

Use of Ketamine for Pain Management in Hospice Care

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Conflict of Interest and Disclosures of Relevant Financial Relationships

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Contact Hours - Nursing 1.0 Contact Hour



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Objectives

- ▶ Review ketamine's labeled and off label indications, mechanism of action, pharmacokinetics and pharmacology
- ▶ Identify contraindications for ketamine
- ▶ Explore pros and cons for using ketamine
- ▶ Understand formulations, routes of administration, dosing and cost
- ▶ Examine case studies involving refractory pain with increasing opioid doses.



History of Ketamine

- ▶ 1956 Phencyclidine (PCP) was synthesized
- ▶ 1962 Ketamine, a shorter acting analog of phencyclidine was synthesized
- ▶ 1964 The first human anesthetic dose of ketamine was administered ¹



History of Ketamine continued

- ▶ Late 70's widespread abuse began
- ▶ Current times used as "club drug" and at dance "rave" parties
- ▶ Current times used in "date rape" ²



Pop Quiz

- ▶ What are some "street names" for ketamine?

Pop Quiz

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Labeled and Off Label Indications for Ketamine

- ▶ Labeled Indication-
 - Anesthesia: Induction and maintenance of general anesthesia
- ▶ Off Label uses
 - Analgesia (using subanesthetic dosing)
 - Complex regional pain syndrome
 - Depressive episode associated with major depressive disorder (unipolar), treatment refractory
 - Procedural sedation/analgesia
 - Status epilepticus (refractory) ⁴

Types of pain

- ▶ Nociceptive- caused by tissue damage, burns, tumors, injury, inflammation
- ▶ Neuropathic- nerve injury or disease leading to abnormal nerve function. May be described as stabbing, electrical, burning or numbness.
- ▶ Often seen in neuropathic pain
 - ▶ Allodynia- pain provoked by a normally non-painful stimulus (light touch causing severe pain)
 - ▶ Hyperalgesia- exaggerated response to pain ⁵

PAIN

Ketamine Use in Hospice Patients

- ▶ Patient's pain doesn't fully respond to typical pain regimens even with increasing doses of opioids
- ▶ May be especially useful in neuropathic pain that does not respond fully to usual pain regimens.⁶ These may include opioids, NSAIDs, tricyclic antidepressants, anticonvulsants, duloxetine, pregabalin, venlafaxine
- ▶ Requires clinical manager approval
 - Not first line pain therapy
 - Can be complex to dose
 - A compound and an off label use

Potential Side Effects of Ketamine Psychotomimetic Effects

- ▶ Hallucinations
- ▶ Delusions
- ▶ Vivid dreams
- ▶ Dreamlike state
- ▶ Confusion
- ▶ Dissociative reactions ^{4, 6, 7}



Potential Side Effects of Ketamine Continued

- | | |
|----------------|--|
| ▶ Sedation | ▶ Increased cerebrospinal fluid pressure |
| ▶ Delirium | ▶ Increased intraocular pressure |
| ▶ Hypertension | ▶ Erythema/pain at injection site |
| ▶ Tachycardia | ▶ Sialorrhea |
| ▶ Diplopia | ▶ Nausea/vomiting ^{4, 6, 7} |
| ▶ Nystagmus | |

Contraindications for Ketamine Use in Hospice Patients

- ▶ Brain mets with uncontrolled swelling or uncontrolled headaches
- ▶ Uncontrolled seizures
- ▶ Uncontrolled psychosis
- ▶ Sepsis

- ▶ Relative contraindications-may not apply to hospice patients
 - ▶ Glaucoma
 - ▶ Open eye injury ⁶

Mechanism of Action

- ▶ Produces a cataleptic-like state in which the patient is dissociated from the surrounding environment by direct action on the cortex and limbic system.
- ▶ Ketamine is a noncompetitive NMDA receptor antagonist that blocks glutamate.
- ▶ Low (subanesthetic) doses produce analgesia, and modulate central sensitization, hyperalgesia and opioid tolerance.
- ▶ Reduces polysynaptic spinal reflexes ⁴



Routes of Administration

- ▶ Intravenous
- ▶ Subcutaneous
- ▶ Intramuscular
- ▶ Epidural
- ▶ Oral
- ▶ Nasal
- ▶ Rectal
- ▶ Topical



Ketamine Pharmacodynamics/Kinetics

(since the indication for analgesia, and some routes of administration are off label use, some information is not available)

Route of Administration	Onset of Action	Duration of Action	Time to Peak
Intravenous	30 seconds for anesthesia	5-10 minutes for anesthesia	Estimated less than 60 seconds
Intramuscular	10-15 minutes	15-30 minutes	5-30 minutes
Intranasal	10 minutes	Up to 60 minutes	10-14 minutes
Oral	30 minutes	Not available	About 30 minutes ⁴

Ketamine Pharmacodynamics/Kinetics Metabolism

- ▶ Hepatic metabolism to four metabolites
- ▶ Metabolite I, Norketamine is 33% as potent as the parent compound
- ▶ Orally administered ketamine results in norketamine concentrations that are higher compared to other routes of administration because of first-pass metabolism in the liver⁴
- ▶ Norketamine plays a significant role in the overall analgesic effect induced by ketamine⁸

Ketamine Scorecard

Advantages

- ▶ Non-opioid for pain
- ▶ No significant effect on pulmonary function
- ▶ Many routes of administration
- ▶ Cost effective

Disadvantages

- ▶ Psychotomimetic effects (less likely with oral than injection)
- ▶ Must be compounded for oral, SL, topical use
- ▶ Not much data on long term use⁶



Ketamine Formulations and Estimated Cost (based on AWP)

▶ Brand Name

Ketalar Injection Solution

10 mg/mL (per 20 mL vial):
\$23.80

50 mg/mL (per 10 mL vial): \$7

100 mg/mL (per 5 mL vial):
\$13



▶ Generic

Ketamine HCl Injection Solution

10 mg/mL (per 20 mL vial): \$20.60

50 mg/mL (per 10 mL vial): \$4.30 - \$9.80

100 mg/mL (per 5 mL vial): \$9.85 - \$11.50⁴

Ketamine Formulations and Estimated Cost Continued

▶ Intravenous/subcutaneous infusion

Cost for ketamine 15 day supply for a 68 kg patient- low dose \$50 PLUS pump, IV diluent, supplies, compounding fees (at maximum dose cost \$250 for the ketamine)

▶ Compounded Oral Solution

\$30-\$40 per 7 day supply

(there may be a wide range of cost depending on the pharmacy, their compounding fees and mark up)

Adult Dosing for Oral or SL Ketamine

- ▶ If patient is on an opioid, consider a dose reduction of 25-50% when starting ketamine and if able continue to reduce opioid by same percent that you increase the ketamine
- ▶ Usual starting dose 10-25 mg po q8h
- ▶ Titrate by 1/4 to 1/3 (25-33%) of total daily dose every 3-4 days
- ▶ Usual maximum dose 50 mg q6h, maximum recommended 2 mg/kg po tid
- ▶ Maximum reported doses 200 mg po q6hrs (800 mg/day) ⁶

Adult Dosing for IV/subcutaneous infusion of Ketamine

- ▶ If patient is on an opioid consider a dose reduction of 30-50%, if able continue to reduce opioid by same percent that you increase the ketamine
- ▶ Usual starting dose is 0.1 mg/kg/hr
- ▶ Various Dose Titrations
- ▶ Increase by 1-2 mg q2hrs for better pain management
- ▶ Increase rate by 20-30% q12-24 hrs ⁶

Adult Dosing for IV/subcutaneous infusion of Ketamine Continued

- ▶ Max rate based on weight 0.5 mg/kg/hr, higher doses may be anesthetic, only persons trained in anesthesia should exceed this dose
- ▶ Usual maximum doses are 20-25 mg/hr
- ▶ For parenteral ketamine the recommended setting is an IPU or skilled nursing facility
- ▶ Subcutaneous infusions may be started in the home if the physician/hospice team is comfortable doing this
- ▶ Subcutaneous Ketamine-if used alone, best diluted with sodium chloride 0.9% (irritant) ⁶

Preventing or Treating Possible Side Effects

- ▶ Psychotomimetic effects less likely with oral administration
Use haloperidol or benzodiazepines to prevent or treat psychotomimetic effects
Injectable haloperidol can be added to infusion
Consider oral haloperidol 2-5 mg at night, haloperidol 0.5-1 mg tid or diazepam 5 mg at night for psychotomimetic effects ^{6, 7}
- ▶ Possible increased salivation and bronchopulmonary secretions
Consider hyoscyamine or other anti-secretory drugs ⁴

Monitoring Ketamine

▶ Parenteral

- ▶ Pain-check every hour
- ▶ RR, BP, HR-check about every 2-4 hours
- ▶ Especially important if on high dose opioids
- ▶ Side effects

▶ Oral/SL

- ▶ Pain
- ▶ Side effects ⁶



Parenteral to Oral Conversion

- ▶ Conversion range is 1-3:1 IV:PO
- ▶ If patient only on parenteral ketamine for a few days use conversion range of 1:1.
- ▶ Give oral dose in three divided doses
- ▶ For the first 24 hours, continue parenteral ketamine at 50% or original rate ⁶

Parenteral to Oral Conversion Continued

- ▶ If possible reduce parenteral ketamine to 25% of original rate on day 2 before stopping
- ▶ Titrate oral dose by 10-25 mg/day q3-4 days or by 20-30% q3-4 days
- ▶ If patient experiences pain before next dose is due consider shortening the dosing interval ⁶

Case Study 1

- ▶ 39 yo male admitted to hospice with squamous cell carcinoma of the maxillary sinus
- ▶ PMH/Comorbid: COPD, T2DM, dyslipidemia, peg tube
- ▶ CC: pain 10/10, neuropathic pain to left side of his face and neck
- ▶ Medications: methadone 40 mg via peg tid, gabapentin 600 mg via peg q8h, dexamethasone 6 mg via peg bid, Dilaudid 12 mg via peg q2h prn pain
- ▶ Prn dilaudid 12 mg used 9 doses/24hrs

Case Study 2

- ▶ 65 yo female admitted to hospice with terminal diagnosis of MS
- ▶ PMH/Comorbid: neuropathic pain, bi-polar disorder, uncontrolled psychosis
- ▶ CC: pain, rating pain 12/10
- ▶ Medications: MS Contin 100 mg po q8h, Gabapentin 100 mg po at bedtime, lamotrigine 100 mg po daily, risperidal 3 mg po daily, haloperidol 1 mg po q4h prn agitation/hallucinations

Case Study 1 Review

- ▶ Starting dose ketamine range 10-25 mg via peg q8h, 20 mg via peg q8hr
- ▶ Decrease methadone by 25-50%, 30 mg via peg tid (25%)
- ▶ Increase ketamine by 1/4 to 1/3 of total daily dose q3-4 days, 25 mg via peg q8hr (1/4 or 25%)
- ▶ Decrease methadone by same percent (25%) ketamine is increased, 20 mg via peg tid (rounded down)
- ▶ Consider decreasing dilaudid prn dose, dilaudid 6 mg via peg q2h prn pain/sob
- ▶ Continue titration q3-4 days until pain is well controlled
- ▶ Consider Haldol or diazepam at bedtime for neuropsychiatric side effects

Case Study 2 Review

- ▶ Patient is not a candidate for ketamine

Pop Quiz Answers-What are some "street names" for ketamine? ³

- ▶ Audience participation



Pop Quiz Answers

- ▶ Vitamin K
- ▶ Special K
- ▶ K
- ▶ K2
- ▶ Super K
- ▶ Super C
- ▶ Lady K
- ▶ Ket
- ▶ Kit Kat
- ▶ Ketaset
- ▶ Ketaject
- ▶ Jet
- ▶ Super Acid
- ▶ Green
- ▶ Purple
- ▶ Mauve
- ▶ Special LA Coke
- ▶ Cat Tranquilizers
- ▶ Cat Valium



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