Monitoring sedation during mechanical ventilation

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Abstract

Sedative medications have been used in intensive care units (ICU) to minimize discomfort, prevent pain/anxiety, allow invasive procedures, reduce stress, and improve synchrony in mechanically ventilated (MV) patients. However, these drugs can have adverse effects resulting in increased length of ICU/hospital stay, health care costs, morbidity, and mortality. This review summarizes the mechanisms of action, usual doses, side effects, adverse effects, contraindications, and recent studies of sedatives which are frequently used in adult ICUs and the sedation assessment tools for measuring quality and depth of sedation in adult ICU patients.

Keywords: sedations, mechanical ventilation, intensive care unit, sedation assessment tools

Introduction

Sedative medications are used in ICUs to minimize discomfort, prevent pain /anxiety, allow invasive procedures, reduce stress, and improve synchrony in MV patients. However, these drugs have adverse effects, and the potential to prolong mechanical ventilation and increase related complications, such as hospital-acquired pneumonia, ventilator-induced lung injury, and ventilator-associated pneumonia, all of which result in increased lengths of ICU/hospital stay, health care costs, morbidity, and mortality. Understanding how to use and monitor sedative medications properly could lead to decreased lengths of stay, decreased related complications, and ultimately better patient outcomes.

Propofol

Propofol is a short-acting medication that results in a decreased level of consciousness and short-term memory. It is used for induction and maintenance of general anesthesia, sedation for mechanically ventilated patients, procedural sedation, and treatment of status epilepticus that is unresponsive to other antiepileptics.

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Mechanism of action

Propofol allosterically increases the binding affinity of gamma-aminobutyric acid (GABA) to the $GABA_A$ receptor and facilitates inhibitory neurotransmission. The onset of maximum effect takes about 2 minutes and typically lasts 5 to 10 minutes. The half-life of elimination has been estimated to be between 2 and 24 hours. However, its duration of clinical effect is much shorter, because propofol is rapidly distributed into peripheral tissues.

Usual doses

The procedural sedation dose for a healthy adult is 1 to 2 mg/kg and for a debilitated adult is 0.5 to 1 mg/kg. For patients on mechanical ventilation, the bolus dose is 0.5 to 2.5 mg/kg, and the maintenance dose is 5 to 50 mcg/kg/min, titrating every 5 to 10 minutes in increments of 5 to 10 mcg/kg/min.

Side effects

The most common side effect is hypotension. It causes decreased systemic vascular resistance, myocardial blood flow, and oxygen consumption, possibly

through direct vasodilation.[2] There are also reports that it may cause green discoloration of the urine.[3] A more serious but rare side effect is dystonia. Mild myoclonic movements are common. A rare, but potentially fatal, side effect is propofol infusion syndrome; unexplained metabolic acidosis, ECG changes (bradycardia, wide QRS complex), and rhabdomyolysis have been reported after a prolonged infusion of high dose propofol, sometimes in combination with catecholamines and/or corticosteroids.[4]

Recent studies

In a large, propensity-matched ICU population, patients treated with propofol had reduced risks of mortality and had both increased likelihoods of earlier ICU discharge and earlier discontinuations of mechanical ventilation, compared to patients treated with benzodiazepines.[5] In critically-ill patients, propofol is superior to lorazepam both in effectiveness and overall cost due to shorter ICU stay lengths. One of the reasons that propofol is thought to be more effective despite having a longer half-life than lorazepam is because benzodiazepines, like midazolam and lorazepam, tend to accumulate in the body resulting in prolonged sedation.[6]

Etomidate

Etomidate is a short-acting intravenous general anesthetic without analgesic activity. It has a rapid onset of action and a safe cardiovascular risk profile and, therefore, is less likely to cause a significant drop in blood pressure than other induction agents.

Mechanisms of Action

Etomidate depresses the reticular activating system and mimics the inhibitory effects of GABA. The (*R*)-enantiomer is tenfold more potent than its (*S*)-enantiomer; it appears to bind to a subunit of the $GABA_A$ receptor, increasing the receptor's affinity for GABA. The duration of action is dose dependent but relatively brief, usually 3 to 5 minutes when an average dose of 0.3 mg/kg is used. The half-life for drug metabolism is about 75 minutes, because etomidate is redistributed from the plasma to other tissues. Etomidate decreases cerebral metabolic rate, cerebral blood flow, and intracranial pressure.

Usual doses

The dose for adults and children over ten years old is 0.3 mg/kg. Etomidate is unsuitable for administration by a prolonged infusion.

Side effects

The most common side effects include venous pain on injection and skeletal muscle movements, namely myoclonus and dystonia. It can cause slight increases in arterial carbon dioxide tension ($PaCO_2$).[7] Etomidate suppresses corticosteroid synthesis in the adrenal cortex by reversibly inhibiting 11β-hydroxylase, an enzyme important in adrenal steroid production, and this leads to primary adrenal suppression.[8,9] Reduced cortisol plasma levels have been reported with induction doses of 0.3 mg/kg etomidate. These persist for approximately 6 to 8 hours and do not reverse with adrenocorticotropic hormone (ACTH) administration. Cortisol levels have been reported to be suppressed up to 72 hours after a single bolus of etomidate in ICU patients at risk for adrenal insufficiency.

Recent studies

A meta-analysis in 2014 concluded that in sepsis patients one dose of etomidate does not appear to change the risk of death.[10] Similarly, another meta-analysis in 2021 showed that etomidate can cause adrenal insufficiency but does not increase mortality in most of the studies analyzed. However, etomidate associated relative mortality rates increased progressively and correlated with the severity of critical illness scores. Intensivists should anticipate and evaluate the need for glucocorticoid supplementation after etomidate in patients with severe critical illnesses and in patients with acute deterioration of vital signs.[11]

A systematic review and meta-analysis included six studies (12,060 patients) published in January 2022 showed that the use of etomidate for induction during rapid sequence intubation is associated with a decreased risk of post-induction hypotension as

compared to the use of ketamine without any effect on the first-pass intubation success rate.[12]

Dexmedetomidine

Dexmedetomidine is a medication used for sedation to treat acute agitation associated with schizophrenia or bipolar disorder and to treat alcohol withdrawal.[13] It may be useful for the treatment of the negative cardiovascular effects of acute amphetamines and cocaine intoxication and overdose.[14,15] It has also been used as an adjunct to neuro-axial anesthesia for lower limb procedures.[16]

Mechanisms of Action

Dexmedetomidine is an α_2 adrenergic agonist, like clonidine. It possesses an α_2: α_1 selectivity ratio of 1620:1, making it eight times more selective for the α_2-receptor than clonidine. It induces sedation by decreasing activity of noradrenergic neurons in the locus coeruleus in the brain stem, thereby increasing the downstream activity of inhibitory GABA neurons in the ventrolateral preoptic nucleus. It results in less amnesia than benzodiazepines and has analgesic effects at the spinal cord level and other supraspinal sites. Intravenous dexmedetomidine exhibits linear pharmacokinetics with a rapid distribution half-life of approximately 6 minutes in healthy people, and a longer and more variable half-life in ICU patients.[17] It is metabolized by the liver, primarily by glucuronidation and oxidation by CYP2A6 and other Cytochrome P450 enzymes and should be used with caution in people with liver disease.[18]

Usual doses

The bolus dose is 1 mcg/kg IV over 10 minutes but is optional and usually not given. The maintenance dose is 0.2 to 1.5 mcg/kg/hr.

Side effects

There is no absolute contraindication to the use of dexmedetomidine. It may enhance the effects of other sedatives and anesthetics when co-administered. Similarly, drugs that lower blood pressure and heart rate, such as beta blockers, may cause more hypotension and bradycardia when co-administered with dexmedetomidine.[18]

Recent studies

A recent systemic review and meta-analysis suggests that the use of dexmedetomidine for sedation in mechanically ventilated adults was associated with a significant reduction in the time to extubation and shorter ICU stays in difficult-to-wean ICU patients. The risk for hypotension was increased, but no other adverse clinical outcomes were observed.[19] A randomized controlled trial (RCT) in May 2018 showed nocturnal administration of low-dose dexmedetomidine in critically ill adults reduces the incidence of delirium during the ICU stay without any changes in patient reported sleep quality .[20]

In mechanically ventilated adults with sepsis who were being treated with recommended light-sedation approaches, outcomes (days alive without delirium or coma during the 14-day intervention period, ventilator-free days at 28 days, death at 90 days, and age-adjusted total score on the Telephone Interview for Cognitive Status questionnaire at 6 months) in patients who received dexmedetomidine did not differ from outcomes in those who received propofol.[21] Dexmedetomidine was not inferior to midazolam and propofol in maintaining light to moderate sedation. It reduced duration of mechanical ventilation compared with midazolam and improved patients' ability to communicate pain compared with midazolam and propofol.[22]

Barbiturates

Barbiturates are used for seizure control, anxiety, insomnia, and anesthesia induction. Currently, they have been largely replaced by benzodiazepines since benzodiazepines have less toxicity in drug overdoses. They are classified based on the duration of action: ultra-short acting (30 minutes): thiopentone, methohexitone; short acting (2 hours): hexobarbitone, cyclobarbitone, pentobarbitone, secobarbitone; intermediate acting (3–6 hours): amobarbitone, butabarbitone; and long acting (6 hours): phenobarbitone.[23]

Mechanisms of Action

Barbiturates depress the reticular activating system in the brainstem by binding to the $GABA_A$ receptor, which is different from the $GABA_A$ site to which benzodiazepines bind. Barbiturates potentiate the action of GABA in increasing the duration of openings of a chloride specific ion channel. Barbiturates also inhibit kainate and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors.

Usual doses

The dose of pentobarbital for procedural sedation is 150 to 200 mg IM. For seizure control, the loading dose is 10 to 15 mg/kg IV, followed by continuous infusion of 0.5 to 4.0 mg/kg/hr. The dose of phenobarbital for procedural sedation is 130 to 200 mg IM, 60 to 90 minutes before surgery. For seizure control, the dose is 100 to 320 mg IV. The dose may be repeated if needed but is usually not more than 600 mg/day. However, higher doses may be needed for certain types of continuing seizures.

Side effects

Common side effects include nausea, hypotension, headache, drowsiness, and skin rash. More serious side effects include confusion, coma, hallucination, and respiratory depression. Rare but serious side effects include agranulocytosis, Stevens–Johnson syndrome, liver injury, and megaloblastic anemia.

Contraindications

Contraindications include variegate porphyria and status asthmaticus because barbiturates cause respiratory depression. It may also exacerbate acute intermittent porphyria or porphyria variegate by inducing the enzymes for porphyrin synthesis.[24]

Ketamine

Ketamine is a dissociative anesthetic used for induction and maintenance of anesthesia. The distinguishing features of ketamine are preserved breathing and airway reflexes, stimulated cardiac function with increased blood pressure, and moderate bronchodilation. It is used for acute pain management. Esketamine nasal spray has been recently approved, in conjunction with an oral antidepressant, for treatment-resistant depression.[25]

Mechanism of action

Ketamine has multiple effects in the central nervous system. It is a N-methyl-D-aspartate (NMDA) receptor antagonist resulting in anesthetic, analgesic, and psychotomimetic effects.[26,27] It also results in analgesia by preventing central sensitization in dorsal horn neurons and interfering with pain transmission in the spinal cord.[28] It functionally dissociates sensory impulses from the limbic cortex; this may cause the patient to appear conscious but unable to process or respond to sensory input.[29]

Usual doses

The procedural sedation dose is 1 to 3 mg/kg IV or 5 to 10 mg/kg IM. For mechanical ventilation the bolus dose is 0.25 to 0.5 mg/kg (maximum dose is 2 mg/kg over 30 min) and the maintenance dose is 0.05 to 4 mg/kg/hr.

Side effects

The most common side effects associated with ketamine are nausea, vomiting, dizziness, diplopia, drowsiness, dysphoria, and confusion. Rarely, patients experience hallucinations. Laryngospasm rarely occurs. Ketamine generally stimulates breathing; however, a high-dose rapid intravenous injection or rapidly administration may cause a transient minimal respiratory depression.[30]

Contraindications

Ketamine is contraindicated in patients with underlying conditions, such as aortic dissection, uncontrolled hypertension, myocardial infarction, or aneurysms, in which increased blood pressure would

pose a risk of complications. In patients with increased cerebrospinal fluid (CSF) pressure, the use of ketamine is controversial due to possible elevations of the CSF pressure caused by ketamine.[30]

Recent studies

A systematic review and meta-analysis in October 2022 suggests using ketamine as an adjunct analgosedative due to the potential to reduce opioid exposure in postoperative and MV patients in the ICU.[31]

Benzodiazepines

Benzodiazepines have psycholeptic, sedative, hypnotic, anxiolytic, anticonvulsant, muscle relaxant, and amnesic effects. They have been used to treat alcohol dependence, seizures, anxiety disorders, panic, agitation, and insomnia.[32,33] Tolerance can develop to their effects, there is also a risk of dependence, and upon discontinuation a withdrawal syndrome may occur.

Mechanisms of Action

Benzodiazepines enhance the effect of the neurotransmitter GABA by binding to the $GABA_A$ receptor (the same set of receptors in the central nervous system as barbiturates but at a different site), which increases the frequency of openings of the associated chloride ion channel. Flumazenil (an imidazobenzodiazepine) is a specific benzodiazepine–receptor antagonist that effectively reverses most of the central nervous system effects of benzodiazepines

Usual doses

The midazolam dose for procedural sedation is 2 to 2.5 mg IV initially, with further 1 mg doses repeated after 2 to 5 minutes, titrated to effect. In adults older than 60 and those chronically ill, starting dose is 0.5 to 1 mg (and 1 mg over at least 30 seconds). A total dose of more than 5 mg is not usually necessary in a healthy young adult; less than 3.5 mg is the required dose in debilitated and older subjects. For continuous infusion, the loading dose is 0.01 to 0.05 mg/kg (0.5 to 4 mg), and the maintenance dose is 0.02 to 0.1 mg/kg/hr.

For procedural sedation, the lorazepam dose is 1 to 2 mg IV. For continuous infusion, the loading dose is 0.02 to 0.04 mg/kg; the maintenance dose is 0.01 to 0.1 mg/kg/hr. An intermittent dose can also be given at 0.02 to 0.6 mg/kg IV every 2–6 hours.

For procedural sedation, the loading dose of diazepam is 0.05 to 0.2 mg IV/kg (usual dose range 5 to 10 mg), and the maintenance dose is 0.03 to 0.1 mg/kg every 0.5 to 6 hours (1 to 7 mg). Continuous infusion is not recommended.

Side effects

The most common side-effects are related to their sedating and muscle-relaxing action, including drowsiness, dizziness, and decreased alertness and concentration.

Recent studies

A systematic review and meta-analysis in August 2021 concluded that sedation with propofol compared to midazolam is associated with improved clinical outcomes in the ICU with reduced ICU stay, mechanical ventilation time, and extubation time in acute surgical patients and reduced extubation time in critically ill patients.[34] A systematic review in October 2018 determined that the majority of included studies demonstrated that benzodiazepine use in the ICU is associated with delirium, symptoms of posttraumatic stress disorder, anxiety, depression, and cognitive dysfunction.[35]

Sedation monitoring

The Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit published in the Society of Critical Care Medicine 2013[36] and the updated version in 2018[37] recommend that maintaining light levels of sedation in adult ICU patients is associated with improved clinical outcomes, shorter duration of

Table 1. Richmond Agitation Sedation Scale (RASS)

Score	Term	Description
+4	Combative	Overtly combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tubes, or catheters; aggressive
+2	Agitated	Frequent non-purposeful movement, fights ventilator
+1	Restless	Anxious but movements not aggressive vigorous
0	Alert and calm	
−1	Drowsy	Not fully alert, but has sustained awakening (eye opening/eye contact) to voice (>10 seconds)
−2	Light sedation	Briefly awakens with eye contact to voice (<10 seconds)
−3	Moderate sedation	Movement or eye opening to voice (but no eye contact)
−4	Deep sedation	No response to voice, but movement or eye opening to physical simulation
−5	Unarousable	No response to voice or physical stimulation, communicate or follow commands

mechanical ventilation, and a shorter ICU length of stay. This approach increases the physiologic stress response but is not associated with an increased incidence of myocardial ischemia.

Using nonbenzodiazepine sedatives (either propofol or dexmedetomidine) may be preferred over sedation with benzodiazepines (either midazolam or lorazepam) to improve clinical outcomes in mechanically ventilated adult ICU patients. Routine daily sedation interruption or a light target level of sedation should be used in mechanically ventilated adult ICU patients.

Currently, the Richmond Agitation-Sedation Scale (RASS) (Table 1) and Sedation-Agitation Scale (SAS) (Table 2) are the most valid and reliable sedation assessment tools for measuring quality and depth of sedation in adult ICU patients. Obtaining a RASS score is the first step in administering the Confusion Assessment Method in the ICU (CAM-ICU), a tool to detect delirium in ICU patients. This instrument to assess sedation and agitation in adult ICU patients is simple to use and has discrete criteria and sufficient levels for sedative medication titration and agitation

Table 2. Sedation-Agitation Scale (SAS)

Score	Term	Description
7	Dangerous agitation	Pulling at endotracheal tube or catheters, trying to remove catheters, climbing over bedrail, striking at staff, thrashing side-to-side
6	Very agitated	Does not calm, despite frequent verbal reminding of limits; requires physical restraints, biting endotracheal tube
5	Agitated	Anxious or mildly agitated, attempting to sit up, calm down to verbal instructions
4	Calm and co-operative	Calm, awakens easily, follows commands
3	Sedated	Difficult to arouse, awakens to verbal stimuli or gentle shaking, but drifts off again, follow simple commands
2	Very sedated	Arouse to physical stimuli, but does not communicate or follow commands, may move spontaneously
1	Unarousable	Minimal or no response to noxious stimuli, does not communicate or follows commands

evaluation. It showed very good inter-rater reliability and validity across a broad spectrum of adult ICU patients.[38]

Other objective measures of brain function (e.g., auditory evoked potential [AEPs], Bispectral Index [BIS], Narcotrend Index [NI], Patient State Index [PSI], or state entropy [SE]) can be used as an adjunct to subjective sedation assessments in adult ICU patients who are receiving neuromuscular blocking agents.

Recent studies

In an RCT published in March 2020, 700 patients were enrolled, and mortality in mechanically ventilated ICU patients at 90 days did not differ significantly between those assigned to a plan of no sedation and those assigned to a plan of light sedation with daily interruption.[39] A cross-sectional study in 2019 showed that the Richmond Agitation-Sedation Scale showed excellent inter-rater agreement compared with a weak inter-rater agreement of Ramsay scale. The results also support that RASS has consistent agreement with clinical observation and practice among different observers. The results suggest that use of RASS is linked to a more reliable assessment of sedation levels in the ICU.[40]

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