Safely Prescribing Ketamine for Pain: A Guide for Palliative Care Clinicians

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INTRODUCTION

Physical pain is a common health problem that considerably undermines the quality of life of those in the hospice and palliative care population.[1] Although opioids can provide effective pain control in many cases, they may not completely relieve pain for all patients.[2,3] Subsequently, these patients require the addition of one or more adjuncts to their pain regimen.[3-5] The use of ketamine as an adjunct for moderate to severe pain has gained interest, in part because ketamine improves pain refractory to standard therapy and has an opioid-sparing effect.[6]

Although ketamine is prescribed for pain at 1/10th to 1/100th anesthetic doses, concerns exist regarding its dose-related adverse effects.[7] At the lower doses used for pain, side effects are dose-dependent and include dissociative feelings ("spaced out"), nausea, sedation, delirium, and hallucinations and are reported more frequently with intravenous administration. There is increasing concern about the potential for neuropsychiatric, urinary, and hepatobiliary toxicity with long term exposure.[8] Additionally, federal, state and local level regulations and policies can make it more difficult to prescribe and use ketamine for the management of pain. These regulations coupled with ketamine's dose-related adverse effects and clinicians' general inexperience with the use of ketamine for pain management can create challenges to safely using ketamine for pain management.[9]

This article provides a general review of ketamine and guidance to healthcare practitioners for making decisions and overcoming challenges to safely use ketamine in their own practice.

ROLE OF NMDA RECEPTOR BLOCKERS IN PAIN

Pain syndromes can be challenging and are often associated with a reduction in opioid-responsiveness. Some patients may require high doses of opioids to manage pain that are often associated with adverse effects without achieving adequate analgesia. Reduction in opioid-responsiveness arises from cross-talk between opioid receptors and the N-methyl-D-aspartate (NMDA) receptor-channel in the central nervous system (CNS). Opioid receptor activation by opioids results in opening of the NMDA receptor channel leading to a cascade of events that ultimately down-regulates the opioid receptor and its effects, thereby contributing to opioid tolerance, allodynia, hyperalgesia or other neuropathic pain syndromes.[10] Activation of the NMDA receptor also plays a role in progressive changes in neuronal excitability in central sensitization and the reduction of opioid analgesia.[12-14]

Medications with NMDA receptor antagonist activity include ketamine, methadone, memantine (Namenda®), amantadine (Symmetrel®) and dextromethorphan (Delsym®, Nuedexta® (in combination with quinidine)). Ketamine has higher affinity for the NMDA receptor than other agents making them weaker NMDA receptor blockers in comparison.[11] This means less potential to block the sensitization process and, as a result, appear to be less effective for neuropathic pain than ketamine.[15,16] In addition, other NMDA blockers, such as methadone, may not be the most appropriate choice for all patients due to the potential for significant drug-drug interactions.[17] These factors coupled with growing evidence that ketamine can be effective for a variety of types of pain, especially difficult-to-treat pain, led to the renewed interest in ketamine.

DETERMINING APPROPRIATE CANDIDATES

Ketamine can be effective and generally well tolerated for patients with difficult-to-treat central pain, painful peripheral neuropathy, postherpetic neuropathy, orofacial pain, fibromyalgia pain, stump or phantom limb pain, and cancer-related neuropathic or bone pain.[18-21] The evidence base regarding the use of ketamine, however, is primarily anecdotal evidence consisting of case reports, case series and small uncontrolled trials. In these reports, though, ketamine is most commonly used in conjunction with an existing opioid regimen. Conversely, Hardly J, et al conducted a randomized, double-blind controlled trial that showed “burst dosing” of subcutaneous ketamine provided no greater benefit than placebo in providing pain relief with an increased risk of adverse effects in patients with refractory chronic cancer-related pain.[22] Additionally, a Cochrane review concluded that insufficient data exists to assess the benefits and harms of ketamine as an adjunct to opioids for pain relief.[23] Given the overall weak evidence base coupled with the propensity for adverse effects, ketamine may be best reserved as a third- or fourth-line choice for the management of neuropathic or chronic pain syndromes that are poorly responsive to titrated opioids and other traditional oral adjuvant analgesics (e.g., gabapentin, pregablin, antidepressants).

SAFE PRESCRIBING PRACTICES

Prescribing ketamine safely considers patient-specific factors along with the contraindications, pharmacokinetics, dosing, available dosing formulations, adverse effects, monitoring parameters and federal, state or local regulations or policies regarding ketamine.

Contraindications and Precautions [24-29]

- Contraindicated for patients where a significant elevation of blood pressure would constitute a serious hazard (e.g., uncontrolled hypertension, stroke, head trauma, heart failure, cardiac disease).
- Exercise caution when prescribing for patients with a history of psychiatric disorders, recent delirium, or substance abuse due to increased risk of precipitation of psychosis and potential for abuse.

Pharmacokinetics and Drug Interactions [26,29-32]

Absorption	Distribution	Metabolism	Elimination
Water-soluble, lipophilic Onset of Action: • IV: 15-30 seconds • IM: 5 minutes • SC: 15-20 minutes • PO: 15-20 minutes	Widely distributed into highly perfused tissues first (e.g., heart, lung, brain) Low protein binding Duration of Action: • IV: 10-15 minutes • IM: 0.5-2 hours • PO: 4-6 hours	Ketamine is metabolized by the Cytochrome P450 (CYP 450) system in the liver, specifically by these enzymes: • 3A4 (major) • 2C9 (minor) Metabolites: • Norketamine • Hydroxy-norketamine Bioavailability: • IM: 93% • PO: 20%	Metabolites are primarily excreted: • Renally (90%) • Fecally (5%) • < 5% unchanged in the urine Half-life is ~ 2-3 hours

- Azole antifungals, such as fluconazole (Diflucan®), inhibit certain CYP 450 enzymes and may increase ketamine serum concentrations, while inducers of enzymes, such as carbamazepine (Tegretol®), may decrease ketamine concentrations. These combinations should be used with caution.
- Ketamine can potentiate CNS or respiratory depression when prescribed with other CNS depressants (e.g., opioids, sedatives).
- Concomitant use of low doses of benzodiazepines or haloperidol to prevent the psychomimetic effects of ketamine is usually well tolerated.

Routes of Administration

- Although several routes of administration and dosing strategies have been studied for ketamine, no one route of administration or regimen has been shown to be superior to another.[24-28,32] Therefore, the use of ketamine remains highly individualized to the patient and regimens are often based on prescriber's experience or pre-determined policies or protocols. Table 1 offers general dosing guidelines which are extrapolated from the literature.[18,24-26,29]
- Ketamine is usually administered orally, subcutaneously or intravenously for the management of pain. Other less common routes of administration include the rectal, intranasal and topical route.[25]
- Limited evidence suggests that ketamine is effective and well tolerated when compounded into a gel alone or in combination with amitriptyline and applied topically for localized peripheral neuropathy.[29,33,34] The amount of the application does not have to cover the entire area of pain, only to the most painful area of intact skin. Usually an effective dose is 0.4mg/kg/dose of ketamine applied three times a day.
- Limited evidence suggests that when converting from oral (PO) to intravenous (IV) or subcutaneous (SC) and vice versa, a reasonable conversion ratio is 1:1.[29] However, after continued use of ketamine administered IV or SC (i.e., weeks to months), a smaller PO daily dose (25-50% of IV/SC) may continue to provide pain relief, due in part to the increase in the presence of the norketamine metabolite after oral administration.[26]

Dose-Related Considerations

- The effect of ketamine can persist for several days to weeks to months after analgesia is achieved, even with short-term use (i.e., a few days to a few weeks).[18,26] Long-term use of ketamine is associated with persistent memory and cognitive dysfunction and may be associated with urinary toxicity. Therefore, once analgesia is achieved consideration should be given to stopping ketamine.
- Although no specific data is available to guide dosing in patients with renal or liver impairment or in the frail, elderly, given ketamine's pharmacokinetics and the fact that NMDA receptor binding is decreased with age, it may be prudent to reduce the dose initially in these patients (e.g., 25-50%).[28]
- Although some clinicians routinely reduce the opioid dose by 25-50% when starting ketamine,[23] downward adjustment of concomitant opioid regimen should be considered if sedation occurs with onset or increasing ketamine doses.[29] Further, reduction of opioid dose should be attempted as pain relief is achieved with ketamine.[24]
- Although abrupt discontinuation after the short-term use of ketamine does not usually result in withdrawal phenomena, gradual discontinuation is preferred for patients after long-term use (> 2-3 weeks of continued use).[26] Whole body hyperalgesia and allodynia have been reported after sudden cessation of ketamine after 3 weeks of use. No specific recommendations are available regarding titration but decreasing the dose over a minimum period of one week would be a reasonable strategy.

Table 1

"Burst" Parenteral	Continuous Parenteral	Enteral
Consider loading dose*	Consider loading dose*	Consider loading dose*
Initial: 0.6mg/kg administered over 4 to 24 hours, up to 60mg IV or 100mg SC	*Initial*: 0.01mg/kg/hour to 0.1mg/kg/hour IV/SC	*Initial:* 10mg to 25mg PO TID or 0.5mg/kg HS initially
Titrate: Consider increasing by 30% with each subsequent infusion until pain relief or dose-limiting adverse effects occur. Burst dosage may be repeated daily for 5 days.	*Titrate:* Consider increasing by 30% every 12 hours until pain relief or dose-limiting adverse effects occur. Maximum reported dose in the literature is 3.6grams/24 hours IV/SC.	*Titrate:* Consider increasing by 10mg to 25mg every 24 hours until pain relief or dose-limiting adverse effects occur. Maximum reported dose in the literature is 200mg PO QID.

*Although not required for initiation of ketamine therapy, a test dose of 0.25mg/kg to 0.5mg/kg IV/SC administered over 30 minutes or 20mg PO may help predict analgesic response and potential adverse effects.[29]

Dosage Forms

- Ketamine is available as a solution for injection which is often administered orally or parenterally. It is commercially available in concentrations of 50mg/ml and 100mg/ml.
- When administered orally, ketamine solution for injection can be very bitter; therefore, diluting the dose just prior to administration with juice (preferably grape juice) or requesting a pharmacy to compound an oral solution (most common concentration is 20mg/ml) can facilitate administration.[29,30]
- When administered parenterally, ketamine can be diluted into 0.9% sodium chloride (normal saline) to a concentration of 1mg/ml and is compatible with haloperidol, fentanyl, morphine, and midazolam. There is no data on compatibility with lorazepam and therefore co-administration should be avoided.[26,29]

Adverse Effects [6,26,28-31]

- The adverse effects of ketamine are primarily dose-related, predominantly occurring with doses above 1mg/kg. Adverse effects are more likely to occur with the use of ketamine IV or SC and less likely when used PO. The common adverse effects of ketamine include those which are psychomimetic, cardiovascular or gastrointestinal in nature. The less common adverse effects of ketamine include urinary tract toxicity and increased skeletal muscle tone.
    - The psychomimetic effects of ketamine are often the most bothersome and include: Vivid dreams, hallucinations or floating sensations, visual spatial disorders, blunted affect, emotional withdrawal, thought disorders, sedation and delirium. To prevent these effects, either lorazepam or haloperidol should be prescribed initially around the clock for 24 to 48 hours and then continued an as needed basis.
    - Effects on the cardiovascular system include elevated blood pressure and heart rate and an increase in stroke volume.
    - Effects on the gastrointestinal system include increased salivation and nausea and vomiting. Co-administration of an anticholinergic such as glycopyrrolate or atropine on an as needed basis can be helpful.
    - Less frequently, ketamine is associated with urinary tract symptoms such as frequency, urge, and dysuria and complications such as interstitial nephritis, detrusor overactivity and renal failure. In patients who already have underlying urinary disorders or who are at risk, “burst dosing” of ketamine may minimize exposure. If patients experience urinary symptoms without evidence of an infection, ketamine should be discontinued, and the patient referred to a urologist.
    - Tonic/clonic movements, which can resemble seizures and are believed to result from enhanced skeletal muscle tone, have occurred with ketamine.

Monitoring[27,30,35]

- The following monitoring parameters should be obtained at baseline and observed regularly with the initiation and dose titration of ketamine:
    - Vital signs (e.g., blood pressure, heart rate, respiratory rate)
    - Presence of adverse effects such as psychomimetic effects (e.g., agitation, insomnia, fear, hallucinations), nausea/vomiting, excessive secretions, profound sedation or change in level of consciousness.
    - Pain assessment
- Specifically, patients should be monitored 15 minutes (IV/SC) or 60 minutes (PO) after initial administration or dose titration. Continuous monitoring should occur every 1-2 hours for the first 24 hours and then daily as the dose and patient remain stable. If the patient is stable after the first 8 hours of monitoring, less frequent (e.g., 2-4 hours) and/or less intensive monitoring may be appropriate based on the patents therapeutic response and presence of adverse effects. Although some prescribers have experience with using ketamine PO in an outpatient setting, given the intense monitoring consideration should be given to prescribing ketamine initially while in a closely monitored setting such as an inpatient unit (IPU).

REGULATORY CHALLENGES

Ketamine is a Class III controlled substance. As such, prescribers of a Class III controlled substance must be registered with the Drug Enforcement Agency (DEA) and licensed to prescribe controlled substances by the state(s) in which they practice. Further, the prescribing information for ketamine states that ketamine “should be administered by or under the direction of physicians experienced in the administration of general anesthetics, maintenance of a patent airway, and oxygenation and ventilation. Continuously monitor vital signs in patients receiving...”[36]

State regulations may also extend to the administration of ketamine. Some states provide specific guidelines for different levels of nurses (e.g., RN, LPN), whereas other states only advise it is within the scope of practice for nurses under certain conditions in a palliative care setting. Lastly, local facilities (e.g., hospitals) may not have policies that are

conducive to the use of ketamine for pain management.[9] Consequently, it is crucial that those who prescribe and administer ketamine be familiar with these federal, state, and local regulations or policies. Most importantly, in the interest of patient safety and to address the challenges and potential barriers that these regulations or policies may present, hospices and palliative care organizations should have their own policies guiding the safe prescribing and administration of ketamine for pain management.

SUMMARY

Ketamine is an NMDA-receptor antagonist that can be effective for the management of difficult-to-treat pain. However, due to the weak evidence base and its propensity to cause serious adverse effects, ketamine may be best reserved as a third- or fourth-line choice for the management of neuropathic or chronic pain syndromes that have not responded well to opioids or other adjuvant therapies. Prescribing ketamine safely should always consider patient-specific factors along with related contraindications, pharmacokinetics, dosing, adverse effects, monitoring parameters and federal, state or local regulations or policies.

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