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

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 analgesic 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...
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 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 asthmatics [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.

With respect to the CNS, ketamine has both excitation and depressant 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 skew 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

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Pharmacokinetics and pharmacology of IV ketamine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Linear pharmacokinetics but larger variability in critically ill patients</td>
</tr>
<tr>
<td></td>
<td>• Alpha half-life ( \approx 5-17 ) min; beta half-life ( \approx 180 ) min (healthy volunteers, surgery) to ( \approx 300 ) min (critically ill patients); volume of distribution (beta phase) ( \approx 5 ) L/kg in healthy volunteers undergoing surgery vs ( 16 ) L/kg in critically ill patients</td>
</tr>
<tr>
<td></td>
<td>o Clinical implications: immediate onset of action; peak effect of analgesia (and elevation in blood pressure) (&lt; 5 ) min; duration of analgesia (&lt; 5 ) min if dose is ( \leq 0.125 ) mg/kg (10-20 min if higher)</td>
</tr>
<tr>
<td></td>
<td>• Protein binding ( \approx 47% ) (greater affinity for alpha-1-acid glycoprotein than albumin)</td>
</tr>
<tr>
<td></td>
<td>o Clinical implications: protein binding interactions unlikely</td>
</tr>
<tr>
<td></td>
<td>• Clearance by cytochrome P450 mediated via N-demethylation and hydroxylation of parent compound to norketamine (1/3 as potent as ketamine) and dehydroxynorketamine (analogical effect unclear); ( \approx 19 ) mL/(min kg) in surgical patients vs ( \approx 36 ) mL/(min kg) in critically ill patients</td>
</tr>
<tr>
<td></td>
<td>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)</td>
</tr>
<tr>
<td></td>
<td>• Blood concentrations for analgesia: 100-150 ng/mL (( &gt;600 ) ng/mL for anesthesia)</td>
</tr>
<tr>
<td></td>
<td>• Pharmacological actions</td>
</tr>
<tr>
<td></td>
<td>o Opioid receptor blockade: delta, kappa, and mu receptor blockade but analgesia not reversed by naloxone</td>
</tr>
<tr>
<td></td>
<td>o CNS anticholinergic: psychic and sedative effects</td>
</tr>
<tr>
<td></td>
<td>o GABA inhibition: involved in anesthesia but not analgesia</td>
</tr>
<tr>
<td></td>
<td>o NMDA blockade: important for many pharmacological properties including antinociceptive effect and psychosis</td>
</tr>
<tr>
<td></td>
<td>o Hyperadrenaline state: increased release and decreased neuronal uptake of norepinephrine, dopamine, and serotonin (potential for interactions with drugs affecting these mediators)</td>
</tr>
</tbody>
</table>

GABA indicates gamma-aminobutyric acid.
properties may predispose patients to delirium, which is associated with poor outcomes [26]. For example, in a recent systematic review of critically ill patients with or without delirium, patients with delirium were more likely to die (risk ratio, 2.19; 95% confidence interval [CI], 1.78-2.70; *P* < .001) and had longer durations of ICU and hospital lengths of stay (standard mean difference, 1.38; 95% CI, 0.99-1.77; *P* < .001 and standard mean difference, 0.97; 95% CI, 0.61-1.33; *P* < .001, respectively) [27]. Anecdotally, benzodiazepines, which themselves are often avoided in the critically ill because of their association with delirium, have been shown to blunt this reaction [22]. In addition, benzodiazepines interact with ketamine via the P450 pathway, extending the duration of effect of ketamine. This could result in drug accumulation and prolonged recovery. In general, it is best to avoid ketamine administration in patients with a history of psychosis or other conditions such as drug withdrawal (eg, alcohol, amphetamines) that may cause or mimic psychotic reactions. When ketamine is used for analgesia, we suggest gradual dose titration with careful monitoring for psychotomimetic effects.

The effect of ketamine on the cardiovascular system is particularly noteworthy because it differs greatly in this regard to other commonly used sedatives (eg, propofol, midazolam). Ketamine is sympathomimetic and facilitates adrenergic transmission, which in animal and isolated heart muscle studies offsets its direct myocardial depressant actions. It also increases the systemic catecholamine concentrations by inhibiting reuptake. This is expected to result in an increased heart rate and blood pressure, which is opposite of other sedatives. This can be advantageous in patients with hypotension who require analgesia. Even though this effect is seen in healthy adults, it is uncertain if this would occur in patients with prolonged critical illness who are catecholamine depleted. For instance, in one study, a subset of critically ill patients had reduced blood pressure and cardiovascular performance with ketamine [28]. Although concerns have been raised about potential detrimental increases in intracranial pressure associated with ketamine, a recent systematic review found no evidence of increased intracranial pressure or associated adverse neurologic outcomes associated with ketamine administration in critically ill patients [29]. Although ketamine appears to be safe in titrated doses for analgesia in most critically ill patients with cardiovascular instability, it is best avoided in patients with a history of ischemic cardiac disease, patients with cardiovascular conditions such as hypertensive crisis or heart failure that may be aggravated by ischemic injury, and patients with structural impediments to blood or cerebrospinal fluid flow such as hydrocephalus that may be aggravated by increases in pressure.

4. Studies of ketamine in the ICU setting

There have been 6 randomized studies of at least 24 hours’ duration comparing ketamine to nonketamine alternatives (Supplementary Table 1 in the online version at http://dx.doi.org/10.1016/j.jcrc.2016.05.016 [30–35]). With the exception of the 93 patients in the study by Guillou et al that demonstrated morphine-sparing effects of ketamine [31], there were no more than 30 evaluable patients in each of the remaining studies that focused on end points such as gastrointestinal function, or cerebrovascular or cardiovascular hemodynamic indices. Taken as a whole with the caveat of the small sample sizes, the studies suggest no substantial adverse effects of ketamine on cerebrovascular indices even in patients with severe head injuries. When small elevations (eg, 1–2 mm Hg) in intracranial pressure were found, usually in association with large doses of ketamine, concomitant elevations in cerebral perfusion pressure typically occurred. The systemic hemodynamic changes associated with ketamine administration are unlikely to be consequential in most patients but have the potential to be beneficial (eg, reduced doses of vasopressors in patients with hypotension) or harmful (eg, aggravation of preexisting heart failure or myocardial ischemia) depending on ketamine doses and specific patient characteristics. Other data from nonrandomized evaluations of ketamine in critically ill patients are consistent with these conclusions, albeit with other potential adverse effect considerations such as psychotomimetic disturbances [36–41]. Of note, many of the important advantages and disadvantages of ketamine administration use in the clinical setting, including its ability to produce dissociative anesthesia (ie loss of sensation and contact with environment while eyes remain open and protective laryngeal and ocular reflexes remain intact), had been identified in the anesthesia literature by 1968 [42].

5. Dosing and monitoring IV ketamine for analgesia in critically ill patients

Table 2 provides recommendations for the dosing and monitoring of IV ketamine in critically ill patients with severe pain states unresponsive to conventional therapies, whereas Table 3 provides a list of the more common and problematic adverse effects of ketamine broken down by rate- and non–rate-related reactions. The dosing recommendations focus on patients with more severe pain states based on the assumption that more conventional pharmacological (eg, opioids, NSAIDS) and nonpharmacological options are preferred as first-line interventions for patients with less severe pain. The justification for unresponsiveness to conventional regimens is based on clinician discretion but is likely due to maximum doses of analgesics such as NSAIDS or clinically important adverse effects related to analgesics such as NSAIDS and opioids.

The dosing recommendations listed in Table 2 require some explanation. A wide variety of ketamine dosing regimens have been used in published studies, particularly in older studies conducted at a time when mechanically ventilated patients received continuous sedation often without interruption and often with doses capable of inducing anesthesia [43]. Examples include the studies of patients with traumatic brain injury where daily doses of ketamine were sometimes in the hundreds of milligrams. The dosing recommendations provided in this article are of a more conservative nature in an attempt to avoid dose-related reactions such as psychotomimetic episodes that could lead to complex differential diagnoses in critically ill patients who are prone to delirium and other CNS disturbances. A prolonged infusion of ketamine may lead to drug accumulation and a longer recovery process, similar to other commonly used lipophilic analgesics and sedatives.
Thus, we recommend that the use of sustained ketamine infusions should only be done while using daily awakening trials. One option is to use a 1-time 4-hour infusion as described in Table 2. This has been used in a variety of cancer and noncancer pain states, with pain relief sometimes lasting for several days. Bolus doses may be needed during acute agitation. We have listed a bolus dose range of 0.2 to 0.5 mg/kg but recommend that clinicians should start on the lower end of the range because in one study in health volunteers, all patients became temporarily unconscious at the high end of the range [44]. However, this may not be the case in patients in severe acute pain in the ICU. Also, a loss of consciousness may be desirable in some situations in the critically ill. If sedation is required before a procedure, then even higher doses such 1 mg/kg will likely be needed. Note that some state nursing statutes preclude IV push injections of medications considered to be anesthetics such as ketamine. Some institutions have such restrictions based on dose used. Thus, the decision to use bolus dosing of ketamine into analgosedation regimens needs to consider the need for physician presence at the bedside and institution-specific policies.

Ketamine is compatible with morphine, fentanyl, or hydromorphone, and investigators primarily in non-ICU settings have evaluated such combinations as continuous infusions or by patient-controlled analgesia [45,46]. We recommend avoiding fixed combinations because it reduces flexibility in dosing. However, ketamine infusions can be Y-sited with these other opioids if required as part of a multimodal regimen when IV access is limited in the critically ill.

### 6. Summary

Ketamine is increasingly being used for analgosedation in critically ill patients because of its unique pharmacological profile compared with more traditional agents such as opioids that are used for analgosedation. Unfortunately, there is a lack of high-level evidence from studies performed in the ICU setting upon which to base decisions to use, dose, and monitor ketamine. This article summarizes the pharmacology and evidence for use of ketamine in the ICU. It also provides suggestions for dosing and monitoring IV ketamine when used for analgosedation in critically ill patients.

Supplemental data to this article can be found online at http://dx.doi.org/10.1016/j.jcrc.2016.05.016.

### Table 2

Dosing and monitoring IV ketamine for analgosedation in critically ill patients

<table>
<thead>
<tr>
<th>Use</th>
<th>Precautions, warnings, contraindications</th>
<th>Dosing</th>
<th>Monitoring</th>
</tr>
</thead>
</table>
| Severe pain unresponsive to conventional therapies (not an FDA-approved indication; ketamine is a schedule III medication in the US) | Contraindications: hypersensitivity, acute intermittent porphyria, acute myocardial infarction or decompensated heart failure, acute psychosis | IV infusion dosing (concentration 1 mg/mL; stable in normal saline or 5% dextrose):  
Option 1:  
• Ketamine 0.6 mg/kg given as a 1-time 4-h IV infusion (~2.5 μg/[kg min])  
Option 2:  
• Ketamine 0.2-0.5 mg/kg IV bolus given over at least 1 min followed by continuous infusion started at 1 μg/[kg min] (0.06 mg/[kg h])  
• If inadequate pain control, bolus doses may be increased up to a maximum of 0.5 mg/kg, and the infusion may be increased in 1-μg/[kg min] increments every 15 min up to a maximum dose of 20 μg/[kg min] (1.2 μg/[kg h]) or until adverse effects occur | Pain, sedation, and delirium scores to assess for efficacy and adverse effects  
Of particular concern are:  
• Persistent unrelieved pain (eg, score ≥4 on 0-10 numeric rating scale)  
• Hemodynamic instability (eg, SBP < 90 or >160 mm Hg, HR < 60 or >120)  
• Respiratory depression (rate < 12 or oxygen saturation < 92%)  
• Excessive sedation (particular concern when ketamine is combined with other sedatives)  
• Psychotic or psychotomimetic episodes including delusions, dysphoria, hallucinations, impaired or disorganized thinking, vivid dreams or nightmares  
• Tonic/clonic movements  
• With prolonged administration (eg, weeks), alldynia and hyperalgesia have been reported with abrupt discontinuation of ketamine  
BIS monitoring is not useful because ketamine administration does not change and may even increase the index |

The dosing regimens were derived primarily from studies involving the use of ketamine for postoperative pain control and the limited number of studies conducted in the ICU setting; note that much higher doses of ketamine were administered in some of the studies of critically ill patients with neurotrauma who received ketamine for analgosedation with combined clinical and hemodynamic endpoints. SBP indicates systolic blood pressure; HR, heart rate; BIS, bispectral index.

### Table 3

Adverse effects related to IV ketamine administration

<table>
<thead>
<tr>
<th>Rate-related adverse effects</th>
<th>Other adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Larger IV doses infused over ~60 s increase the risk of respiratory depression, high blood pressure, and tachycardia</td>
<td>Emergence and psychotomimetic reactions</td>
</tr>
</tbody>
</table>
| Emesis (does not appear to be dose related)  
Sympathomimetic effects of most concern for aggravation of preexisting conditions such as hypertensive crisis and symptomatic coronary disease  
Hypotension, bradycardia, and enhanced skeletal muscle tone (muscle movement or clonus), but uncommon with low doses  
Potential for increases in intracranial and intraocular pressure (usually not clinically important)  
Neurological and urinary toxicity concerns with more prolonged dosing  
For use during pregnancy, animal data suggest low risk but data in humans in limited; case report data suggest that abuse during the last trimester may be responsible for growth retardation and hypoplasia  
To avoid venous irritation, dilute to a maximum concentration of 5 mg/mL with 5% dextrose or normal saline |