

## FAST FACTS AND CONCEPTS #132 KETAMINE USE IN PALLIATIVE CARE

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Ketamine is FDA approved as a rapid-acting IV dissociative general anesthetic. There has been increased interest in its off-label use for pain control, administered via various routes. This *Fast Fact* reviews the use of ketamine in palliative care primarily for analgesia.

**Mechanism of Action** The N-methyl-D-aspartate/glutamate receptor (NMDA) is a calcium channel closely involved in the development of central (dorsal horn) sensitization. This channel has a role in opioid-resistant pain, neuropathic pain, allodynia, and hyperalgesia. Ketamine enters and blocks the open channel at a phencyclidine site, thereby inhibiting the excitatory effects of glutamate and aspartate. Ketamine also interacts with nicotinic, muscarinic, and opioid receptors. Pre-clinical data suggests it may also have anti-inflammatory effects.

**Pharmacology** As an anesthetic, ketamine is given IV or IM. For pain, the parenteral solution can be delivered at much lower doses by oral, intranasal, transdermal, rectal, and subcutaneous routes. Onset of analgesia is 15-30 minutes; duration of action is 15 minutes to 2 hours, possibly longer orally. A greater portion of ketamine is metabolized to a breakdown product with less affinity for NMDA receptors (norketamine) when taken orally versus IV. It is not yet clear if this reduces the analgesic properties of oral ketamine in a clinically significant way. Ketamine is physically stable when mixed with morphine, low-dose dexamethasone, haloperidol, and metoclopramide. Drugs that interact with CYP3A4 may affect its metabolism (e.g. azole antifungals, macrolides, HIV protease inhibitors, and cyclosporine).

**Side Effects** Undesirable effects of high dose ketamine used for general anesthesia (1-2 mg/kg IV or 6.5-13 mg/kg IM) include psychotomimetic phenomena (dysphoria, blunted affect, psychomotor retardation, nightmares, hallucinations), excessive salivation, and tachycardia. Co-administration with either lorazepam or haloperidol is a common empiric practice to minimize the potential for psychotomimetic side effects. Side effects at the lower doses used for pain are dose dependent, with dissociative feelings (“spaced out”), nausea, sedation, delirium, and hallucinations reported more frequently with IV administration. There is increasing concern about the potential for neuropsychiatric, urinary, and hepatobiliary toxicity with long term exposure to ketamine. In particular, delusions, memory impairment, dysuria, and abnormal liver functional tests have been associated with therapeutic analgesic doses of just 2 weeks duration. Ketamine can enhance its own metabolism via hepatic induction. This likely contributes to the rapid and dangerous tolerance to desired euphoric feelings among abusers.

**Analgesic Effectiveness** There is an absence of large controlled trials supporting ketamine as an analgesic for cancer or neuropathic pain. While there is a large body of case reports, retrospective surveys, and uncontrolled trials suggesting that ketamine effectively relieves cancer and non-cancer pain from neuropathy, ischemia, bone metastasis, or mucositis, smaller controlled trials have had mixed results. If used as an analgesic, a short term, “burst” treatment (e.g. appropriate ketamine dosing given over 2-4 days) should be considered, as evidence suggests the analgesic effects of “burst” treatment can extend several weeks.

**Analgesic Effectiveness in Children** Literature on the pediatric use of ketamine as an analgesic is scarce. In a case series, 8 of 11 children with cancer pain had opioid sparing effects as well as subjective improvements in pain and alertness with an IV ketamine infusion dosed at 0.1 to 1 mg/kg/hour. No significant psychotropic side effects were noted, but all patients had lorazepam co-administered

### Other Potential Palliative Uses of Ketamine

- Single use of IV ketamine (typically 2.5 to 5 mg prn) often in combination with morphine or midazolam has been described for peri-operative use, dressing changes, and orthopedic emergencies.

- Topical ketamine as an oral rinse has been described to treat mucositis, and as a gel for neuropathy.
- Ketamine has antidepressant effects in depressed patients perhaps even within hours after one dose. However, its use for depression is experimental and should be restricted to controlled trials.

**Titration Schedule** There are no studies comparing various titration or dosing schedules, nor routes of administration. Usual initial analgesic oral dose in adults is 10-25 mg TID to QID with titration in steps of 10-25 mg. The maximum reported oral dose is 200 mg QID. A common initial IV dose in adults is 50-100 mg/day, with titration at increments of 25-50 mg/day, and a usual effective dose of 100-300 mg/day. Careful monitoring of blood pressure, heart rate, and psychotomimetic effects should occur. Drowsiness may ensue when patients are on background opioids. Consequently, some clinicians empirically reduce opioid doses by 25-50% when starting IV ketamine.

**Summary** The current collection of evidence is likely insufficient to fully assess the potential benefits versus harms of ketamine as an analgesic. A short course of low-dose ketamine (at sub-anesthetic doses) can be considered in the palliative care setting with the following notes of caution:

- Ketamine should be reserved for pain refractory to opioids and other standard analgesics due to its potential for neuropsychiatric, urinary tract, and hepatobiliary toxicity.
- If urinary symptoms occur in the absence of an infection, clinicians likely should stop the ketamine.
- Analgesic use should be limited to palliative care and/or pain specialists.
- In patients with a prognosis more than a few weeks, attempts to withdraw ketamine at least 2-3 weeks after initiation should be made in earnest.

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