Medication Safety Alerts

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SEDATION IN THE ICU: A WAKE-UP CALL

Pharmacologic therapy for agitation or anxiety is a mainstay in the intensive care unit (ICU). However, sedating medications are commonly associated with adverse drug events. In fact, in one hospital study, morphine and midazolam were among the top 10 drugs associated with preventable adverse drug events.[1] Other studies have confirmed that sedatives are among the highest-risk medications for adverse drug events.[2,3]

Extra care is needed when dealing with high-risk medications in critical care settings relative to general care wards. In a prospective cohort study of over 4000 adult admissions over a 6-month period, the rate of preventable or potential adverse events in either a surgical or medical ICU was 19 events per 1000 patient days — almost twice that for non-ICU patient care areas.[4] The severity of the adverse drug events and the length of stay were also greater in the ICU setting. One observational study of almost 6000 courses of medication therapy given to 851 patients found that one-quarter of all medication administration errors in the ICU occurred with sedative or analgesic medications.[5]

There has been a great deal of research on the use of sedation in critically ill patients. This paper outlines key issues that pharmacists and other clinicians should consider for the appropriate and safe use of sedation in the ICU. It focuses on the "typical" ICU patient and therefore does not cover the use of sedation or neuromuscular blockers for complex ventilation strategies or as part of complex pain control regimens.

Anxiety and Agitation in the ICU

Most critical care patients experience distress or agitation during their ICU stay. The causes of anxiety in critically ill patients are multifactorial and include the patient's underlying disease, diagnostic or therapeutic procedures, physical isolation from loved ones, unfamiliar surroundings, noise, sleep deprivation, and life-sustaining therapies such as mechanical ventilation or electronic pacing.[6,7] Furthermore, extreme anxiety, delirium, adverse drug effects, or pain can lead to agitation, which occurred at least once in 71% of patients in a medical–surgical ICU.[8] Patients aware of unpleasant or frightening memories of their ICU stay may also experience post-traumatic stress disorder.[9,10]

Under-sedation and Over-sedation: A Difficult Balance

The use of sedatives may be essential to maintain patient safety and comfort. Pain and other physiologic stress may be associated with increases in sympathetic tone, catecholamines, growth hormone, vasopressin, cortisol, glucagon, fatty acids, and protein catabolism that can lead to ischemia, fluid and electrolyte problems, and poor wound healing.[11] Under-sedation may lead to unwanted outcomes such as ventilator asynchrony, increased oxygen consumption, removal of devices and catheters by the patient, and post-traumatic stress disorder.[7] Over-sedation may lead to prolonged mechanical ventilation with the potential for ventilator-associated pneumonia, ventilator-associated lung injury, or critical care myopathy or neuropathy.[12]

Although the importance of appropriate sedation is clear, the concept of a "target" for sedation has been elusive. Startlingly, scrutiny of the use of sedation and analgesia in the ICU is a relatively novel concept, and the first validation of a sedation scale for use in the ICU did not appear in the literature until the late 1990s.[13] In fact,

the practice guidelines of the Society of Critical Care Medicine (SCCM) of the American College of Critical Care Medicine published in 1995 were based on some published research, but relied primarily on expert opinion.[14] Since then, the literature on this topic has greatly expanded with the creation and validation of a variety of sedation scoring tools and protocols for the use of sedation in the ICU.[12] However, acceptance of sedation protocols and clinical guidelines has not been universal, perhaps because different health care providers have different goals for sedation.[15] In 2002, the SCCM and the American Society of Health-System Pharmacists (ASHP) released an updated clinical practice guideline based on a significantly larger body of evidence.[7] The key recommendations from those guidelines are summarized in Table 1.

Choosing a Sedative Agent

The SCCM–ASHP guidelines review therapeutic choices for analgesics and sedatives, including their pharmacokinetic properties, usual dosing, adverse effects, and typical costs.[7] If opioid analgesics of IV administration are required, the preferred agents are fentanyl, hydromorphone, and morphine. Fentanyl or hydromorphone should be considered for patients with renal failure or hemodynamic instability. Only after adequate analgesia has been achieved should a sedative be considered. Acutely agitated patients should be given midazolam or diazepam, and haloperidol should be used if the acute agitation is a result of delirium. Continuous use of sedatives should follow a trial of intermittent dosing such that the dose required to meet sedation goals can be estimated. In situations where rapid awakening is required, propofol may be the preferred choice. For patients requiring sustained sedation, lorazepam should be considered the first-line drug. Long-term infusion of midazolam produces unpredictable awakening and time to extubation, so its use should not exceed 48 to 72 h. Despite this limitation, midazolam continues to be popular in the ICU. Diazepam and midazolam have active metabolites that can accumulate in renal failure, but renal failure has a minimal effect on the pharmacokinetics of propofol.

Benzodiazepines and propofol (either alone or with opioid analgesics) are the most commonly used sedating agents in the ICU. Unfortunately, despite studies confirming the difficulty of predicting weaning and extubation in patients receiving midazolam for prolonged periods, this drug continues to be commonly used in critical care. Propofol has been shown to allow for earlier extubation than midazolam, although this does not necessarily lead to a shorter length of stay in the ICU.[16] The use of propofol is not without safety concerns.[17] It has been shown to cause a greater risk of hypotension and bradycardia than midazolam, and when used for prolonged periods in doses exceeding 4 mg kg^{-1} h^{-1} can lead to a lethal "propofol infusion syndrome" characterized by arrhythmia, hyperkalemia, rhabdomyolysis, metabolic acidosis, and myocardial failure. A recent adverse drug reactions bulletin from Australia reported cases of lactic acidosis and torsade de pointes in infusions of only 24 h duration at doses considerably lower than 4 mg kg^{-1} h^{-1}.[18] In addition, propofol is not approved in Canada for use as a sedative

Table 1. Key Recommendations Adapted from the 2002 Clinical Practice Guidelines for the Sustained Use of Sedatives in the Critically Ill Adult, Developed by the Society for Critical Care Medicine and the American Society of Health-System Pharmacists[7]

Sedation of agitated patients should be considered only after reversible physiologic causes have been treated and adequate analgesia has been provided.
A sedation goal or end point should be established with a validated scale for assessment of sedation, and regular assessment should be performed to determine response to therapy, with appropriate changes and redefinition of end point as appropriate.
Midazolam or diazepam should be used for rapid sedation of acutely agitated patients.
Propofol is the preferred sedative when the patient may need rapid awakening (such as for neurologic assessment or extubation).
Midazolam is recommended for short-term use only, as awakening time is unpredictable after 48–72 h of continuous midazolam infusion.
Lorazepam is the recommended agent for intermittent or continuous IV sedation for most patients.
The sedative dose should be titrated to a defined end point, and systematic tapering or daily interruption should be used to minimize the effects of prolonged sedative use.
Sedation guidelines, an algorithm, or a sedation protocol should be used.
The potential for opioid, benzodiazepine, or propofol withdrawal should be considered in patients receiving high doses or greater than 7 days of continuous therapy with sedative medications.
Routine assessment for delirium should be performed for patients in the intensive care unit, with haloperidol the preferred agent for the treatment of delirium in critically ill patients.

in patients under 18 years of age. Health Canada's Therapeutic Products Directorate circulated a notice in May 2001 outlining the results of a study that found higher death rates among children sedated with propofol than among those sedated with other agents.[19]

Importance of Sedation Scales and Sedation Protocols

Goal-directed sedation therapy is a recommended standard for avoiding over-sedation in the ICU.[7] The objective use of sedation scales and sedation protocols can promote weaning and earlier extubation, which may influence critical care costs and outcomes, including length of stay.[20-23] Choosing an appropriate sedation scale for use in the ICU is difficult. Very few of the available scales have been appropriately tested for reliability and validity in the critical care setting.[24-26] Of the scales that have been validated, only one has been shown to detect changes in sedation status over time as correlated with level of consciousness and administration of sedative medications.[27] To date, there is no consensus about the best tool to evaluate sedation or how frequently such tools should be used.

Within any institution, the introduction of a sedation algorithm or protocol must have multidisciplinary acceptance. The choice of sedation scale should take into account its ease of use, time constraints related to staffing, and the concordance of the sedation ratings in the scale to the sedation "culture" within a particular ICU. A review of the validity and reliability of various sedation scores for use in critically ill patients is beyond the scope of this paper, but a summary paper has recently been published.[12] The latest sedation rating scale separates the domains of arousal and motor activity, as the latter is less important in determining subsequent sedative use.[28] Regardless of the specific scale chosen, the inclusion of a sedation scale in the goal-directed delivery of sedation is recommended as a standard of care for ICUs. Unfortunately, the implementation of scores to evaluate sedation in critically ill patients varies widely (16% to 67% of ICUs surveyed).[17]

The Role of the Hospital Pharmacist

The presence of a pharmacist on rounds, as a full member of the critical care team, leads to a substantially lower rate of adverse drug events caused by prescribing errors.[29] A recent British study demonstrated that errors in propofol prescribing were among the top 5 most common prescription errors and accounted for 3% of all such errors in the ICU.[30] The use of ICU sedation guidelines and pharmacist interventions reduces the overall use of midazolam and propofol and reduces sedative drug costs by 75% without adversely affecting the ability to wean patients from mechanical ventilation.[31] Since those findings were published, other researchers have demonstrated that goal-directed sedation with clear sedation targets (assessed through a validated sedation scoring system) can reduce the duration of intubation or the total ICU stay.[21-28] These are exciting developments for critical care pharmacy. Working with other members of the critical care team, pharmacists can help with the development of protocols or guidelines, the selection of a sedation score, and the prescription of safe and appropriate sedation. Furthermore, pharmacists can help to identify and prevent unsafe practices, such as high-dose propofol infusions or prolonged infusions of propofol or midazolam, and can also make suggestions for alternative agents for patients at risk of over-sedation (e.g., those with renal or liver disease, those who are obese, and elderly patients). Because up to 40% of errors are due to incorrect infusion rates, pharmacists should routinely review settings on infusion pump devices.[5] The American Society of Health-System Pharmacists has already played an important role in the development of clinical practice guidelines for the sustained use of sedatives in the critically ill adult.[7] Individual hospital pharmacists can help to promote the use of those guidelines within their own institutions with the goal of improving the safe and appropriate use of sedation in their critically ill patients.

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