Ketamine Dosing for Refractory Pain Control (End of Life)

Policy Number: _ _-_ _ _

NHPCO Standard(s):

Regulatory Citation / Other:

POLICY STATEMENT: Ketamine is a final-line adjuvant pain treatment to be used after poor responsiveness to escalating opioid and other adjunct analgesic therapies in terminal patients with refractory nociceptive and neuropathic pain. Usage will be determined upon consultation with physician and patient/power of attorney before administration.

BACKGROUND: Ketamine was granted FDA approval in 1970 for the use of anesthesia induction and maintenance, and is a Schedule III controlled substance.[4,9] Ketamine induces catalepsy, catatonia, analgesia, and amnesia and generally can be more known as a "dissociative anesthetic".[1] Most importantly with respect to this protocol, increasing literature within the past two decades has shown arguable support for as an adjunctive analgesic therapy in refractory nociceptive and neuropathic pain, which can be particularly beneficial in a hospice and palliative care setting.[4,10]

Ketamine's primary mechanism acts as a noncompetitive antagonist at the phencyclidine binding site of *N*-methyl-*D*-aspartate (NMDA) receptors residing in the central nervous system (CNS). Yet, ketamine also acts on a multitude of other non-NMDA pathways that play integral roles in pain and mood regulation, including antagonistic effects on nicotinic and muscarinic cholinergic receptors, the blockade of sodium and potassium channels, activation of high-affinity D_2 dopamine receptors and L-type voltage-gated calcium channels, facilitation of $GABA_A$ signaling, and the enhancement of descending modulatory pathways. For these reasons, ketamine may provide relief with patients experiencing hyperalgesia by increasing responsiveness to opioids and consequently reduce total opioid dosages (i.e. opioid-sparing).[4] While ketamine has affinity for the opioid receptors at high doses (mu > kappa > sigma), it is 10,000 times weaker than that of morphine. Therefore, naloxone does not have any effect against ketamine.[2]

Regarding its high lipid solubility and low protein binding properties, ketamine can be administered successfully with extensive distribution in the body and rapid crossing of the blood-brain barrier. Administration can be done by intravenous (IV), intramuscular (IM), subcutaneous (SQ), transdermal (TD), oral (PO), rectal (PR), and intranasal routes (IN), as well as via the neuroaxial routes (intrathecal; IT).[2]

This policy/protocol will detail parameters and criteria for optimal use of ketamine and reduce possible risks when treating patients' refractory nociceptive and/or neuropathic pain.

INDICATION(S):

Treat opioid refractory nociceptive and neuropathic pain.

**Other extended uses have been studied and may be considered upon additional evaluation[2,5,8,9]:

- Pain related to central sensitization[12]:
  - Headaches
  - Allodynia
  - Neuropathic pain
  - Complex regional pain syndrome
  - Fibromyalgia
  - Postherpetic neuralgia
  - Sickle cell disease
  - Ischemic pain
- Depression[4]
- Pediatric population

SIDE EFFECTS:

General side effects[4] –

- Increased heart rate
- Increased systolic and diastolic blood pressure
- Salivary and tracheobronchial secretions
- Bronchodilation

Dose-related psychomimetic effects occur in about 40% if administered by IV, but less with PO: catalepsy, euphoria, dysphasia, blunted affect, psychomotor retardation, vivid dreams, nightmares, impaired attention, memory and judgment, illusions, hallucinations, altered body image.[9]

Ketamine has been shown to enhance epileptic discharges, which may explain the rare occurrence of seizures. However, growing evidence has also shown ketamine as a treatment for refractory seizures.[4]

If a patient experiences dissociative or hallucination effects, these effects may be prevented or aborted with concurrent use of low-dose benzodiazepines (such as lorazepam 1 mg PO or diazepam 5 mg PO) [Number-needed-to-harm (NNH) for hallucinations without benzodiazepines: 21; NNH for hallucinations with benzodiazepines: 35] or α2 agonist (such as clonidine).[4]

Past studies showed antipsychotics were a prophylactic option along with benzodiazepines[7,8]; however, it has been disapproved by recent guidelines likely due to its risks related to the class's black box warning and its side effects.[4]

PHARMACOKINETICS[4]:

Route of Administration	Bioavailability, %	Time of Onset	Duration of Action After Dosing
Intravenous (IV)	N/A	30 s	5-10 min for bolus doses
Intramuscular (IM)	75-95	2-5 min	30-75 min
Intranasal (IN)	25-50	5-10 min	45-120 min
Subcutaneous (SQ)	75-95	10-30 min	45-120 min
Oral (PO)	10-20	5-20 min	2-4 h
Rectal (PR)	25-30	5-15 min	2-3 h
Topical	< 5	< 2d	N/A

T ½: 2.3 ± 0.5 h (ketamine)[4], ~4-12 h (norketamine)[3,9] → Steady state ~1 day

- Metabolized by the liver and excreted by the kidney
- Extensive first pass when given orally from ketamine to norketamine.[8]
    - Norketamine is one-third as potent as ketamine as an anesthetic and equipotent as an analgesic[6]
    - Serum norketamine levels after oral ketamine are 2 to 3 times higher than after parenteral ketamine[6,9]
    - Peak analgesic effect of oral ketamine corresponds with peak serum level of norketamine, not ketamine[3,6]
- When switching from oral to parenteral ketamine and vice versa, a ratio of 1:1 is acceptable.[8]

ELIGIBILITY CRITERIA:

1. Pain score ≤ 7 (0 = no pain; 10 = most excruciating pain)
2. Pain has to be refractory from at least 3 analgesic/adjuvant regimens evaluated by hospice physician, or patient is susceptible to opioid toxicity or has strict intolerance.
3. Informed consent by patient or caregiver/power of attorney
4. Age ≥ 18

CONTRAINDICATIONS[4]:

Absolute –

- History of hypersensitivity or known allergy to ketamine
- Poorly controlled cardiovascular disease (e.g. hypertension, coronary artery disease)
- Individuals with poorly controlled psychosis
- Severe hepatic impairment (i.e. cirrhosis)
- Uncontrolled hyperthyroidism (due to possible potentiation of sympathomimetic effects)

Relative –

- Use lower dosages with extreme caution in patients with elevated intracranial and intraocular pressure

- Monitor closely in people with moderate hepatic impairment
- History of seizures
- Previous cerebrovascular accidents

**Ketamine is metabolized by the liver and excreted by the kidney, but prolonged effects on hepatic or renal functions have not been noted with subanesthetic doses. Therefore, contraindications for anesthetic doses of ketamine may be relative contraindications or precautions when using subanesthetic doses.[4]

FORMULATION/COST:

Ketamine is supplied as an oral or injection solutions from OnePoint pharmacy. As of 11/25/2019, an oral flavored, compounded solution for a quantity of 10 ml (50 mg/ml) is $13.99 and 30 ml is $36.98. For injections, it is only available from the manufacturer in a set of 20 vials of 20 ml (10 mg/ml) for about ~$200. Under outpatient setting, the pharmacy cannot draw the medication beforehand and therefore a nurse or caregiver must prepared and administer when needed. If intranasal is an applicable route, administering with nasal atomizers on syringes is a possible option.

DOSING/ADMINISTRATION:

<table>
<tr><th>Route</th><th>Dose</th><th>Comments</th></tr>
<tr><td rowspan="2">Oral[9]</td><td>10-25 mg TID-QID, or
0.5 mg/kg every 6 hours</td><td>• May titrate 5 mg per dose or 20 mg per day, up to 100 mg QID. Max reported dose 200 mg QID.
• Breakthrough pain: 1/10th to 1/6th of total daily scheduled as needed (not well-studied)</td></tr>
<tr><td colspan="2">**The range in effective dosages of orally administered ketamine varies extensively between patients. Variability in hepatic metabolism resulting in an increased or reduced bioavailability and variance in plasma levels of norketamine can lead to intra-individual variability.[3]

**At the end of the first week evaluate efficacy and adverse effects. Continue oral therapy for 1-3 months if effective and consider progressive withdrawal after that. The suggested maximum de-escalation is 15-20 mg every 3 days (5 mg for each intake).[14]</td></tr>
<tr><td>Intranasal[4]</td><td>1-5 sprays of 10 mg, or
25 mg spray every 6 hours</td><td>• For breakthrough pain</td></tr>
</table>

<table>
<tr><td rowspan="3">Intravenous[4,7]</td><td>Bolus: Up to 0.35 mg/kg then
Infusion: 0.1-0.5 mg/kg/hr

"Burst": Infuse at 0.1 mg/kg/hr then increase by 2 mg/kg/hr every 2 hours or until 20 mg/hr based on patient comfort and pain control</td><td rowspan="2">• The "burst technique" interrupts pain crisis by increasing infusion rate until patient is comfortable. Infusion can continue for approximately 24 hours followed by gradual dose reduction as tolerated. Ketamine infusion can be safely discontinued once it reaches less than 10 mg/hr.
○ Normally a 3-6 day process</td></tr>
<tr><td>Dilute to a concentration of 1 mg/ml with NS or D5W</td></tr>
<tr><td colspan="2">** For IV: When pain score is improved ≥ 30% , continue infusion of 0.1 – 0.5 mg/kg/day. After 24 hours, consider reducing dose to 10 mg/h. After 72 hours, consider converting 1:1 of total dose to oral three times daily.[4,8,13]</td></tr>
<tr><td colspan="3">• Consider an empiric opioid dose reduction of 25% if commencing with ketamine for pain. Unnecessary if pain is refractory unless sedation or pain scores decrease. If respiratory depression occurs with concomitant use of ketamine and opioids, reduce opioid dose as ketamine is unlikely to cause significant respiratory depression.[9]
• Although there is not a consistently defined subanesthetic dose range[10], the doses shown above should likely fall under subanesthetic.[4,10]</td></tr>
</table>

DRUG PRECAUTIONS:

Ketamine may decrease or reverse opioid tolerance which means possible risk of increased side effects from opioids such as sedation and respiratory depression. Therefore, proper opioid dose adjustment prior to ketamine administration is imperative unless patient has refractory pain. If dissociative effects are prominent, administering a low-dose benzodiazepine or clonidine may help subside or eliminate the effects.[4] Alternatively, decreasing ketamine is a possible option. **If ketamine is used with methadone, be alert for the possibility of opioid toxicity developing over several days as a consequence of the long and variable half-life of methadone.**[11]

To caution against risk of aspiration, avoid solids or liquids by mouth a few hours prior to administration.[10]

MONITORING[4,10]:

- Close monitoring of the patient is crucial. Monitor respiratory rate, oxygen saturation, heart rate, blood pressure, pain score (e.g. visual analogue scale, numeric rating scale), sedation score (e.g. Richmond agitation-sedation scale, Pacero opioid sedation scale), and any psychomimetic side effects.

Richmond Agitation-Sedation Scale (used for ICU only)

Points	Classification	Description		
4	Combative	Overtly combative, violent, immediate danger to staff (e.g. throwing items); +/- attempting to get out of bed or chair		Observe patient for 20 seconds
3	Very agitated	Pulls or removes lines (e.g. IV/SQ/Oxygen tubing) or catheter(s); aggressive, +/- attempting to get out of bed or chair		
2	Agitated	Frequent non-purposeful movement, +/- attempting to get out of bed or chair		
1	Restless	Anxious or apprehensive but movements not aggressive or vigorous		
0	Alert and calm			
-1	Drowsy	Not fully alert, but has sustained awakening (eye-opening/eye contact) to voice (10 seconds or longer)	Verbal Stimulation	
-2	Light sedation	Briefly (less than 10 seconds) awakens with eye contact to voice		
-3	Moderate sedation	Any movement (eye or body) or eye opening to voice (but no eye contact)		
-4	Deep sedation	No response to voice, but any movement (eye or body) or eye opening to stimulation by light touch	Gentle Physical Stimulation	
-5	Unarousable	No response to voice or physical stimulation		

Pacero Opioid Sedation Scale (POSS) – Outpatient

S = Sleep, easy to arouse	*Acceptable; no action necessary; may increase opioid dose if needed*
1 = Awake and alert	*Acceptable; no action necessary; may increase opioid dose if needed*
2 = Slightly drowsy, easily aroused	*Acceptable; no action necessary; may increase opioid dose if needed*
3 = Frequently drowsy, arousable, drifts off to sleep during conversation	*Unacceptable; monitor respiratory status and sedation level closely until sedation level is stable at<3 and respiratory status is satisfactory; decrease opioid dose 25%-50%† or notify primary‡ or anesthesia provider for orders; consider administering a nonsedating opioid-sparing nonopioid, such as acetaminophen or a nonsteroidal antiinflammatory drug, if not contraindicated; ask patient to take deep breaths every 15-30 minutes.*
4 = Somnolent, minimal or no response to verbal and physical stimulation	*Unacceptable; stop opioid; consider administering naloxone§; call Rapid Response Team (code blue); stay with patient, stimulate, and support respiration as indicated by patient status; notify primary‡ or anesthesia provider; monitor respiratory status and sedation level closely until sedation level is stable at <3 and respiratory status is satisfactory*

- A positive response should be measured by objective measures of benefit in addition to satisfaction such as ≥ 30% decrease in pain score.
- Prolonged use with higher doses and repeated exposures may affect the bladder and liver. Monitor for worsening symptoms of discomfort, abdominal pain, yellowing of skin, nausea or vomiting, or urinary symptoms such as stinging.
- General inpatient for IV route
    - Clinicians who are overseeing the administration of ketamine in acute pain settings should be trained in airway management and Advanced Cardiac Life Support (ACLS).
    - Administering clinicians should be either a registered nurse or physician assistant who has completed formal training in safe administration of moderate sedation.
    - Monitor:
        a) At baseline
        b) 60 minutes of initiation of infusion and then every 4 hours
    - Refer to respective taper schedule under "**DOSING/ADMINISTRATION**" if planning to discontinue.
- Outpatient for PO route
    - Monitor:
        a) At baseline
        b) _____
    - Refer to respective taper schedule under "**DOSING/ADMINISTRATION**" if planning to discontinue.

Respectfully submitted,

Dave Lindqvist, PharmD Candidate 2020

December 5, 2019

Reference

1. Absalom A., Menon D.K., Adapa R. (2014) Dissociative Anesthetics. In: Stolerman I., Price L. (eds) Encyclopedia of Psychopharmacology. Springer, Berlin, Heidelberg. https://link.springer.com/referenceworkentry/10.1007%2F978-3-642-36172-2_341
2. Alon Ben-Ari, Michael C. Lewis & Elyad Davidson (2007) Chronic Administration of Ketamine for Analgesia, Journal of Pain & Palliative Care Pharmacotherapy, 21:1, 7-14, DOI: 10.1080/J354v21n01_04
3. Blonk M, Koder B, Van den Bemt P, et al. Use of Oral Ketamine in Chronic Pain Management: A Review. *European Journal of Pain*. 2009 September; 14:466-472
4. Cohen SP, Bhatia A, Buvanendran A, Schwenk ES, Wasan A, Hurley R, et al. Consensus guidelines on the use of intravenous ketamine infusions for chronic pain from the American Society of Regional Anesthesia & Pain Medicine (ASRA), the American Academy of Pain Medicine (AAPM) and the American Society of Anesthesiologists (ASA). *Reg Anesth Pain Med.* 2018;43(5)521-546.
5. Fallon MT, Wilcock A, Kelly CA, et al. Oral Ketamine vs Placebo in Patients With Cancer-Related Neuropathic Pain: A Randomized Clinical Trial. *JAMA Oncol.* 2018;4(6):870–872. doi:https://doi.org/10.1001/jamaoncol.2018.0131
6. Fitzgibbon EJ, Hall P, Schroder C, Seely J, Viola R. Low dose ketamine as an analgesic adjuvant in difficult pain syndromes: A strategy for conversion from parenteral to oral ketamine. *J Pain Symptom Manage*. 2002;23:165–70
7. Loveday B A, Sindt J. Ketamine protocol for palliative care in cancer patients with refractory pain. *Journal of the Advanced Practice in Oncology*. 2015;6(6):555–561.
8. Prommer EE (2012) Ketamine for pain: an update of uses in palliative care. J Palliat Med 15:474–483. doi:10.1089/jpm.2011.0244
9. Quibell Rachel, Prommer Eric E, Mihalyo Mary, Twycross Robert, Wilcock Andrew. Ketamine*. *Journal of pain and symptom management*. 2011;41:640–649.
10. Schwenk ES, Viscusi ER, Buvanendran A, Hurley RW, Wasan AD, Narouze S, et al. Consensus guidelines on the use of intravenous ketamine infusions for acute pain management from the American Society of Regional Anesthesia and Pain Medicine (ASRA), the American Academy of Pain Medicine (AAPM) and the American Society of Anesthesiologists (ASA). *Reg Anesth Pain Med.* 2018;43(5):456-466
11. Specialist Guidelines for Using Ketamine. Wales (UK): All Gwent Palliative Medicine Consultants Group. 2013 Oct. Available from http://www.wales.nhs.uk/sites3/documents/814/ketaminespecialistguidelinesonuse.pdf
12. Woolf CJ Central sensitization: implications for the diagnosis and treatment of pain. Pain 152, S2–15 (2011).
13. Gorlin AW, Rosenfeld DM, Ramakrishna H. Intravenous sub-anesthetic ketamine for perioperative analgesia. *J Anaesthesiol Clin Pharmacol*. 2016;32:160–167.

14. Marchetti F, Coutaux A, Bellanger A, et al. Efficacy and Safety of Oral Ketamine for the Relief of Intractable Chronic Pain: A Retrospective Five Year Study of 51 Patients. *European Journal of Pain*. 2015; 19(2015);984-993.