Chapter 8

Drug-Induced Coma and Delirium

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Adverse drug events are common in the ICU and frequently have a negative impact on patient outcome and healthcare costs.1 A number of factors specific to the ICU setting account for this high incidence, including the complexity of the disease states present and the urgency with which they must be treated, the large number of medications administered, the presence of end-organ dysfunction, the frequent need for high-risk medications with narrow therapeutic indices, and the frequent use of intravenous infusions.2 Although a medication-induced coma was previously considered the most “humane” state to optimize comfort in the critically ill, it has now been associated with increased mortality, a prolonged duration of ventilation and ICU stay, increased delirium, and greater long-term neuropsychological dysfunction including posttraumatic stress disorder.3-5 Delirium occurs frequently in the ICU and is associated with higher mortality, a longer duration of mechanical ventilation, increased ICU and hospital lengths of stay, and a number of adverse post-ICU sequelae.4,6 Acute brain dysfunction (ie, the development of new-onset coma and/or delirium) is a frequent and serious adverse event during critical illness, and its development is frequently related to medications that the critically ill patient is administered. This chapter reviews the medications that are routinely used in the ICU that have been associated with coma and delirium, highlights those factors shown to increase the risks for these medications to cause acute brain dysfunction, and provides strategies to minimize the incidence of medication-associated coma and delirium in the critical care setting.

COMA

Before implicating a medication as the source of coma, it is important to establish a consistent definition for the term coma. Most ICU sedation scales define a range of patient behaviors extending from unresponsiveness to severe agitation.7,8 Although such behaviors are likely not a true linear function, labeling the various levels and distinguishing between them with behavioral descriptors remains challenging. Perhaps the most elegant approach to this effort comes from Plum and Posner, who in 1966 first dissected consciousness into 2 components: content and arousal.9 Plum and Posner define coma as a state of unresponsiveness in which the patient lies with eyes closed and cannot be aroused to respond appropriately, even with vigorous stimulation. They further state that a patient in coma may grimace to painful stimuli but will not localize or make discrete defensive movements and that as the coma deepens, responsiveness to even painful stimuli may disappear. Last, they emphasize the need to differentiate between the true comatose patient and one who may be locked-in.

These sentinel concepts from Plum and Posner have not been consistently applied to ICU patients. Recent papers addressing the negative outcomes associated with drug-induced coma in the ICU have used varying definitions. Ely et al10 considered patients to be comatose if the Richmond Agitation and Sedation Scale (RASS) score was –4 or –5. The incidence of coma was 60%, 40%, 30%, and 25% on ICU days 1 through 4, and patients spent 35% of their ICU days comatose. Ouimet et al1 initially defined coma as a RASS of –5, with an incidence of 21%. They further divided coma into 3 types: medical coma (coma due to underlying medical condition), induced coma (sedation related), or multifactorial coma (both medical and induced). Of note,
induced coma related to sedation therapy was associated with the development of delirium in their cohort, whereas medical coma was not. A follow-up study by Skrobik et al.\textsuperscript{11} defined coma as RASS –4 or –5 and showed a reduction of coma incidence from 21\% to 8\% using a sedation and analgesia protocol. Drawing on these concepts of coma and deep coma, one may assign categories to the commonly used ICU sedation scales as shown in Table 8-1.

Table 8-1. Identification of Coma in the Critically Ill

<table>
<thead>
<tr>
<th>Sedation Scale</th>
<th>Coma\textsuperscript{a}</th>
<th>Deep Coma</th>
</tr>
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<tbody>
<tr>
<td>Ramsay</td>
<td>4 or 5</td>
<td>5</td>
</tr>
<tr>
<td>Sedation-Agitation Scale (SAS)</td>
<td>1 or 2</td>
<td>1</td>
</tr>
<tr>
<td>Richmond Agitation Sedation Scale (RASS)</td>
<td>3\textsuperscript{b}, 5</td>
<td>5</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Uses the Plum and Posner threshold of a patient who will not respond appropriately even with vigorous stimulation.

\textsuperscript{b}Although patients with a RASS of 3 may move or open their eyes, a significant subset will not “respond appropriately” to commands or interact.

Although current guidelines recommend that most patients admitted to the ICU be maintained in a pain-free and wakeful state, a number of observational studies suggest that these end points are often not attained in clinical practice.\textsuperscript{3,12,13} Patients who become comatose cannot self-report pain, be screened for delirium, be evaluated for readiness to wean and extubate, or participate in early mobilization efforts; they form fewer factual memories that may help prevent posttraumatic stress disorder and are more likely to die.\textsuperscript{3,4} Coma that results from the administration of sedative or opioid medications usually stems from 2 main factors: (1) failure to use strategies that have been shown to reduce oversedation and coma, such as sedation protocolization and daily interruption, and (2) failure to consider the numerous pharmacokinetic, pharmacodynamic, and pharmacogenetic factors that influence analgesic and sedative response, recovery, and safety in the critically ill.\textsuperscript{14-19}

Compared with propofol or dexmedetomidine, the benzodiazepines, particularly when administered as a continuous infusion, are more likely to result in excessive sedation and coma because of the important pharmacokinetic and pharmacodynamic differences between these classes of medications. For example, patients administered a prolonged (>72 hours) infusion of midazolam are at a particularly high risk for protracted sedation and should therefore receive lower doses of midazolam and management with a daily sedation interruption protocol or down-titration protocol.\textsuperscript{15,16,20} Benzodiazepine dosing requirements are generally lower in the elderly, given the greater volume of distribution and lower clearance seen in this population. One of the metabolites of midazolam, 1-hydroxymidazolam, has central nervous system (CNS) depressant effects and may accumulate in the critically ill patient, especially in the presence of kidney failure.\textsuperscript{21,22}

Compared with the benzodiazepines, propofol and dexmedetomidine are usually associated with faster neurological recovery after discontinuation.\textsuperscript{23-25} For example, lorazepam administered continuously without daily interruptions or down-titration led to a greater incidence of coma and less time within the desired sedation range than continuously infused dexmedetomidine.\textsuperscript{24} Even when administered intermittently, lorazepam can lead to a longer duration of mechanical ventilation than propofol.\textsuperscript{23} Similarly, continuous midazolam infusions led to a longer duration of mechanical ventilation than continuous dexmedetomidine.\textsuperscript{25}
Increasing data have suggested that the activity of CYP3A5, the primary isoenzyme for midazolam metabolism, is influenced by genetic polymorphism. For example, individuals who are homozygotic for the CYP3A5*3 or *6 alleles will have decreased hepatic CYP3A5 activity and will clear midazolam more slowly than patients who are homozygotic for the CYP3A5*1 allelic variant. It has been reported that individuals who are homozygotic for the CYP3A5*3 or *6 alleles have decreased hepatic levels of the protein CYP3A5 compared with individuals who are homozygotic for the CYP3A5*1 allelic variant. Critical illness itself has been associated with a substantial decrease in CYP450 isoenzyme 3A4 activity, which could also further increase the risk for midazolam-related coma.

Coma resulting from the use of opioids is most often seen with the use of continuous infusions and may be higher among obese patients administered fentanyl. The metabolite of morphine, morphine-6-glucuronide, has significant analgesic activity and may accumulate in patients with decreased renal function. Methadone may cause excessive sedation if the dose is not titrated downward after days of use or if a CYP3A4 or CYP2D6 inhibitor is concomitantly administered. In contrast, remifentanil, an intravenous opioid with an ultrashort half-life, allowed patients to spend more time in the desired sedation range and reduced the duration of mechanical ventilation when compared with infused morphine.

**DELIRIUM**

Delirium, characterized by fluctuations in mental status, inattention, disorganized thinking, hallucinations, disorientation, and altered level of consciousness, occurs frequently in the ICU and has been associated with increased mortality. Current guidelines, including the soon to be published 2012 American College of Critical Care Medicine clinical practice guidelines for the management of pain, agitation and delirium in adult ICU patients, recommend that critically ill patients be routinely screened for delirium using a validated tool such as the Confusion Assessment Method for the ICU or the Intensive Care Delirium Screening Checklist. Risk factors for delirium in the ICU can be categorized into 3 broad categories: (1) baseline risks including a history of dementia, hypertension, or alcoholism and a higher severity of illness at ICU admission; (2) environmental factors such as prolonged physical restraints or immobilization; and (3) medications. Although a number of medications may cause or worsen delirium in the ICU, sedatives and opioids have recently received the most attention (Table 8-2). It should be appreciated that this listing almost certainly underestimates the extent to which drugs can affect these behaviors. A recent search of Micromedex disclosed that delirium, confusion, and agitation are associated with 82, 231, and 107 medications, respectively, that are commonly used in the ICU.

**Table 8-2. ICU Medications Commonly Associated With Delirium**

<table>
<thead>
<tr>
<th>Category of Medication</th>
<th>Examples</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesics</td>
<td>Fentanyl</td>
<td>GABA antagonism</td>
</tr>
<tr>
<td></td>
<td>Hydromorphone</td>
<td>GABA antagonism</td>
</tr>
<tr>
<td></td>
<td>Morphine</td>
<td>GABA antagonism</td>
</tr>
<tr>
<td></td>
<td>NSAIDs</td>
<td>Anticholinergic activity</td>
</tr>
<tr>
<td>Category of Medication</td>
<td>Examples</td>
<td>Mechanism</td>
</tr>
<tr>
<td>------------------------</td>
<td>-------------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Anti-infectives</td>
<td>Acyclovir</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>Amphotericin</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>Cefepime</td>
<td>GABA antagonism</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
<td>Serotonergic dysfunction</td>
</tr>
<tr>
<td></td>
<td>Macrolides</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>Quinolones</td>
<td>GABA antagonism</td>
</tr>
<tr>
<td></td>
<td>Voriconazole</td>
<td>Unknown</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>Atropine</td>
<td>Anticholinergic activity</td>
</tr>
<tr>
<td></td>
<td>Benztropine</td>
<td>Anticholinergic activity</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Serotonin release inhibitors</td>
<td>Serotonergic dysfunction</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>Diphenhydramine</td>
<td>Anticholinergic activity</td>
</tr>
<tr>
<td>Cardiac medications</td>
<td>α-Blockers</td>
<td>Anticholinergic activity</td>
</tr>
<tr>
<td></td>
<td>Amiodarone</td>
<td>Anticholinergic activity</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Haloperidol</td>
<td>Anticholinergic activity</td>
</tr>
<tr>
<td></td>
<td>Olanzapine</td>
<td>Anticholinergic activity</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Dexamethasone</td>
<td>Anticholinergic activity</td>
</tr>
<tr>
<td></td>
<td>Hydrocortisone</td>
<td>Anticholinergic activity</td>
</tr>
<tr>
<td></td>
<td>Methylprednisolone</td>
<td>Anticholinergic activity</td>
</tr>
<tr>
<td>Dopaminergics</td>
<td>Amantadine</td>
<td>Excess dopaminergic activity</td>
</tr>
<tr>
<td></td>
<td>Bromocriptine</td>
<td>Excess dopaminergic activity</td>
</tr>
<tr>
<td>Prokinetics</td>
<td>Metoclopramide</td>
<td>Excess glucocorticoid activity</td>
</tr>
<tr>
<td>Sedatives</td>
<td>Ketamine</td>
<td>NMDA antagonism</td>
</tr>
<tr>
<td></td>
<td>Lorazepam</td>
<td>GABA antagonism</td>
</tr>
<tr>
<td></td>
<td>Midazolam</td>
<td>GABA antagonism</td>
</tr>
<tr>
<td></td>
<td>Propofol</td>
<td>GABA antagonism</td>
</tr>
</tbody>
</table>

Abbreviations: GABA, γ-aminobutyric acid; NMDA, N-methyl-d-aspartate; NSAIDs, nonsteroidal anti-inflammatory agents.
A number of factors have been shown to predispose patients to drug-induced delirium: (a) the number of agents administered (>3); (b) pharmacokinetic derangements, whether associated with aging, organ dysfunction, or drug interactions; (c) medical comorbidities such as dementia or stroke, which are associated with impaired integrity of the blood–brain barrier; and (d) the use of psychoactive medications. It is interesting to note that age has not been consistently identified as an independent risk factor for the development of delirium in the ICU, which is in contrast to findings in non-ICU patients. The diagnosis of drug-induced delirium is challenging and is generally one of exclusion based on temporal onset and offset relationships. Heightened awareness of the potential for a deliriogenic effect is required for drugs in which a clear temporal relationship is not seen. For example, cefepime is associated with a several-day delay in both onset and offset of delirium.

Although there are no unifying neurotransmitter themes to define the exact mechanisms or common pathways for drug-induced delirium, the majority of data support the importance of pharmacological interference with cholinergic activity. The risk for delirium correlates with cumulative anticholinergic effect as measured by serum anticholinergic activity. It is interesting to note that this relationship holds true even if administered drugs do not have traditional anticholinergic activity (eg, digoxin, lithium, histamine-2 receptor blockers, diltiazem, or furosemide). Other suggested mechanisms for drug-induced delirium include an excess of dopamine, norepinephrine, and glutamate release along with both increased and decreased serotonergic and γ-aminobutyric acid (GABA) activity. The complexity of this issue is exemplified by the quinolone antibiotics, which may exert their deliriogenic activity via GABA receptor antagonism as well as via weak dopaminergic activity.

The role of cytokines (interleukins-1, -2, -6, and -8 as well as interferon and tumor necrosis factor) in the development of delirium has been recently described and has been evoked to help explain the intriguing findings that haloperidol use may be associated with lower mortality in the ICU population and may prevent delirium.

**SEDATIVES AND ANALGESICS**

There is emerging evidence that ICU delirium is associated with the administration of benzodiazepines; strategies to avoid this class of agents may reduce delirium and shorten duration of mechanical ventilation. Although the increase in deliriogenic neurotransmitters such as dopamine, serotonin, and acetylcholine, through the GABAminergic effect of benzodiazepines, is the most commonly reported mechanism for benzodiazepine-associated delirium, other mechanisms may also play a role. For example, recent data suggest that patients who are deeply sedated with benzodiazepine therapy and deemed to have delirium may not always have delirium when they are awakened.

Five studies evaluated the development of delirium in patients randomized to receive either dexmedetomidine or a benzodiazepine for sedation. Delirium was reported in terms of frequency of occurrence, prevalence, and delirium-free days. Four studies suggested that dexmedetomidine may reduce delirium incidence. Data are insufficient to determine the relationship between the use of propofol and delirium in adult ICU patients. In mechanically ventilated patients who are at risk for developing delirium, dexmedetomidine infusions administered for sedation may be associated with a lower prevalence of delirium compared with benzodiazepine infusions administered for sedation.

Opioids may cause hallucinations, agitation, euphoria, and sleep disturbances and have been associated with the development of delirium. Conflicting data have been reported on the relationship between the use of opioids and the development of delirium in adult ICU patients. For example, although some analyses report data on individual opioid medications, others provide only the medication class and still others combine opioid use with other sedatives. Conversely, pain itself has been associated with delirium, and thus the administration of opioid therapy may in fact decrease delirium. Of the opioids, methadone may be the least deliriogenic due to its antagonistic activity at the N-methyl-D-aspartate receptor.
NONSEDATIVE AND ANALGESIC MEDICATIONS

Although sedatives, hypnotics, and analgesics are the most frequent cause of medication-induced delirium in the ICU, a number of other medications that are routinely administered in the ICU may cause delirium. Ophthalmic medications, especially those containing anticholinergic agents, should be considered as causes of delirium. Furthermore, delirium is not only seen with drug use; it can also occur when chronic nonsedative medications are discontinued. Examples include gabapentin, selective serotonin reuptake inhibitors, and even nicotine.

Another group of drugs frequently administered to ICU patients and reported to cause delirium and encephalopathy is the antibiotics. Across all antibiotic drug classes, common mechanisms for these effects have been proposed, starting with structural aspects of individual drugs that may decrease GABA release or inhibit GABA receptors (with varying GABA affinity from drug to drug, which appears to directly correlate with neurotoxicity) or activation of excitatory N-methyl-D-aspartate receptors or binding to glutamate. Other factors that appear to increase CNS toxicity of antibiotics include the extremes of age, smaller body mass, prior CNS disease, inflammatory conditions, renal dysfunction (which may lead to increased CNS penetration of drugs and increased systemic levels related to impaired clearance), and coadministration of other medications with neurotoxic or nephrotoxic effects.

Because many patients reported to have developed delirium or encephalopathy related to antibiotic use have multiple potential causes for these symptoms, including organ dysfunction, sepsis, systemic inflammation, and other metabolic issues, it is difficult to assign an incidence or prevalence to specific drugs. In addition, the overlap between symptoms such as delirium, confusion, encephalopathy, and seizures (including nonconvulsive status epilepticus, which may present with little or no evidence of seizure activity but as lethargy or confusion) only further complicates determination of specific rates for these adverse events. Using available reviews and case reports, we have attempted to provide a semiquantitative estimate for specific drug classes and medications, but this remains a crude effort.

Cephalosporins are among the most commonly reported antibiotics to cause delirium and neurotoxicity. Specific agents available in the United States that appear to be associated with the highest risk of neurotoxicity include cefepime, cefazolin, ceftazidime, and cefoperazone. The carbapenems, particularly imipenem, are also associated with neurological adverse events, especially in the setting of renal dysfunction, preexisting CNS disease, low body weight, and advanced age.

Many antibiotics have fewer reports of associated delirium, encephalopathy, or seizures. This group includes gentamicin, piperacillin, ampicillin, fluoroquinolones (including ciprofloxacin, norfloxacin, ofloxacin and its levo-isomer levofloxacin, gatifloxacin, gemifloxacin, and moxifloxacin), trimethoprim–sulfamethoxazole, linezolid, metronidazole, and polymyxin B.

STRATEGIES TO PREVENT MEDICATION-INDUCED COMA AND DELIRIUM IN THE ICU

As with most drug-induced adverse events, management of suspected drug-induced coma or delirium includes stopping the suspected medication but in the case of coma may include additional diagnostic interventions such as a head computed tomography or electroencephalography or the cautious administration of flumazenil (Tables 8-3 and 8-4). Based on the soon to published 2012 ACCM pain, agitation and delirium guidelines, patients should receive sedation only if required, and if sedatives are administered, they should be titrated using validated assessment tools to facilitate patient responsiveness and awareness; this will enable clinicians to assess patients for the presence of pain and delirium, evaluate patients for early mobility efforts, and institute spontaneous breathing trials. Nonbenzodiazepine sedation strategies should be considered, particularly if delirium develops.
One useful strategy to reduce delirium and coma involves a protocolized, integrated management approach that includes valid and reliable assessment tools to monitor pain, agitation, and delirium; automatic sedation-minimizing strategies, such as daily interruption, down-titration, or lighter targets for sedation; and an early mobilization strategy in select patients. A protocolized approach not only facilitates better communication of sedation goals between the bedside nurses administering the medications and the ICU physicians ordering them but also has been shown to significantly improve patient outcomes by reducing the duration of mechanical ventilation and ICU length of stay; avoiding the complications associated with inadequate or inappropriate management of pain, agitation, and delirium; and decreasing healthcare costs. Although the impact of routine delirium monitoring on ICU outcomes has never been rigorously evaluated, early recognition may facilitate more appropriate patient treatment, allow for early identification of reversible causative factors, and prevent or reduce subsyndromal delirium.
Nonpharmacological delirium prevention strategies shown to be of benefit in non-ICU patients (eg, noise reduction, music therapy) have not been evaluated in the critically ill. Recent preliminary data suggest that the administration of short-term, low-dose haloperidol may reduce delirium incidence in surgical critically ill adults having a low baseline severity of illness.46,63

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. The occurrence of withdrawal has been linked to high doses and longer duration of administration (>5 days) in both pediatric and adult populations.64 Recently, withdrawal was also associated with delirium in adult patients.65

Delirium is distressing for patients, families, and caregivers and, when accompanied by agitation, frequently leads to the consideration of pharmacological therapy given that use of restraints may actually worsen delirium.3 However, only one small, double-blind, randomized placebo-controlled trial has established that antipsychotic therapy with quetiapine may be safe and efficacious in critically ill patients with delirium, and a post hoc analysis of this study reveals that agitation is slower to resolve with treatment than other delirium symptoms.66,67 Given that the current evidence to support treatment of ICU delirium with antipsychotic therapy is weak, that potential safety concerns associated with this class of medications are numerous (particularly if treatment exceeds a short duration), and that recent data suggest that medications once thought to reduce delirium (eg, rivastigmine) in fact worsen patient outcome, current practice guidelines, including the soon to be published ACCM guidelines, do not advocate that antipsychotic therapy be routinely administered in patients with delirium, particularly if agitation is not present.3,63,68

SUMMARY

Many different medications have been reported to cause delirium, coma, and, less commonly, seizures and other neurotoxic adverse events. Specific medications (such as the benzodiazepines midazolam and lorazepam), drug classes (such as cephalosporins and opiates), and receptor effects (such as anticholinergic activity) have been implicated. Keeping a low threshold to suspect drugs in the origin of delirium and using proven strategies to avoid drug-induced coma (such as daily interruption, down-titration, or targeting a lighter level of sedation) may reduce the incidence and duration of these adverse events as well as their costly and life-altering sequelae.

REFERENCES


