

PALLIATIVE PEARLS

BY ENCLARA PHARMACIA

Ketamine for the Treatment of Refractory Pain June 2023

This month, we revisit a popular Palliative Pearls case study published in March 2018. A recent pharmacist review has confirmed that the information in this case study remains relevant and in alignment with best practices.

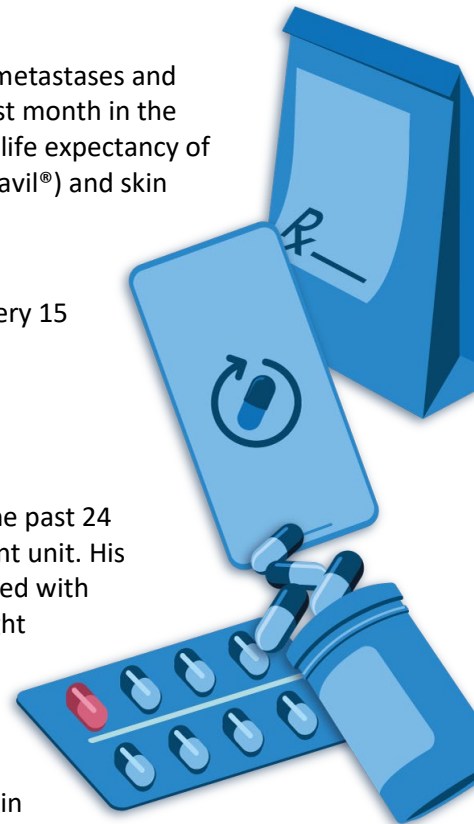
Patient Case

PL is a 57 year old male patient with Stage IV lung cancer with widespread bone metastases and comorbidities of HTN and depression. He has been enrolled in hospice for the past month in the long term care facility where he resides. His prognosis is poor, with an estimated life expectancy of 1-2 weeks. Allergies include GI upset with lisinopril (Zestril®) and amitriptyline (Elavil®) and skin rash with NSAIDs.

Current medications related to his pain management include:

- Hydromorphone at a continuous IV rate of 22mg/hour and 7mg bolus every 15 minutes PRN
- Dexamethasone 8mg po bid
- Duloxetine (Cymbalta®) 30mg po once daily

PL is currently rating his pain 9 out of 10 despite 20 hydromorphone boluses in the past 24 hours. To better manage his pain, he is being transferred to the hospice's inpatient unit. His history reveals mixed pain including a dull, achy pain primarily in his hips associated with movement and a sharp, shooting pain in his lower back that radiates down his right extremity. The dull, achy pain with movement is managed well with dexamethasone, however the sharp, shooting pain has been persistent. He has tried various opioid regimens including oral morphine, oral methadone and more recently, the high dose hydromorphone infusion. PL has also had trials of adjuvant neuropathic pain agents including gabapentin (Neurontin®), pregabalin (Lyrica®), and amitriptyline without significant relief. Considering patient's history of depression with no active management, he was recently switched to duloxetine, however, it is causing stomach irritation and only mild pain relief. Oral ketamine has been suggested by the unit medical director.



Role of NMDA Receptor Blockers

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.^{1,2}

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.³

Ketamine Overview:

Ketamine is a, “rapid-acting general anesthetic producing an anesthetic state characterized by profound analgesia, normal pharyngeal-laryngeal reflexes, normal or slightly enhanced skeletal muscle tone, cardiovascular and respiratory stimulation, and occasionally a transient and minimal respiratory depression”.³ Ketamine’s minimal effect on muscles makes it a preferred anesthetic for procedures that do not require skeletal muscle relaxation. Ketamine is a Class III controlled substance, therefore, prescribers must be registered with the DEA and licensed to prescribe controlled substances in the state of their practice.

Labeled indications:^{4,5}

- General anesthesia induction
- General anesthesia maintenance
- Anesthesia supplement for low-potency agents, such as nitrous oxide

Off-label uses:^{4,6,7,8}

- Acute bronchospasm
- Adjuvant to opioids in chronic cancer pain
- Depression
- Neuropathic pain refractory to traditional agents (opioids, NSAIDs, steroids)
- Procedural sedation
- Reduction of postoperative opioid requirements (a.k.a. opioid-sparing effects)
- Refractory pain not relieved by opioids
- Severe pain

Which patients may benefit the most from Ketamine?

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. The evidence base regarding the use of ketamine is primarily anecdotal consisting of case reports, case series and small uncontrolled trials. In these reports, ketamine is most commonly used in conjunction with an existing opioid regimen.

Routes of Administration:

Ketamine is administered intravenously as a weight-based dose for anesthesia, either intermittently at 1-4.5 mg/kg for brief anesthesia or via continuous infusion at a rate of 0.5 mg/kg/min. Much lower IV doses have been cited in the literature for pain management, especially when used in combination with an opioid.⁷ A single dose of ketamine 0.25 mg/kg or 0.5 mg/kg was effective for patients with cancer and neuropathic pain who were already taking morphine.⁴

For ambulatory patients experiencing chronic pain, the intravenous route may be impractical in addition to being invasive.⁸ Ketamine can also be administered orally or via less common routes including rectal administration for systemic pain and topically for local pain.⁹ The intranasal route has demonstrated efficacy in patients with acute pain in the emergency department, however due to small patient size and lack of larger randomized studies, its role in refractory pain needs to be investigated further.¹⁰

Dosing:

No specific route has been shown to be more effective than another for managing pain.¹ Due to the various dosing strategies, ketamine use should be individualized to the patient and based on prescriber experience or established protocols.

Suggested dosing for refractory pain:^{1,11}

Burst Parenteral (IV/Subcut)

- Initial: 0.6mg/kg administered over 4 to 24 hours, up to 60mg IV or 100mg subcut
- 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

Continuous Parenteral (IV/Subcut)

- Initial: 0.01 mg/kg/hr to 0.1 mg/kg/hr
- Dose may be titrated by 30% every 12 hours until pain relief or dose-limiting adverse effects occur
- Maximum reported dose in the literature is 3.6 grams (3600mg)/24 hours

Oral (compounded solution)

- Initial: 0.5mg/kg HS OR 10-25mg TID
- Dose may be titrated in steps of 10-25mg up to 100mg Q.I.D.
- Maximum reported dose in the literature is 200mg Q.I.D.

Duration Considerations:

Long term use of ketamine may be associated with tissue damage, cognitive defects such as memory loss, and urinary damage defined as irritation of the upper and lower urinary tract (symptoms of urinary frequency, urgency, urge incontinence, dysuria, hematuria and lower abdominal pain). It is recommended as a short term “burst” treatment (appropriate dosing over 2-4 days), as evidence suggests the analgesic effects of “burst” treatment can extend several weeks.^{1,9} In patients with a prognosis of more than a few weeks, an attempt should be made to withdraw ketamine over a 2-3-week period, once analgesia has been obtained.¹²

Drug Interactions:

Ketamine is metabolized by the CYP-450 enzyme system in the liver. Azole antifungals, such as fluconazole (Diflucan®), inhibit certain enzymes and may increase ketamine serum concentrations, while inducers, such as carbamazepine (Tegretol®), may decrease ketamine concentrations. These combinations should be used with caution.¹

Adverse effects, contraindications and precautions:

Ketamine may cause elevation in blood pressure so it is contraindicated for patients where blood pressure elevation may constitute a hazard. Such comorbidities include, but are not limited to the following:⁴

- Hypertension
- Stroke
- Head trauma or intracranial mass
- Intracranial bleeding
- Patients with increased intraocular pressure (i.e., glaucoma)

Caution should be used in patients with psychiatric disorders such as schizophrenia or psychosis as ketamine may cause psychosis or exacerbate symptoms. Ketamine is associated with abuse potential therefore caution should be used in patients with history of substance abuse.⁴

Due to ketamine’s strong affinity as an NMDA antagonist, it may have a higher propensity for greater severity and frequency of adverse effects especially compared to the other NMDA receptor antagonists. The most common adverse effects are primarily CNS-related:^{7,8}

- Anxiety
- Dissociative mental state
- Dizziness

- Hallucinations
- Insomnia
- Lightheadedness
- Paranoid ideations
- Vivid dreams or nightmares

Adverse effects of ketamine are more commonly observed with intravenous administration, likely due to lower plasma concentrations when given orally.^{2,7} Oral ketamine may also cause gastrointestinal adverse effects such as nausea, vomiting, loss of appetite and abdominal pain.⁸

Pharmacist Assessment:

Although ketamine has been shown to be effective in limited clinical trials, other pain management strategies should be exhausted before its consideration. Due to lack of data with clinical evidence and potential for adverse effects, ketamine should be reserved as third or fourth line therapy. There are few randomized controlled trials published and most studies have been based on anecdotal experience.⁷

For PL, whose pain is assessed as neuropathic and refractory to standard pain management strategies, ketamine may have a role in controlling his pain. PL's blood pressure is currently controlled without medication, however, ketamine has the potential to increase blood pressure so vital signs should be monitored closely. He should be frequently monitored in the IPU and titrated carefully based upon the information above.

Recommendations:

PL was initiated on oral ketamine compounded solution 100mg/mL at 0.25mL (25mg) PO T.I.D. His oral dexamethasone and IV hydromorphone infusion were continued as well as the duloxetine for depression. His pain management was monitored using a visual analog scale and non-verbal cues when he wasn't able to verbalize. His blood pressure increased slightly but blood pressure lowering medication was deemed unnecessary. Over the next 24 hours, he was titrated to 50mg PO T.I.D. where he achieved adequate pain relief. In the following 72 hours, his hydromorphone IV continuous rate was decreased by 25% to 16mg/hr and 5mg bolus every 15 min as needed. After the 4th day in the IPU, oral ketamine was tapered off. PL passed away peacefully and pain-free 24 hours later.

For additional information on this topic, please review these references:

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