agonist, with roughly 10 times the affinity for the alpha-2 receptor than clonidine. Its sedative and analgesic properties result from the presynap-
tic inhibition of descending noradrenergic activation of spinal neurons and activation of postsynaptic alpha-2 adrenergic receptors coupled to potassium-channel activating G-proteins. The end result of these effects is a decrease in sympathetic outflow from the locus coeruleus, and a decrease in tonic activity in spinal motor neurons and spinothalamic pain pathways. At recommended doses respiratory drive is not compromised.

Rationale for ICU use and adverse reactions

An advantage of dexmedetomidine, as compared with other classes of sedatives, is the mild reduction in level of arousal. For patients with clinical goals for lighter levels of sedation, this agent can provide effective sedation without the loss of attentive behavior and cognition. Thus, reliable neurological assessment can be preserved while still maintaining a non-anxious and non-agitated patient [35]. Additional benefits of dexmedetomidine are the ability to lower the shivering threshold [37], which can pose a benefit in therapeutic hypothermia protocols, and its ability to blunt the autonomic response [38]. The combination effects of sedation/anxiolysis and analgesia provided by dexmedetomidine may permit single drug therapy for both sedation and mild analgesia during the post-operative and ICU period in some patients. Its mechanism of action can allow for lower doses of traditional sedatives in patients requiring deeper levels of sedation.

Dexmedetomidine can cause bradycardia and hypotension that is frequently observed during the initial loading dose (which many practitioners opt to omit) and rapid titrations. Treatment is supportive and decrease or discontinuation of the infusion often alleviates the effect; IV fluids, pressors, or vagolytics may be required. For the management of TBI patients, clonidine has no significant effect on ICP, but may decrease CPP due to reduction in systemic arterial pressure [39]. The same effect was noted in a study of 39 neurosurgical patients receiving dexmedetomidine [40]. Mean CPP increased while ICP decreased during sedation. Agitation was noted as the primary adverse reaction, whereas hypotension occurred in 10 of 39 patients.

Drug-drug interactions

Because of its sedating properties, dexmedetomidine can potentiate the effects of other centrally acting depressants. Similar to the previously mentioned sedatives, caution should be used when combining alpha-2 agonists with multiple medications, especially in hypovolemic or otherwise hemodynamically unstable patients.

Pharmacokinetics

Dexmedetomidine is only given as an IV infusion, and rapidly distributes to the brain with an equilibrium half-life of 6 to 9 minutes. The elimination half-life in healthy volunteers is approximately 2 hours, but due to extensive hepatic metabolism this may increase up to 7.5 hours in individuals with hepatic insufficiency. Its relatively short half-life allows for easy titration of dexmedetomidine. Excretion is primarily via the kidneys as inactive methyl- and glucuronide-conjugates. Dexmedetomidine is 94% bound to plasma proteins and has a volume of distribution of between 100 and 120 L.
**Ketamine**

Ketamine is a non-barbiturate sedative/analgesic structurally related to phencyclidine. It has a mechanism of action unlike other agents. It causes a functional and electrophysiological dissociation between the thalamo-neocortical and limbic systems which produces an effect of “sensory isolation”, thereby exerting its potent analgesic, sedative, and amnestic properties.

**Mechanism of action**

The exact mechanism of ketamine’s sedative and analgesic effects is not fully elucidated. It is a noncompetitive antagonist of the N-methyl-D-aspartate receptor, but also interacts with opiate receptors at central and spinal sites, as well as norepinephrine, serotonin, and muscarinic cholinergic receptors.

**Rationale for ICU use and adverse reactions**

Unlike other sedatives, which can often induce hemodynamic compromise, ketamine typically allows hemodynamic stability to be maintained due to its ability to induce catecholamine release. This is potentially advantageous in settings where circulatory depression should be avoided, such as with neurological compromise. However, it should be used with caution in patients with poor cardiac function due to its myocardial depressant effects. Other benefits include its lack of impairment of laryngeal and pharyngeal reflexes or respiratory depressant effects and potential anticonvulsant effects.

Ketamine use in patients with brain injury is controversial. Earlier data and historical teaching suggest that ketamine use can increase ICP. However, more recent published studies in children and adults suggest that when used in combination with other agents such as propofol or benzodiazepines it has no detrimental effect on cerebral hemodynamics and ICP[41-45].

Other adverse effects include a psychomimetic (emergence) phenomenon which can produce hallucinations, vivid dreams/nightmares, and physical combativeness which can occur in up to 30% of patients. These typically disappear upon awakening, but illusions and “flashbacks” have been reported to occur weeks after therapy. Benzodiazepines are typically effective in treating these reactions. Transient hypertension due to the catecholamine release is also a potential adverse effect as well as hypersalivation (which can be treated with anticholinergics) and nausea and vomiting.

**Drug-drug interactions**

There are limited clinical data regarding drug interaction with ketamine. However, given that it is metabolized by the cytochrome P450 system, specifically CYP2B6 and to a lesser degree CYP3A4 and CYP2C9, caution should be exercised when used in conjunction with inhibitors of these enzyme systems as they may prolong ketamine’s effects. Ketamine may also compound the sedating effects of other agents and caution is likewise advised when combining with other sedating agents.
Pharmacokinetics

Ketamine, owing to lipophilicity and large volume of distribution, has a rapid onset (<1 minute) and rapid offset (5-10 minutes) with single doses. Ketamine’s elimination half-life is 2-3 hours, and it is primarily hepatically metabolized to an active metabolite (nor-ketamine) with approximately one-third the potency of the parent compound.

Neuroleptics

Neuroleptics are considered the drug of choice for patients with delirium. The lack of respiratory depression makes them potentially attractive alternatives to more conventional sedatives in non-intubated patients.

Mechanism of action

Neuroleptics produce both therapeutic and adverse effects by blocking cerebral and peripheral (but not spinal) dopamine, adrenergic, serotonin, acetylcholine, and histamine receptors, with variable selectivity depending on the agent. These effects include sedation (tolerance develops with repeated dosing), anxiolysis, restlessness, suppression of aggression and emotional outbursts, antiemetic properties, hypotension (variable by agent), and extrapyramidal side effects. With repeated doses they can produce a reduction in delusions, hallucinations, and disorganized thoughts. Haloperidol and droperidol have limited anticholinergic properties compared to other neuroleptics, reducing the occurrence of side effects of blurred vision, urinary retention, and gastrointestinal hypo-motility.

Rationale for ICU use and adverse reactions

The utility of neuroleptics is in the treatment of acute agitation secondary to psychosis or delirium. Their adverse effects negate the use of these agents for mild sedation. However, when appropriate the anxiolytic effects can be dramatic and provide the necessary conditions to enhance ICU patient management. Unfortunately, these agents have many potential physiological and neurological complications that limit their use in the ICU, including extrapyramidal side effects.

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

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

Other potential side effects including anticholinergic effects, increased prolactin secretion, and neuroleptic malignant syndrome have all been reported for neuroleptics. As with all medications, nonspecific adverse effects have been reported which can include anaphylaxis, laryngospasm, and bronchospasm.

**Drug-drug interactions**

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

**Pharmacokinetics**

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

Olanzapine, quetiapine, and risperidone are the atypical agents that have been utilized in the ICU patient population for treatment of delirium. All of the atypicals are highly protein bound to plasma proteins and metabolized extensively via cytochrome P450 enzymes in the liver. Following oral administration, peak plasma levels are reached in 6, 1.5, and 1 hour for olanzapine, quetiapine, and risperidone respectively. The respective plasma half-lives for each of the agents are approximately 30, 6, and 25 hours. Quetiapine dosing is typically initiated at 25-50 mg twice daily and can be titrated up to 200 mg twice daily. In one pilot study, quetiapine in addition to PRN haloperidol resulted in faster time to delirium resolution compared to haloperidol plus placebo (1 vs. 4.5 days, p=0.001)[46]. Of note, patients with neurologic injury were excluded from this study. Duration of treatment of delirium with the atypical agents typically ranges from 7 to 14 days.
Propofol

Propofol is an ultra-short acting alkyphenol. Although structurally distinct, its clinical effects and effects on cerebral activity and intracranial dynamics are similar to short acting barbiturates.

**Mechanism of action**

The specific mechanism of action for propofol remains unclear. Propofol is a phenolic compound with general anesthetic properties whose mechanism is unlike any other agents currently in use. A GABAergic mechanism is hypothesized based on in vivo and in vitro binding studies, with evidence that propofol may directly bind to GABA$_A$ receptors and activate inhibitory chloride channels in the absence of GABA. Other studies suggest a nonspecific, but structurally dependent effect on neuronal plasma membrane fluidity [47].

**Rationale for ICU use and adverse reactions**

The ultra-short duration of action of propofol allowing for rapid titration and rapid elimination are the main advantages of this agent. It can suppress EEG activity similar to barbiturates, ranging from increasing theta and delta activity to a flat EEG pattern during deep general anesthesia. Thus, this drug can be used to suppress seizure activity at high doses. As a sedative-hypnotic agent, propofol provides sedation devoid of any analgesia. Due to a dose-dependent reduction of cerebral metabolism, propofol may be used in the treatment of intracranial hypertension by decreasing cerebral blood volume through flow-metabolism coupling.

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

Due to its insolubility in water, propofol is suspended in an emulsion of soy, glycerol, and egg phospholipids leaving it susceptible to bacterial contamination. Some emulsions contain disodium edentate or ethylenediaminetetraacetate as bacteriostatic agents, but vials should still be handled in an aseptic manner. The infusion tubing and any unused solutions should be discarded within 12 hours once the sterile seal is broken. Injection site pain is a common adverse effect due to the carrier solution, which can be lessened by administration through a central or larger vein, or by pretreatment with IV lidocaine (0.5 to 1 mg/kg). Anaphylactoid reactions with propofol are rare, and most immunological reactions are due to the emulsion carrier that contains egg and soy proteins. Thus, its use is contraindicated in patients with severe allergic reactions to these food substances. Hypertriglyceridermia may also occur, particularly at higher doses or with prolonged infusions, due to the lipid vehicle. Addition-
<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting Dose</th>
<th>Titration</th>
<th>Half-life</th>
<th>Protein Binding</th>
<th>Metabolism/Active metabolite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>25 – 50 mcg IV every 5–10 min</td>
<td>Titrate every 15–30 min, up to 50 – 100 mcg/h</td>
<td>30 – 60 minutes (single IV dose)</td>
<td>70%</td>
<td>Plasma esterases</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>0.5 – 1 mcg/kg IV bolus</td>
<td>Caution: metabolites may accumulate</td>
<td>1.5 – 4.5 hours IV, IM, SQ</td>
<td>20%</td>
<td>Morphine-3-glucuronide, Morphine-6-glucuronide</td>
</tr>
<tr>
<td>Morphine sulfate</td>
<td>5 – 20 mg IM every 4 hours</td>
<td>Caution: metabolites may accumulate</td>
<td>20 – 30%</td>
<td>47%</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Ketamine</td>
<td>0.1 – 1 mg/kg IV every 10 min</td>
<td>Caution: metabolites may accumulate</td>
<td>1.5 – 4.5 hours IV, IM, SQ</td>
<td>20%</td>
<td>Hepatic/ N-Desmethylmorphine-3-glucuronide, Morphine-6-glucuronide</td>
</tr>
<tr>
<td>Diazepam</td>
<td>2 mg IV every 30 – 60 min</td>
<td>Infusion: 0.05 – 0.2 mcg/kg/min</td>
<td>10 – 20 hours</td>
<td>91%</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>0.25 mg – 1 mg IV every 5 – 30 min</td>
<td>Infusion: 0.01 – 0.1 mg/kg/hour</td>
<td>1 – 2.5 hours</td>
<td>97%</td>
<td>Hepatic/1-hydroxymethylmidazolam</td>
</tr>
<tr>
<td>Midazolam</td>
<td>0.5 – 1 mg IV every 5 – 30 min</td>
<td>Infusion: 0.25 – 1 mcg/kg/min</td>
<td>2 – 3 hours</td>
<td>99%</td>
<td>Hepatic/1-hydroxymethylmidazolam</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>0.5 – 5 mg IV</td>
<td>--</td>
<td>12 – 36 hours</td>
<td>92%</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>2.5 – 5 mg PO daily</td>
<td>--</td>
<td>21–54 hours</td>
<td>93%</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>25 – 50 mg PO twice daily</td>
<td>--</td>
<td>6 hours</td>
<td>83%</td>
<td>Hepatic/9-desalkylquetiapine</td>
</tr>
<tr>
<td>Risperidone</td>
<td>0.5 mg PO</td>
<td>--</td>
<td>20–30 hours</td>
<td>90%</td>
<td>Hepatic/9-hydroxyrisperidone</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>1 mcg/kg IV bolus over 10 min</td>
<td>Infusion 0.2 – 1 mcg/kg/h</td>
<td>2 hours</td>
<td>94%</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>10–20 mg/kg IV</td>
<td>0.5–3 mg/kg/hr</td>
<td>15–50 hours</td>
<td>35–55%</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>10 mg/kg IV at 100 mg/min</td>
<td>50 mg/min until seizures are controlled</td>
<td>36–117 hours</td>
<td>20–60%</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Propofol</td>
<td>1.0 – 2.5 mg/kg IV (anesthesia induction)</td>
<td>Increase infusion 5 – 10 mcg/kg/min every 5 – 10 min to maintenance of 25 – 80 mcg/kg/min, up to 100 – 300 mcg/kg/min</td>
<td>4 – 10 min</td>
<td>&gt; 90%</td>
<td>Hepatic and extra hepatic</td>
</tr>
</tbody>
</table>

IM, intramuscular; IV, intravenous; PCA, patient-controlled analgesia; SQ, subcutaneous; PO, oral
ally, the lipid vehicle provides 1.1 kcal/mL due to the fat content, and nutritional requirements should be adjusted for this consideration.

“Propofol related infusion syndrome” (PRIS) has been described in pediatric and adult patients receiving doses greater than 80 mcg/kg/min for prolonged periods of time [48]. While the exact mechanism of PRIS is still unclear, the clinical signs include metabolic acidosis, hyperkalemia, rhabdomyolysis, hypoxia, and progressive myocardial failure. Routine monitoring for electrolyte derangements or increases in lactic acid, creatinine kinase, or triglycerides is recommended in patients receiving higher doses (>80 mcg/kg/min) for greater than 48 hours.

Drug-drug interactions

Propofol may potentiate the sedating or cardio-depressant effects of concomitant alcohol, opioids, benzodiazepines, barbiturates, other general anesthetics, antihypertensives, and antiarrhythmic medications. Propofol does not appear to alter metabolism, elimination, or plasma protein binding of other drugs.

Pharmacokinetics

Propofol is rapidly distributed to the brain following IV administration due to its lipophilicity. The distribution half-life ranges from 1 to 8 minutes, with an equally rapid recovery following redistribution to other less perfused tissues. Propofol has a high total body clearance (1.5 to 1 L/min), which is greater than that of hepatic blood flow; this is suggestive that there are extra-hepatic sites of metabolism. The short elimination time allows for more rapid recovery following cessation of a continuous infusion. Propofol has a volume of distribution of about 60 L/kg and is also extensively bound to plasma protein (97 to 99%), with elevated free circulating levels in hypoalbuminemic states.

SUMMARY

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

REFERENCES


SEDATION AND ANALGESIA QUESTIONS

1. The major disadvantage to the use of opioids in the ICU is:
   a) High rate of anaphylaxis
   b) Suppression of respiratory drive and gastrointestinal motility
   c) Truncal rigidity
   d) Long time to onset

2. Routine use of sedation scales in the ICU is recommended to:
   a) Minimize the amount of drug required to obtain the therapeutic goal
   b) Facilitate communication among providers
   c) Provide an objective target for the depth of sedation
   d) All of the above

3. Which of the opioids listed possesses the fastest onset and shortest duration?
   a) Morphine
   b) Fentanyl
   c) Meperidine
   d) Remifentanil

4. Which of the opioids has a renally eliminated metabolite that may induce seizures?
   a) Morphine
   b) Fentanyl
   c) Meperidine
   d) Remifentanil

5. Which of the following pharmacokinetic parameters predicts the time to onset and time to offset following a single dose of a benzodiazepine?
   a) Half-life
   b) Lipophilicity
   c) Elimination rate constant
   d) Degree of protein binding

6. Which of the following benzodiazepines contain propylene glycol as a solvent?
   a) Diazepam and midazolam
   b) Lorazepam and midazolam
   c) Diazepam and lorazepam

7. Which of the following benzodiazepines are subject to numerous drug-drug interactions mediated by inducers and inhibitors of the cytochrome P450 system?
   a) Diazepam and midazolam
   b) Lorazepam and midazolam
   c) Diazepam and lorazepam
8. The mechanism of action by which clonidine and dexmedetomidine exert their effect is:
   a) alpha-2 adrenergic receptor antagonist
   b) GABA<sub>α</sub> receptor agonist
   c) Mu receptor agonist
   d) alpha-2 adrenergic receptor agonist

9. Which sedation scale(s) have included neurologically injured patients in their validity/reliability studies?
   a) Ramsay and SAS
   b) NICS and RASS
   c) MAAS and SAS
   d) AV RIPAS and RASS

10. Which of the following is NOT an adverse effect of propofol:
    a) Hypertriglyceridemia
    b) Hypotension
    c) Increased intracranial pressure
    d) Pain on injection
SEDATION AND ANALGESIA ANSWERS

1. The correct answer is B. In addition to analgesia, mu-receptor agonists such as the opioids have potent effects in suppressing respiratory drive. Diminished respiratory rate, with relative preservation of tidal volume is a hallmark of the action of these agents on the respiratory physiology. An increase in end-tidal CO$_2$ (ETCO$_2$) is also an expected consequence of moderate to high doses of narcotics, and this can lead to cerebral vasodilation as a secondary effect.

2. The correct answer is D. Ideally, the purpose of using a sedation scale or score is to more safely titrate and monitor the action of sedative agents, while also providing a useful method of communication that rapidly provides health care providers with useful information regarding the need whether to adjust the dosing of sedative agents.

3. The correct answer is D. Remifentanil is a synthetic product of fentanyl, with an ester linkage specifically engineered to not antagonize the potency of this opioid, but to permit rapid ester hydrolysis by circulating plasma esterases. Hence, this drug was specifically created to last but a few minutes in the circulation.

4. The correct answer is C. Meperidine is metabolized by hepatic enzymes to the active metabolite normeperidine, which has been linked to seizures in laboratory animals, and is presumed to incur that risk in humans as it has excitatory action on nerve terminal neurotransmitter release. Other than meperidine, narcotics tend to have an excellent safety profile for use in critically ill patients, including patients with neurological illness or injury.

5. The correct answer is B. Although the half-life provides kinetic data on biologic presence of the drug within the vascular fluid compartment, the lipophilicity of the drug better equates to the rapidity of effect upon the CNS (a highly lipophilic compartment), as well as the re-distribution of the drug out of the plasma compartment into muscle and fat. Hence, highly lipophilic agents penetrate rapidly into brain, but typically have brief clinical duration of action.

6. The correct answer is C. Both diazepam and lorazepam are poorly soluble in water, and require a solvent such as ethylene glycol to provide intravenous administration. This solvent can, in moderate-high doses, induce a metabolic acidosis, acute renal failure, and central nervous system toxicities such as depressed level of consciousness and seizures. Propylene glycol also should not be administered intramuscularly as it may induce myonecrosis.

7. The correct answer is A. Both diazepam and midazolam are metabolized by the hepatic P450 cytochrome enzymes. Inducers of the P450 enzymes may enhance the clearance of these drugs, while inhibitors may decrease clearance and cause prolonged sedation.

8. The correct answer is D. Dexmedetomidine and clonidine each act as an agonist at the alpha-2 receptor, thereby diminishing central sympathetic expression.
9. The correct answer is B. The sedation scales differ in numerous ways; some are targeting deep sedation, others may not have been applied specifically or fully validated for neurocritical care patients. The NICS & RASS scales have been demonstrated valid and reliable, and have been assessed in patients with neurologic injury.

10. The correct answer is C. By decreasing cerebral oxygen utilization, propofol diminishes the brain’s requirement for arterial cerebral blood flow; hence via a vasoconstrictive response, this induction agent decreases intracranial pressure. However, by concomitantly decreasing systemic vascular resistance and thereby promoting a decrease in systemic blood pressure, propofol may diminish cerebral perfusion pressure despite lowering ICP. Therefore, close monitoring of mean arterial pressure is critical in assuring that adequate cerebral perfusion exists.