Ketamine for the Management of Treatment Refractory Pain in Veterans Overseen by VHA Hospice or Palliative Care Teams*

National Protocol Guidance

August 2024

VA Pharmacy Benefits Management Services, the VHA National Formulary Committee, and the VHA National Office of Hospice and Palliative Care

Purpose: To establish protocol guidance for the administration of parenteral or oral ketamine for the management of treatment refractory pain for non-sedation purposes in VHA Hospice or Palliative Care under the care or direction of a palliative care team.* This document has been reviewed by office of Patient Care Services and National Anesthesia Program office and there is no restriction in Directive 1073 Appendix E VHA Directive 1073(1) - Moderate Sedation by non-Anesthesia Providers DEC 2022 to the provision of intravenous infusion or SQ/IM administration of ketamine for palliative care purposes.

***NOTE: "Palliative Care Team" member can also include a locally identified expert**

Disclaimer: To be consistent with the purpose of this general guidance and not to be overly proscriptive, this guidance allows facilities the flexibility to exercise modifications to protocols as necessary to operationalize the use of ketamine for treating pain in the hospice or palliative care setting.

There is not an established guideline for dosing, duration, or route for ketamine in this setting. The information provided in this guidance document is based on literature review and expert consensus. Treatment with ketamine in this population must be individualized and under the guidance of providers with experience in palliative and hospice medicine.

Background

When clinically indicated, ketamine may be recommended for pain control when conventional modes of treatment have failed or when ketamine is determined to be a more suitable agent. Due to its unique pharmacological properties, sub-anesthetic ketamine doses do not produce many of the potentially adverse respiratory or hemodynamic effects of other analgesics and may be used as a safe and effective alternative or adjunct to opioids.

This guidance does not apply to the use of ketamine for the primary purpose of sedation or when used for the purposes of securing an endotracheal airway (e.g. rapid sequence intubation) or when used in the care of mechanically ventilated patients.

Ketamine is a noncompetitive inhibitor of the N-methyl-D-aspartate (NMDA) receptor. Ketamine reduces hyperalgesia and opioid tolerance and provides analgesia by blocking N-methyl- D-aspartate (NMDA) receptors to reduce glutamate release and by binding to sigma-opioid receptors. Ketamine has been studied in patients with pain who are opioid tolerant as an adjunct to opioid therapy in a hospice/palliative setting.

Departments Affected

Pharmacy, Nursing, Palliative Care/Hospice, and General Medicine providers

Pharmacokinetics

a. Onset – IV: within 30 seconds; SQ: onset variable (approximately 15 minutes); oral within 30 minutes
b. Duration – 4-12 hour (PO); 20-45 min (IV, IM, SQ); Duration of analgesia may be prolonged (e.g. 1-2weeks) after repeated or continuous administration.
c. Half-life – ketamine 2 to 3 hours; norketamine approximately 6 hours
NOTE -- ketamine has multiple active metabolites (e.g. norketamine, dehydronorketamine, hydroxynorketamine) the pharmacokinetics of which are not well established, especially when dosed continuously or serially, except that active metabolite concentrations are several-fold higher, due to first pass effect, when ketamine is administered orally.

Indication

a. Pain (nociceptive, neuropathic) refractory to first line therapies or where first line therapies are contraindicated, and care is being provided in an inpatient or a Community Living Center (CLC) and care is directed by or in consultation with the Hospice or Palliative care team (or locally identified expert).

Contraindications

a. Hypersensitivity to ketamine or any excipient

Precautions

a. Active psychosis, delirium, or inability to report side effects
b. Patients for whom significant elevations in blood pressure would constitute a serious hazard
c. Patients with or at risk of increased intracranial pressure
d. Unstable cardiovascular disease
e. Consider lower dosing for older patients or patients with comorbidities to mitigate adverse effects

Continuous Infusion

a. Initial dose -- 0.1 to 0.2mg/kg/hr Ideal Body Weight (IBW): may be administered via continuous intravenous or subcutaneous infusion
    - Titrate no sooner than 12-hour interval; Max titration 0.1mg/kg/hr
b. Recommended MAXIMUM DOSE should not exceed 0.5mg/kg/hr of Ideal Body Weight (IBW)
c. Duration of Treatment – Ranges from 1 to 5 days in case reports and clinical trials. Consider titrate to effect (or max tolerated dose) and continue for additional 48 hours, then discontinue.
NOTE: Consistent with VHA Directive 1073 for infusions lasting longer than 5 days or greater than 0.5mg/kg/hr IBW consider consult Anesthesia if adjustments to the care plan are necessary
d. IV Compatibility: Dextrose 5% in water (D5W), Normal Saline (NS) or Sterile Water.
e. MONITORING – Recommend check vital signs*, pain, affect, and psychomimetic adverse effects at baseline, at 1 hour after infusion starts, at 4 hours and then with each shift change. Repeat initial monitoring process after each dose change.
*If vital signs assessment is not c/w patient goals, palliative care team may adjust monitoring as needed

Intravenous piggyback (IVPB) infusion or subcutaneous (SQ) bolus

a. Initial dose: 0.1 to 0.3mg/kg
    - IVPB – administer over 30 minutes
    - SQ – onset of analgesia is more variable than with IV administration, but side effects are typically reduced vs. IV administration

b. Additional doses: If an additional dose is indicated, options include:
    - Repeat dose as per above if effective or convert to alternate means of administration (e.g. oral or continuous infusion)
    - Frequency of intermittent administration varies in medical literature reports. Not to exceed q8hr dosing
    - May increase dose not to exceed 0.5mg/kg with,
    - MAXIMUM total daily dose not to exceed 1mg/kg of ideal Body Weight (IBW)

c. MONITORING – Recommend check vital signs*, pain, affect, and psychomimetic adverse effects at baseline, at 1 hour after infusion starts or subcutaneous administration, then with each shift change. Repeat initial monitoring process after each dose change.
*If vital signs assessment is not c/w patient goals, palliative care team may adjust monitoring as needed

NOTE: there are case reports of using intermittent ketamine via intramuscular (IM) administration for pain in hospice/palliative setting but repeated IM not preferred if other routes available

Oral Administration of Ketamine *NOTE – ketamine is only manufactured in solution for intravenous use. See Clinical Pearls section below*

a. Test dose / Initial dose: 10mg PO once, then 5-10mg PO q8hours based on response
    - Initial titration -- 5 to 10mg per dose, per 24 hours

b. MAXIMUM dose: 400mg PER DAY (e.g. 100mg q6h)

c. Parenteral to oral conversions – Calculate total 24 hour administered dose and replace at 2/3rds of the intravenous/subcutaneous dose (e.g. ketamine 100mg/day IV = 66mg oral total daily dose)
    - *NOTE – Ketamine taken orally undergoes significant first pass metabolism with an active metabolite, norketamine, achieving plasma levels 2-3 times higher than with parenteral administration of ketamine*.

d. MONITORING – Recommend check vital signs*, pain, affect, and psychomimetic adverse effects at baseline, and 1 hour after first dose or any dose increase.
*If vital signs assessment is not c/w patient goals, palliative care team may adjust monitoring as needed

Adverse Effects (at Sub-Dissociative Doses)

a. Common – dizziness, sedation, sense of unreality, nausea
    i. *NOTE: Adverse effects requiring additional management were generally mild or manageable in clinical trials reviewed. Dizziness and perceptual changes were attenuated with lower doses or routes of administration with slower peak effect.*

ii. Patients must be educated on this potential effect and prepare to report anything that is bothersome. Treatment does not necessarily need to be discontinued if patient is not bothered and feels safe.

b. Uncommon -- Increase in blood pressure
   i. Per Ketalar package insert, transient (e.g. 15 minutes) increases in heart rate and blood pressure, 10 to 50% above baseline, are common when used at anesthetic doses. Anecdotal reports when using at lower doses administered over a slower time period for pain have not found increase HR/BP to be common. If blood pressure and heart rate are being monitored as part of the Hospice/Palliative care plan, then
   ii. Recommend to alert provider if Systolic blood pressure change > 20 mmHg or Heart rate change < or > 20 beats/minute
c. Rare – excess sedation, respiratory compromise
   i. Recommend to alert provider if respiratory rate < 12 breaths/minute or persistent episodes of shallow breathing or apnea, oxygen saturation <90% or RASS score -2 or below

Clinical Pearls

a. Depending on the clinical scenario, consider decreasing opioids by 15-50% at initiation of ketamine due to opioid sparing effect with antagonism of NMDA receptor; may need to continue to taper if excessive respiratory depression or hemodynamic instability occur.
b. Withdrawal symptoms are not common when stopping ketamine however, hyperalgesia and allodynia have been reported after abrupt discontinuation of ketamine after 3 weeks of use. If receiving for more than 10 days, patients can be safely tapered off of ketamine over 48-72 hours Monitor for withdrawal signs including nausea, dizziness, diarrhea, depression, anxiety, and schizophrenic-type behaviors.
c. Addition of a benzodiazepine or haloperidol for psychomimetic side effects (most of the drug literature used lorazepam) and decrease ketamine dose to previously tolerated dose if psychomimetic side effects develop
d. Patients may have increased secretions, lacrimation and salivation which can be managed with the use of an anticholinergic agent such as glycopyrrolate, atropine ophthalmic drops, or scopolamine patch
e. Consider using actual body weight if less than Ideal Body Weight to calculate dose
f. In Palliative Care patients, where the primary goal of care is comfort, the provider may authorize changes in monitoring
g. For oral administration, the IV formulation of ketamine may be drawn up directly from the vial, but as ketamine is very bitter, it is recommended to administer in combination with a sweet liquid (e.g. fruit juice, cola)

Additional Information

a. Mucositis – focus of this guidance document is on systemically administered ketamine for

pain in a Hospice or Palliative episode of care. This guidance document does not address use of topical-oral ketamine for mucositis. Refer to Ryan, et al 2009 for additional information.

b. This document does not address oral use of ketamine on an outpatient basis. Individual cases can be adjudicated locally

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