Ketamine was approved for use as an anesthetic agent by the US Food and Drug Administration (FDA) in 1970 and is an analog of the hallucinogen phencyclidine, commonly known as PCP. Ketamine’s development was driven by the observation that phencyclidine was a useful anesthetic agent but caused serious neuropsychiatric adverse events (eg, delirium, psychosis, dissociative states). Despite being one-tenth as potent as phencyclidine, ketamine was recognized as a drug associated with neuropsychiatric adverse events. These neuropsychiatric events led to ketamine being exploited illegally. In the 1990s, increasing reports of recreational ketamine use resulted in the FDA reclassifying ketamine as a schedule III-controlled substance.

Despite concerns of drug diversion or abuse, the number of clinical and experimental uses of ketamine in a variety of patient populations has grown significantly over the last decade. This growth is due in part to ketamine’s unique pharmacologic profile. Uses beyond the FDA-approved indication as an anesthetic include the management of various pain types (eg, neuropathic, musculoskeletal, burn related), procedural sedation and sedation during rapid sequence intubation (RSI), rapid amelioration of depressed mood, alcohol withdrawal management, acute undifferentiated agitation, continuous infusion sedation, and status epilepticus. In this Drug Update column, practical considerations for use of ketamine in the intensive care unit (ICU) are reviewed, as are its most common uses, including as an analgesic and during RSI and procedural sedation.

Pharmacology

The best known and most explored pharmacologic mechanism of ketamine involves noncompetitive blockade of N-methyl-D-aspartate glutamate receptors. This blockade may result in anesthetic and analgesic effects and, in part, the neuropsychiatric adverse effects associated with ketamine. Other effects of ketamine include blockade of L-type, voltage-dependent calcium channels that results in relaxation of airway smooth muscle and causes negative cardiac inotropy. Ketamine also blocks voltage-gated sodium channels, which results in decreased parasympathetic tone and local anesthetic effects. Effects of
ketamine on large-conductance potassium channels can have benefit for neuropathic pain. Ketamine’s interactions with opioid receptors, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors, and γ-aminobutyric acid A receptors may improve pain control, reduce depression, and contribute to anesthetic effects, respectively. Other putative mechanisms involve influence on monoaminergic and cholinergic systems. Although mechanisms describing ketamine mostly have been related to clinical effects from receptor binding, secondary effects such as regulation of gene expression and neoplastic changes continue to be explored.

Ketamine is approved as a solution for intravenous (IV) injection. However, off-label routes of administration include intramuscular injection, which is used primarily for managing acute agitation. In the palliative care setting, the injectable formulation often is given orally. Ketamine routes of administration may include rectal, subcutaneous, epidural, and intrathecal; compounding pharmacies may create ketamine products for topical or nasal administration. The extent of absorption, onset, and duration depends on the route of administration.

In critical care settings, the IV route is preferred for most indications because of the quick time to effect and complete absorption, especially for induction during RSI and when administered for procedural sedation. The anesthetic effect of ketamine is approximately 1 hour after a single injection, corresponding to an α-elimination half-life of approximately 10 to 15 minutes. Ketamine elimination depends on hepatic metabolism, primarily via cytochrome P450 pathways that convert ketamine to norketamine. Norketamine is approximately one-third as potent as ketamine and depends on renal elimination. Ketamine is only partially dialyzable owing to extensive distribution into fat stores.

**Ketamine in the Intensive Care Unit**

Analgesia

The use of ketamine as an analgesic has increased over the last 2 decades. Ketamine investigations have focused primarily on use as an opioid-sparing therapy; however, the use of ketamine may reduce or prevent central sensitization, opioid-induced hyperalgesia, and tolerance to opioid medications. As an analgesic, evaluated ketamine uses include administration via IV bolus, continuous IV infusion, and as patient-controlled analgesia. Of these administration routes, IV bolus and continuous IV administration have had the most positive outcomes.

Zakine and colleagues evaluated the effectiveness of ketamine when added to morphine in 77 patients undergoing major abdominal surgery. The researchers evaluated 3 groups: (1) ketamine 0.5 mg/kg IV bolus followed by 2 μg/kg per minute ketamine intraoperatively and 48 hours after the procedure (PERI group); (2) ketamine 0.5 mg/kg IV bolus followed by 2 μg/kg per minute ketamine intraoperatively and 48 hours after surgery was reduced significantly in the PERI group (27 mg [PERI group] vs 48 mg [INTRA group] vs 50 mg [placebo group]; \(P < .008\)). This effect of reduced morphine requirements was sustained during all predetermined time frames: 0 to 4 hours, 4 to 24 hours, and 24 to 48 hours following surgery. In addition, visual analog scale scores were significantly lower in the PERI and INTRA groups as compared with the placebo group for all times assessed. The use of ketamine perioperatively was associated with significantly less nausea or vomiting (\(P = .001\)) as compared with intraoperative ketamine or placebo. No patients in the INTRA or PERI groups reported psychiatric disorders, delusions, or nightmares. In this study, Zakine et al demonstrated an opioid-sparing effect of ketamine without compromising pain control or increase in the risk of neuropsychiatric adverse events.

The use of IV bolus ketamine has been studied in several operative populations. Doses studied range from 0.15 to 1 mg/kg given either before or after surgery. In a quantitative systematic review, Subramaniam and colleagues found the addition of ketamine had an overall benefit, with improved visual analog scale scores and prolonged time to first analgesic administration in the postoperative period.

Weinbroum studied the effects of morphine 30 μg/kg IV bolus versus morphine 15 μg/kg with ketamine 250 μg/kg administered as an IV bolus up to 3 times during the postoperative period. Both groups Weinbroum studied were allowed the use of diclofenac...
for rescue pain relief if pain was not controlled with either regimen; patients randomly assigned to the morphine plus ketamine combination (n = 131) received significantly less total morphine, fewer injections, and less rescue diclofenac than those randomly assigned to morphine alone (n = 114).13 In addition, patients in the morphine plus ketamine group reported significantly less pain intensity, faster decline in pain intensity, and longer duration of pain control than did the morphine group.13

There are a limited number of high-quality studies on the use of ketamine for pain control specifically in critically ill patient populations. However, the information found in the literature suggests ketamine may have a role in pain control in patients who are critically ill, allowing for less opioid use, and reducing opioid-associated adverse effects, including nausea, vomiting, constipation, ileus, and tolerance. To our knowledge, the available ICU literature on ketamine is limited to use in patients following surgery but is promising in terms of reporting overall reduction of opioid requirements and improved pain control while avoiding adverse effects associated with ketamine. Ketamine use in managing pain in other patient populations would need to be extrapolated from non-ICU literature, which may not be appropriate.

Rapid Sequence Intubation

Ketamine’s quick onset and relatively short duration of action make it an attractive sedative during RSI. Induction is accomplished through a single 1 to 2 mg/kg IV dose, with onset of anesthesia occurring within 1 minute.2 Ketamine has become a favorite agent for induction in patients with hypotension because of its positive sympathomimetic effects. These result in increased arterial pressures and pulse rates, and, to a lesser extent, cardiac output.2 However, in certain populations, positive sympathomimetic effects may be unwanted and result in an increase of intracranial pressure.

Few studies have directly compared the hemodynamic effects of etomidate and ketamine for induction for RSI. In a randomized, controlled trial, Jabre and colleagues14 found significantly reduced cortisol levels and increased rates of adrenal insufficiency in adults who are acutely ill (n = 655) receiving etomidate for induction in RSI, compared with those receiving ketamine. These researchers found no differences between group needs for vasopressor support or in mortality rate. However, the patients in the study were in the prehospital or emergency department setting and less than 20% were diagnosed with sepsis.14

In their retrospective analysis of patients with sepsis in a medical ICU (n = 384), Van Berkel et al15 found greater rates of clinical hypotension among patients who received etomidate compared with those who received ketamine for induction during intubation (73% vs 51.3%, respectively). Patients who were administered etomidate had significantly lower mean arterial pressures 6 to 12 hours after intubation; these effects were maintained through the first 24 hours following endotracheal tube placement. Despite these effects on measured mean arterial pressures, Van Berkel et al did not find any differences in the incidence of shock, vasopressor use, lengths of stay, or mortality rates.15

Ketamine should be considered as an induction agent for RSI in patients who are hypotensive or hemodynamically unstable, have reactive airway disease, or have known adrenal insufficiency. Caution should be taken when administering ketamine to patients who are catecholamine depleted. Ketamine administration results in dilation of bronchial smooth muscles and relieves bronchospasm; it also may increase orotracheal secretions and promote laryngospasm.2 Thus, whereas ketamine may be beneficial in patients with reactive airway disease, initial advancement of the laryngoscope and placement of the endotracheal tube may be more difficult. Other concerns are negative inotropy and chronotropy that may occur after administration of ketamine in patients who are catecholamine depleted, leading to hemodynamic instability.2,16 In those patients, a dose of 1.5 mg/kg should not be exceeded for induction.16

Procedural Sedation

Ketamine appears to possess many ideal sedative properties for short, painful procedures in the ICU2,17,18; however, clinicians must be vigilant in anticipating and identifying emergence phenomenon and respiratory depression in adults who are critically ill. Procedures are often necessary for patients who are critically ill; these patients require adequate sedation and analgesia strategies to reduce anxiety, pain, and agitation. Ketamine
has many properties that make it a desirable sedative for a variety of procedures in the ICU.\textsuperscript{2,17,18}

Ketamine provides a dissociative, trance-like sedation, causing amnesia, which may aid patients in not remembering painful or difficult procedures, allowing for enhanced neuropsychiatric recovery once they leave the ICU. Second, ketamine’s analgesic properties may provide additional pain control and allow for reduced opioid requirements for certain procedures such as debridement and dressing changes in burn victims.\textsuperscript{2,16} Finally, because ketamine preserves airway muscle tone, dilates bronchial smooth muscle, and promotes spontaneous breathing, sedation may be facilitated for quick procedures; thus, invasive respiratory support may be avoided.\textsuperscript{2,18} However, if deeper levels of sedation are desired, or dissociative doses of ketamine are administered (ie, > 1 to 1.5 mg/kg given intravenously), endotracheal tube placement may be needed in the event of abrupt respiratory decompensation in patients who are not already intubated.

Ketamine typically is given at a dose of at least 1 mg/kg before initiating procedures, providing a nearly immediate onset of action.\textsuperscript{19} If a deeper level of sedation is desired or prolonged sedation is necessary for longer procedures, IV bolus doses may be repeated every 5 to 10 minutes at a dose of 0.25 mg/kg to 0.5 mg/kg. If parenteral access is not available, procedural sedation can be achieved through a 4-mg/kg dose given intramuscularly. If there is an inadequate response within 10 minutes, repeated intramuscular doses may be administered at the same or half dose.

Most studies evaluating the use of ketamine for procedural sedation outside of the operating room originate in the emergency-department setting for procedures such as fracture reductions, cardioversion, and abscess incision and drainage.\textsuperscript{17} The intense and relatively short duration of pain associated with these procedures mimic the characteristics of many procedures performed in the ICU including invasive vascular line placement, drain insertion, ultrasound-guided drainage, and dressing changes in burn victims.

In a randomized, prospective study, ketamine was compared with propofol for sedation in short, painful procedures in the emergency department.\textsuperscript{20} The ketamine group required less redosing of sedatives; however, similar procedural success was observed between the groups. Patients who received ketamine experienced greater rates of respiratory depression based on study definitions; however, interventions for respiratory depression did not differ between the groups. Patients in the ketamine group also had a clinically and statistically greater incidence of emergence phenomenon (36.2% vs 8%; 95% CI, 12.4%-43.9%). This phenomenon is of great concern with the use of ketamine, particularly for procedural sedation.

### Adverse Drug Effects

Clinicians should understand the many adverse drug effects associated with the use of ketamine. Nausea and vomiting are among the most common, occurring in up to 15% of patients and typically persisting even after therapy has stopped.\textsuperscript{21} Standard antiemetics should be offered. Because of ketamine’s sympathomimetic effects, blood pressure and heart rate should be monitored and sympatholytics, such as \(\beta\)-blockers, should be administered as needed.

Apnea and transient respiratory depression are rare and are mostly associated with rapid IV administration, larger doses of ketamine (\(\geq 2.5\) mg/kg), or concomitant administration with other medications that depress respiratory drive, such as benzodiazepines and opioids.\textsuperscript{17,21} Accordingly, caution should be taken when administering boluses of ketamine, and patients should be visually monitored to ensure proper chest rise with breaths; patients should have continuous pulse oximetry and rescue respiratory support should be readily available. Administration of a dose over no more than 30 to 60 seconds will help avoid apnea and transient hypoventilation.

Through its sympathomimetic effects, ketamine increases intracranial pressure, which is detrimental to patients with such conditions as head trauma, brain or spinal cord injury, or malignancy.\textsuperscript{2,21} However, the increase in cerebral artery perfusion that is an effect of ketamine may benefit patients with neurologic injury. In a systematic review of 10 studies including nearly 1000 patients receiving ketamine, researchers found no association between ketamine and increased cerebral perfusion pressures or other outcomes, including worsened neurologic status, length of stay, or mortality rate.\textsuperscript{22} The risks of increased
intracranial pressures and benefits of the use of ketamine should be approached on a case-by-case basis.

Though rare in adults, hypersalivation may be an adverse effect of ketamine and may be treated with suctioning or anticholinergics (eg, glycopyrrolate, atropine). Although the clinical impact of this effect is unknown, hypersalivation may be more problematic in patients unable to adequately clear secretions or those already at risk for aspiration.

Despite ketamine benefits relative to other sedatives, widespread use of ketamine in the adult population has been limited owing to its emergence phenomenon in which patients may experience severe agitation with recovery. This phenomenon is associated with disorientation, strange dreams, and hallucinations—all can be frightening for patients in the ICU, a population already at risk for negative psychiatric sequelae.

In a randomized, double-blind, placebo-controlled trial, reduced rates of emergence phenomenon were found when midazolam was coadministered with ketamine for procedural sedation; however, the severity of these events was not reported. Whether prophylactic administration of benzodiazepines to all patients receiving ketamine for procedural sedation is more safe and efficacious than a rescue-bolus dose approach is unknown. Emergence phenomenon has rates of approximately 20% and is not associated with all patients receiving ketamine; therefore, the risks of benzodiazepine coadministration, including further respiratory compromise, may outweigh the potential benefits. As such, it may be preferable to administer rescue doses of benzodiazepines or other sedatives to treat emergence phenomenon symptoms as they appear. However, studies to support this approach are needed.

**Conclusion**

Ketamine is an anesthetic agent with unique pharmacologic properties. The amount of data supporting the use of ketamine for a wide variety of novel indications continues to grow. In critical care settings, ketamine may be used commonly for RSI, procedural sedation, and analgesia. Members of the multidisciplinary critical care team must be familiar with the various off-label applications and dosing strategies of ketamine. Although ketamine has demonstrated safety when used for off-label indications, monitoring for respiratory depression and emergence phenomenon should be routine.

**REFERENCES**


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**CE Evaluation Instructions**

This article has been designated for CE contact hour(s). The evaluation demonstrates your knowledge of the following objectives:

1. Describe the mechanism of action of ketamine.
2. Identify situations in which ketamine is preferred as an induction agent during rapid sequence intubation.
3. Define the emergence reactions that are associated with ketamine use and the strategies for managing these reactions.

Contact hour: **1.0**
Pharmacology contact hour: **1.0**
Synergy CERP Category: **A**

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