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Sedation/Delirium

Ketamine for analgosedation in critically ill patients☆,☆☆,★

Brian L. Erstad, PharmD, MCCM, Asad E. Patanwala, PharmD *

Department of Pharmacy Practice & Science, College of Pharmacy, University of Arizona, 1295 N Martin Ave, PO Box 210202, Tucson, AZ, USA

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ABSTRACT

Purpose: The purpose of this narrative review is to provide practical and useful guidance for clinicians considering the use of intravenous ketamine for its analgosedative properties in adult, critically ill patients.
Methods: MEDLINE was searched from inception until January 2016. Articles related to the pharmacological properties of ketamine were retrieved. Information pertaining to pharmacology, pharmacokinetics, dosing regimens, adverse effects, and outcomes was obtained from relevant studies.
Results: Although the primary mechanism for ketamine's pharmacological effects is *N*-methyl-D-aspartate blockade, there are several potential mechanisms of action. It has a very large volume of distribution due to its lipophilicity, which can lead to drug accumulation with sustained infusions. Ketamine has several advantages compared with conventional sedatives such as preserving pharyngeal and laryngeal protective reflexes, lowering airway resistance, increasing lung compliance, and being less likely to produce respiratory depression. It causes sympathetic stimulation, which is also unlike other sedatives and analgesics. There are psychotomimetic effects, which are a concern in terms of delirium. Dosing and monitoring recommendations are provided.
Conclusions: Ketamine has a unique pharmacological profile compared with more traditional agents such as opioids, which makes it an appealing alternative agent for analgosedation in the intensive care unit setting.

1. Introduction

Ketamine was synthesized in 1962 and was first tested in a clinical trial in 1964 [1]. Although ketamine was initially used in clinical practice as a dissociative anesthetic agent, it soon became used to provide analgesia for a wide variety of painful conditions. The large number of studies involving ketamine for pain control has led to several systematic reviews of its use in noncritically ill patients such as those with chronic pain after surgery, complex regional pain syndrome, phantom limb pain, and postoperative pain and as an adjuvant analgesic to opioids [2–7]. Although opioids are the prototypical medications used for analgosedation, they have adverse effects that often limit their use in critically ill patients. This has led clinicians to seek alternative analgosedative therapies such as ketamine. Given the unique mechanism of action of ketamine with its analgesic and sedative properties in low doses and anesthetic properties in high doses, there are surprisingly few randomized studies evaluating its use in the intensive care unit (ICU) setting.

The lack of evidence pertaining to ketamine is illustrated by the paucity of discussion of ketamine for pain management in the most recent clinical practice guidelines concerning the management of pain, agitation, and delirium in adult patients in ICU settings. In the guidelines, ketamine is only briefly mentioned as a nonopioid option for nonneuropathic pain, citing the lack of comparative outcome studies with other agents [8]. To date, only 1 systematic review has evaluated the efficacy of sustained infusions of ketamine restricted to an ICU population [9]. As authors of this review, we found few trials comparing ketamine to nonketamine analgosedation regimens [9]. The definition of *analgosedation* in the systematic review was the preference for medications that relieve pain and discomfort before instituting therapy with sedative agents that do not have analgesic activity.

Despite the lack of high-level evidence supporting the use of ketamine for analgosedation in critically ill patients, it continues to be used in the ICU setting, raising questions about appropriate patient selection, dosing, and monitoring. In our previous systematic review, we identified the major trials pertaining to the sustained use of ketamine, but we were unable to provide a more in-depth discussion about the pharmacological and pharmacokinetic properties of ketamine [9]. This narrative review complements our previous article by providing this information as well as elaborating on the evidence. The final section provides recommendations for the dosing and monitoring of intravenous (IV) ketamine for analgosedation in the ICU setting with particular emphasis on its use for critically ill patients with severe pain. Much of the information in this article is presented in the form of tables instead of text to facilitate potential incorporation into local protocols or guidelines. Therefore, the purpose of this narrative review is to provide

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* Corresponding author at: 1295 N Martin, PO Box 210202, Tucson, AZ, 85721, US. Tel.: +1 520 626 5404; fax: +1 520 626 7355.
E-mail address: patanwala@pharmacy.arizona.edu (A.E. Patanwala).

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practical and useful guidance for clinicians considering the use of IV ketamine for its analgosedative properties in adult, critically ill patients.

We performed a detailed literature search as described in our previous systematic review, but briefly, MEDLINE was searched from inception until January 2016, and articles related to the pharmacological properties of ketamine were retrieved [9]. Information pertaining to pharmacology, pharmacokinetics, dosing regimens, adverse effects, and outcomes was obtained from relevant studies. Relevancy from an outcomes perspective was considered on the basis of ketamine use for analgosedation in critically ill patients. However, recently published reviews and clinical studies were used to compile the sections pertaining to pharmacology and adverse effects given the relative dearth of ketamine investigations performed in the ICU setting.

2. Pharmacokinetics and pharmacology

As with many other medications, there is substantial interpatient variability with regard to the volume of distribution and clearance parameters of ketamine (Table 1) [10–12]. Furthermore, the variability of these parameters is markedly increased in critically ill compared with noncritically ill subjects. Ketamine has a very large volume of distribution due to its lipophilicity. This raises concerns about accumulation of ketamine in lipophilic tissues with potential redistribution and prolonged clinical effects with sustained dosing, particularly in patients with more severe forms of obesity. Less than 50% of ketamine in human plasma is bound to either albumin or alpha-1-acid glycoprotein, so clinically important protein binding displacement interactions are unlikely [13]. Ketamine is available in the United States as a racemic mixture, whereas the *S*-enantiomer that is a more potent analgesic than either the racemic mixture or the *R*-enantiomer is available as an injectable product in other countries. Ketamine is metabolized by the P450 system primarily to norketamine, an active metabolite with approximately one third the potency of the parent compound, but the specific microsomal enzymes, sites of metabolism, and potential drug-enzyme and drug-drug interactions have yet to be fully elucidated.

Although the primary mechanism for ketamine's pharmacological effects is *N*-methyl-D-aspartate (NMDA) blockade, other potential mechanisms of action depending on factors such as drug dose and concentration include opioid receptor blockade, gamma aminobutyric acid inhibition, and central nervous system (CNS) and peripheral autonomic neurotransmitter alterations (Fig. 1) [14,15]. Although concentration-related analgesic and anesthetic actions have been documented, the capability of therapeutic drug monitoring is unlikely to be available outside of research settings.

3. Potential adverse effects

The unique properties of ketamine, particularly with respect to its adverse effect profile, make it an appealing alternative compared with conventional analgesic options used for analgosedation. For example, ketamine does not appear to have the potential adverse effects of the nonsteroidal anti-inflammatory drugs (NSAIDS) on the gastrointestinal tract (bleeding) and kidneys (acute kidney injury). In contrast to opioids, ketamine does not have the negative effects of the opioids on the mu receptors of the gastrointestinal tract associated with ileus. Furthermore, ketamine preserves pharyngeal and laryngeal protective reflexes, lowers airway resistance, increases lung compliance, and is less likely to produce respiratory depression (assuming large doses are not rapidly administered). The beneficial actions of ketamine on pulmonary mechanics have led to research on its use as an alternative to standard therapies for more severe forms of asthma such as mechanically ventilated patients with status asthmaticus [16]. By increasing pulmonary airway pressures, there is a theoretical concern that ketamine could aggravate pulmonary hypertension, so it should be used cautiously in patients with this condition. In summary, in contrast to other analgesic agents such as opioids, ketamine is unlikely to produce serious adverse effects on gastrointestinal or pulmonary function in the majority of critically ill patients, which makes it an appealing alternative to conventional therapies.

Table 1
Pharmacokinetics and pharmacology of IV ketamine

- Linear pharmacokinetics but larger variability in critically ill patients
- Alpha half-life ≈5-17 min; beta half-life ≈ 180 min (healthy volunteers, surgery) to 300 min (critically ill patients); volume of distribution (beta phase) ≈ 5 L/kg in healthy volunteers undergoing surgery vs 16 L/kg in critically ill patients
  - o Clinical implications: immediate onset of action; peak effect of analgesia (and elevation in blood pressure) < 5 min; duration of analgesia <5 min if dose is ≤0.125 mg/kg (10-20 min if higher)
- Protein binding ≈47% (greater affinity for alpha-1-acid glycoprotein than albumin)
  - o Clinical implications: protein binding interactions unlikely
- Clearance by cytochrome P450 mediated via *N*-demethylation and hydroxylation of parent compound to norketamine (1/3 as potent as ketamine) and dehydronorketamine (analgesic effect unclear); ≈19 mL/(min kg) in surgical patients vs ≈36 mL/(min kg) in critically ill patients
  - o Clinical implications: potential for accumulation of parent drug and/or active metabolites with prolonged administration in patients with severe hepatic or renal dysfunction; potential for increased metabolism by P450 inducers (eg, rifampin) and decreased metabolism by P450 inhibitors (eg, benzodiazepines)
- Blood concentrations for analgesia: 100-150 ng/mL (>600 ng/mL for anesthesia)
- Pharmacological actions
  - o Opioid receptor blockade: delta, kappa, and mu receptor blockade but analgesia not reversed by naloxone
  - o CNS anticholinergic: psychic and sedative effects
  - o GABA inhibition: involved in anesthesia but not analgesia
  - o NMDA block: important for many pharmacological properties including antinociceptive effect and psychosis
  - o Hyperadrenergic state: increased release and decreased neuronal uptake of norepinephrine, dopamine, and serotonin (potential for interactions with drugs affecting these mediators)

GABA indicates gamma-aminobutyric acid.

With respect to the CNS, ketamine has both excitation and depression properties compared with the more general CNS depressive properties of opioids. In the early years of its use, this led to concerns that ketamine might have proconvulsant as well as anticonvulsant activity, and there were case reports in subjects of what appeared to be epileptic seizures [17]. However, follow-up investigations that included subjects with documented histories of focal or generalized seizures failed to confirm this seizure concern and noted that ketamine suppressed or eliminated electroencephalogram discharges in patients having seizures, suggesting a predominant anticonvulsant effect [18,19]. A variety of explanations were offered for seizure-like activity noted in the early case reports including inadequate monitoring, inappropriate conclusions about electroencephalogram recordings and CNS excitation, concomitant trigger events, and misinterpretation of skeletal muscle tonic-clonic activity sometimes seen with ketamine as seizures. More recently, the focus has been on the use of ketamine for treatment of refractory status epilepticus [20], although it is still relegated as more of a last-line medication in published guidelines because of the lack of high-level evidence supporting this purported indication [21]. Taken as a whole, the available evidence suggests that ketamine need not be avoided in patients at risk for seizures (eg, traumatic brain injury), particularly when used for analgosedation for short periods in the ICU setting.

Ketamine has well-known psychotomimetic effects that have been well elucidated in settings such as the emergency department when used for procedural sedation. Up to 30% of adults may have “emergence reactions” that manifest as hallucinations and psychosis occurring during recovery [22]. There is no clear relationship between ketamine dose and psychotomimetic effects, although gradual dose titration was shown in one retrospective study to decrease psychotomimetic adverse events in patients with cancer [23]. Lower doses (<1 mg/kg by slow infusion) and plasma concentrations (<100 ng/mL) have been associated with schizophrenia-like and dissociative symptoms in healthy volunteers [24,25]. In the critically ill, this is concerning because these