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Ketamine for Pain Management

A Review of Literature and Clinical Application

Kelsea Caruso ▼ Dion Tyler ▼ Abbie Lyden

Ketamine is a dissociative anesthetic used increasingly as analgesia for different manifestations of pain, including acute, chronic, cancer and perioperative pain as well as pain in the critically ill patient population. Its distinctive pharmacologic properties may provide benefits to individuals suffering from pain, including increased pain control and reduction in opioid consumption and tolerance. Despite wide variability in proposed dosing and method of administration when used for analgesia, it is important all clinicians be familiar with the pharmacodynamics of ketamine in order to appropriately anticipate its therapeutic and adverse effects.

Introduction

Ketamine is a derivative of phencyclidine (PCP) introduced in the 1960s for medical use as a dissociative anesthetic agent (Bell & Kalso, 2018). Since its inception, clinical use of ketamine has vastly expanded beyond general anesthesia to additional indications including induction of rapid-sequence intubation and management of depression, status epilepticus, reactive airway diseases, and pain (Gales & Maxwell, 2018). The unique pharmacodynamic (the response of the body to medication) properties of ketamine have made it an attractive option for use as an analgesic in a variety of pain syndromes such as acute, chronic, and perioperative pain as well as a sedation strategy in critically ill patients.

Ketamine primarily exerts its pharmacologic effects through noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonism at the phencyclidine binding site within the central nervous system (CNS) (Cohen et al., 2018). The NMDA receptor is normally activated by endogenous glutamate, the principal excitatory neurotransmitter of the CNS, and is thought to contribute to effects on cognition, memory, pain regulation, and opioid tolerance as well as induction and maintenance of chronic pain through increased central sensitization and windup, defined as increased neuronal excitability during nociception conditioning (Cohen et al., 2018). Additional receptors affected by ketamine include opioid, cholinergic, dopaminergic, and monoaminergic receptors as well as sodium, potassium, and calcium channels (Bell & Kalso, 2018; Cohen et al., 2018). Ketamine has anti-inflammatory effects, modulating the production of proinflammatory mediators (Lu et al., 2016). Ketamine is hepatically metabolized and has a half-life of about 2.5 hours. When given intravenous (IV), its onset of action is generally within 5 minutes. The duration of analgesia after ketamine administration is between 20 and 45 minutes.

Different routes of administration for ketamine have been studied including oral, IV infusion, IV push, intranasal, and intramuscular (Hopper et al., 2015). Oral formulations need to be specially compounded and oral administration is generally disfavored due to poor bioavailability and occurrence of adverse effects (Bell & Kalso, 2018). For the treatment of pain the preferred route of administration is IV. There are various dosing strategies for ketamine and dosing depends on indication and route of administration. Ketamine is generally categorized into subdissociative and dissociative doses of ketamine (Castle et al., 2017). Subdissociative ketamine dosing (sometimes referred to as low-dose ketamine) has not been clearly defined, but is utilized for analgesia at bolus doses commonly ranging from 0.3 to 0.5 mg/kg and infusions of 0.1–1 mg/kg/hr (Schwenk et al., 2018). Dissociative doses of ketamine are higher and used for the induction and maintenance of anesthesia with bolus doses of ≥1 mg/kg and infusions ≥10 μg/kg/min (Gales & Maxwell, 2018).

Acute Pain

With the current opioid epidemic, alternative pain management strategies are being increasingly explored. Ketamine has been studied for the treatment of acute pain crises, such as abdominal pain, chest pain, sickle cell pain, and pain associated with trauma (Ahern et al., 2013). When used in the emergency department, ketamine has

Kelsea Caruso, PharmD, Emergency Medicine Clinical Pharmacist, Northwestern Memorial Hospital, Chicago, IL.

Dion Tyler, PharmD, PGY2 Emergency Medicine Pharmacy Resident, Rosalind Franklin University of Medicine and Science and Northwestern Memorial Hospital, Chicago, IL.

Abbie Lyden, PharmD, BCPS, Associate Professor, Rosalind Franklin University of Medicine and Science, and Emergency Medicine Clinical Pharmacist, Northwestern Memorial Hospital, Chicago, IL.

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Correspondence: Kelsea Caruso, PharmD, Department of Pharmacy, Northwestern Memorial Hospital, 251 E Huron LC-700, Chicago, IL 60611 (kelsea.caruso@nm.org).

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been shown to decrease opioid use (Motov et al., 2018). Ketamine has been studied alone and also in combination with opioids (Beaudoin et al., 2014). Compared to morphine, ketamine has been shown to be noninferior for the treatment of acute pain, showing ketamine as an alternative to morphine (Karlow et al., 2018).

For the treatment of acute pain, ketamine has been studied in various doses, but all doses are less than 1 mg/kg and the most commonly reported dose is 0.3 mg/kg (Pourmand et al., 2017). Although less common, some studies have reviewed the use of a continuous infusion after an initial bolus (Ahern et al., 2013). At these doses, side effects are less common and the risk of respiratory depression is less compared with morphine (Karlow et al., 2018). Ketamine, even at these lower doses, has been shown to cause emergence reactions and psychiatric adverse events (Karlow et al., 2018).

When studied for the treatment of acute pain, ketamine has been administered as an IV push and as a short IV infusion. In these scenarios, giving ketamine as a short infusion over 15 minutes causes less sedation and a feeling of unreality compared with IV push over 5 minutes. Giving ketamine as a 15-minute infusion does not change the efficacy (Motov et al., 2017).

Chronic and Cancer Pain

Ketamine has been utilized for the inpatient and outpatient treatment of chronic pain. Most trials reviewing ketamine for this indication have been in patients with chronic neuropathic pain. The dosing and monitoring protocols for ketamine when used for chronic pain vary and the optimal protocol has yet to be determined (Maher et al., 2017). Suggested protocols utilize ketamine IV infusion dosing at 0.1–0.5 mg/kg/hr and incorporate adjunctive medications, such as benzodiazepines, to decrease risk of dysphoric reactions. Consensus guidelines from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists overall support the use of ketamine for chronic pain, but the evidence is still considered low and larger studies would help to determine optimal dose and efficacy (Cohen et al., 2018).

Similarly to chronic pain, the use of ketamine for cancer pain varies widely in its dose and duration. One institution's protocol utilized ketamine for the inpatient management of patients with cancer pain no longer responsive to opioids. A continuous infusion was utilized at a dose ranging from 0.1 to 0.2 mg/kg/hr or 20 mg/hr. Case reports of two patients were discussed and ketamine was found to be effective for pain management in both patients (Loveday & Sindt, 2015). Data to support the use of ketamine for cancer pain are predominately case reports, but a Cochrane review assessed three small trials and concluded that there is a lack of evidence to recommend ketamine as an adjunct to opioids for cancer pain (Bell et al., 2017).

Perioperative Pain

Insufficient perioperative pain control may increase the risk of chronic pain development and may have deleterious effects on quality of life and function (Chou et al., 2016; Kehlet et al., 2006). The American Pain Society (APS) guidelines on the management of postoperative pain provide a strong recommendation for the utilization of a multimodal analgesic approach with nonopioid agents to prevent excess opioid exposure and dependence (Chou et al., 2016). Additionally, opioid use may contribute to the development of tolerance and hyperalgesia (Lee et al., 2011). Ketamine may be a viable option as a component of multimodal analgesia particularly in opioid-tolerant patients and those who may have difficulty tolerating opioids, such as the elderly (Chou et al., 2016).

Ketamine has been investigated for perioperative pain control in numerous surgical procedures, including abdominal surgery, thoracotomy, hip and knee joint replacement, and lumbar fusion (Brinck et al., 2018). Systematic reviews investigating the addition of ketamine to perioperative pain regimens have demonstrated significant reductions in pain intensity, opioid requirements, and postoperative nausea and vomiting, with minimal adverse effects (Assouline et al., 2016; Bell et al., 2005; Brinck et al., 2018). Optimal dosing of ketamine for perioperative pain has not been established due to the significant variability in dosing observed. A Cochran systematic review evaluating the use of ketamine for perioperative pain reported the majority of included studies utilized a bolus dose 0.25 mg/kg or less, although some studies used bolus dosing that exceeded 1 mg/kg (Brinck et al., 2018). The maintenance infusion rate of ketamine used was 2–5 μg/kg/min for most studies, but ranged from 0.7 to 167 μg/kg/min. The APS suggests administering a 0.5-mg/kg bolus dose preoperatively, followed by an infusion of 10 μg/kg/min intraoperatively that may or may not be continued postoperatively at a lower dose (Chou et al., 2016). Alternatively, consensus guidelines from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists suggest a maximum bolus dose of 0.35 mg/kg followed by a continuous infusion with a maximum rate of 1 mg/kg/hr (Schwenk et al. 2018). Future research should assess dose responsiveness in patients receiving ketamine for perioperative pain.

Critically Ill

Critically ill patients frequently experience pain and discomfort secondary to various procedures performed in the intensive care unit (ICU) such as arterial line placement, mechanical ventilation, tracheal suctioning, and patient mobilization (Devlin et al., 2018; Urner et al., 2018). Implementation of a protocol-based analgosedation program, defined as either analgesia-first sedation or use of analgesia in place of sedation, has demonstrated significant reductions in pain intensity, sedative requirements, duration of mechanical ventilation, and ICU length of stay (Devlin et al., 2018).

Ketamine has been used as an adjunct to opioid-containing regimens for pain control in critically ill patients in order to decrease opioid consumption (Buchheit et al., 2019; Guillou et al., 2003). A retrospective study of

93 surgical ICU patients reported a significant decrease in morphine consumption in patients receiving morphine patient-controlled analgesia combined with placebo or ketamine (Guillou et al., 2003). Differences in pain scores were similar and few adverse effects were noted in each group. The investigators utilized a bolus of 0.5 mg/kg followed by a continuous infusion of 2 μg/kg/min during the first 24 hours, and 1 μg/kg/min for the following 24 hours. Another retrospective cohort of 40 mechanically ventilated patients evaluated the impact of low-dose ketamine (1–5 μg/kg/min) on morphine equivalents (ME) (Buchheit et al., 2019). The median dose of ketamine administered was 5 μg/kg/min, and significant reductions in ME, propofol requirements, and phenylephrine equivalents were observed. There were no differences in sedation scores, and adverse effects such as hallucinations were absent. The Society of Critical Care Medicine provides a conditional recommendation for IV ketamine as an adjunct to opioids for pain management in postsurgical, critically ill patients (Devlin et al., 2018). The suggested dosing in this patient population is 0.5 mg/kg given as bolus followed by 1–2 μg/kg/min infusion.

Adverse Effect and Safety Concerns

Ketamine has adverse effects that are considered both dose dependent and non-dose dependent. When ketamine is given at higher doses (>1 mg/kg), it can cause a dissociative state, where patients are unable to speak or verbally respond, but often have their eyes open. After ketamine administration, patients can experience an emergence phenomenon, where patients can experience nightmares, hallucinations, extreme fear, or excitement (Rosenbaum et al., 2020). Pretreating with benzodiazepines can reduce the risk of ketamine-induced emergence phenomenon (Perumal et al., 2015). Caution should be exercised when using ketamine in individuals with preexisting psychiatric history, such as schizophrenia (Gales & Maxwell, 2018).

Ketamine overall causes minimal respiratory depression, but at higher doses and rapid IV administration ketamine may cause laryngospasm. Ketamine is generally avoided in younger children, especially younger than 3 months, due to concerns for respiratory depression (Dolansky et al., 2008).

Ketamine can mount a sympathetic response, which releases norepinephrine, dopamine, and serotonin. This response often causes hypertension and tachycardia. Ketamine can also worsen left ventricular function in patients with heart failure (Rosenbaum et al., 2020). Because of this, ketamine is generally avoided in patients with significant cardiovascular history. Also due to this sympathetic response, ketamine may increase intracranial pressure, but more recent data have shown that ketamine may be used safely in patients with traumatic brain injury (Zeiler et al., 2014).

Ketamine can also cause less severe reactions such as pain at the injection site, erythema and nausea and vomiting. In addition, after prolonged use, ketamine can cause dependence and tolerance and patients may experience withdrawal symptoms if ketamine is stopped abruptly. Lastly, ketamine clearance may be reduced in individuals with hepatic dysfunction and elderly patients (Bell & Kalso, 2018).

Despite the aforementioned potential risks associated with ketamine, the American College of Emergency Physicians supports the use of low-dose ketamine either alone or as part of a multimodal approach for traumatic and nontraumatic pain. Emergency department providers should communicate with patients that ketamine may cause generally minor, transient effects. Ketamine use should be administered under the same policies and procedures as other analgesics, such as opioids (American College of Emergency Physicians, 2017). It should be noted that ketamine administration rights vary by state and some states only allow physicians to administer ketamine.

Conclusion

Ketamine is a multifaceted agent with complex pharmacodynamics and demonstrated efficacy and safety in several pain disorders. Its use in acute and perioperative pain may decrease pain magnitude and overall opioid consumption. Individuals suffering from chronic pain and cancer pain who are highly opioid-tolerant may benefit from adjunctive ketamine administration. Ketamine may also be particularly valuable when used as analgosedation in critically ill patients and to help maintain respiratory drive in patients attempting to wean from mechanical ventilation.

The psychiatric and respiratory adverse effects of ketamine may be mitigated with use of lower doses and slower administration. Ketamine induces a sympathetic response and maintains the hemodynamic profile, but this effect may be detrimental in patients with extensive cardiovascular disease. Concerns regarding the side effects of ketamine may contribute to a negative stigma and hesitation in therapeutic use. However, ketamine has proven to be a versatile analgesic tool, and side effects have been shown to be minimal with lower doses and appropriate administration. Future research should compare the efficacy and safety of various dosing protocols and against therapeutic alternatives.

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