

Ketamine

Low doses may provide relief for some painful conditions.

Ketamine (Ketalar) is a diverse IV anesthetic with dissociative, analgesic, sedative, and amnesic properties. Ketamine was synthesized in 1962 and approved in 1970 by the Food and Drug Administration (FDA) for human and veterinary use. When used as a sole anesthetic, ketamine allows the patient to remain awake and responsive. It also produces significant analgesia—a characteristic that differentiates it from other anesthetic induction agents. Ketamine's other favorable aspects include the fact that it rarely causes respiratory depression at low (subanesthetic) doses and doesn't depress cardiovascular function, hepatic blood flow, or bowel function.¹ The use of ketamine at low doses (such as less than 1 mg/kg IV) is now gaining in popularity as a treatment for some painful conditions.

PHARMACOLOGY OVERVIEW

Ketamine produces analgesia by binding to receptors in both the peripheral and central nervous systems, including opioid receptors, and most notably as an antagonist to the *N*-methyl *D*-aspartate (NMDA) receptors in the dorsal horn of the spinal cord.^{1,2} Ketamine inhibits the binding of excitatory amino acids, such as glutamate, to the NMDA receptors, thus blocking the transmission of painful stimuli. The drug's action as an NMDA-receptor antagonist is thought to be the mechanism behind its analgesic properties, as well as its ability to reverse hyperalgesia (heightened pain sensitivity) and opioid tolerance.¹ It also inhibits the reuptake of dopamine and serotonin and elevates circulating epinephrine and norepinephrine levels. This increases the heart rate, blood pressure, cardiac output, and vascular resistance.³



Ketamine is highly lipid soluble, which causes it to cross the blood-brain barrier rapidly. IV administration, whether for anesthesia or analgesia, results in an extremely fast onset—within 30 seconds, with full effect within one minute—and a short duration, of up to 60 minutes. Its half-life is also short (two to three hours). When taken orally, 80% of the drug undergoes hepatic metabolism to the active metabolite norketamine, which is excreted with other metabolites in the urine.¹ Little is known about the clinical significance of ketamine's metabolites, except that norketamine has one-third the analgesic potency of ketamine.¹

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There is great variance in individual response to the drug, and effects, including duration of analgesia, are dose related.¹ Immediate effects upon administration of anesthetic doses of ketamine include analgesia, sedation, pupil dilation, nystagmus, lacrimation, salivation, and increased muscle tone. Patients under ketamine anesthesia are described as noncommunicative and in a “cataleptic state in which the eyes remain open with a slow nystagmic gaze.”³ Adverse psychotomimetic effects, such as feeling apart from the environment and hallucinations, are minimized with subanesthetic doses⁴ and slow titration,¹ as well as concomitant administration of a benzodiazepine, such as diazepam (Valium) or midazolam (Versed).^{2, 3, 5, 6} Midazolam is recommended because diazepam can inhibit the breakdown of ketamine and prolong its half-life.⁷ A major advantage is that ketamine can be administered by many routes, including orally, intravenously, subcutaneously, rectally, intranasally, transdermally, topically, and epidurally. (See *Low-Dose Ketamine: Clinical Considerations*, page 63.)

ACUTE PAIN

IV ketamine has a long history of relieving acute procedural pain. Its most common use is in the care of burn victims during wound debridement and skin-staple removal.⁶ Both IV and oral ketamine have been used successfully for years to treat procedural pain in children.^{3, 8} Ketamine is considered ideal at subanesthetic doses for procedural pain in children with congenital heart disease, asthma, trauma, hemodynamic instability, burns, or poor intravenous access.³

Although the addition of ketamine to IV morphine in patient-controlled analgesia hasn't been shown to be effective, there has been a surge in research in the past five years on the opioid-sparing effects of subanesthetic doses of ketamine in the treatment of acute postoperative pain (administered in a parenteral or epidural single bolus dose or by infusion).⁴ In one study, women undergoing gynecologic laparoscopic surgery were randomized to receive placebo or preincisional or postincisional IV ketamine. Those who received preincisional ketamine (0.15 mg/kg) reported better pain relief, took a longer time to first request for analgesia, and consumed 50% less morphine after surgery than those who received placebo or postincisional ketamine.⁹

A study evaluating the effects of low-dose ketamine infusion during renal surgery demonstrated

improved postoperative pain relief.¹⁰ All patients (N = 40) received morphine and bupivacaine by thoracic patient-controlled epidural analgesia and were randomized to receive either a placebo or a ketamine IV bolus (0.5 mg/kg) and infusion (0.5 mg/kg/h) during surgery. Those who received ketamine had significantly lower pain scores on a visual-analogue scale at rest and when coughing and required less analgesia during the two-day study period. They also experienced less nausea and pruritus and greater sedation during the first two hours after surgery. No deep sedation, respiratory depression, or dysphoria occurred (diazepam and midazolam were administered at induction of ketamine).

And there may be long-term benefits to perioperative administration of ketamine. Researchers evaluated the effects of subanesthetic doses of ketamine on postoperative wound hyperalgesia and pain relief in a study of 100 patients who were scheduled for rectal adenocarcinoma surgery; a combined epidural-and-general anesthesia was used.¹¹ Patients were randomized to receive no ketamine, one of two subanesthetic regimens of IV ketamine, or one of two subanesthetic regimens of epidural ketamine. Those who received a bolus dose of 0.5 mg/kg followed by a 0.25 mg/kg IV infusion reported significantly reduced areas of hyperalgesia at all study periods, consumed less analgesic, and reported less residual pain through the sixth postoperative month, compared with patients in the other groups. The researchers concluded that these subanesthetic ketamine doses given during anesthesia are a useful adjuvant to perioperative analgesia and that the systemic route is best for administering ketamine. Another group of researchers, however, reported more effective analgesia with the epidural route than with the IV route.¹²

Finally, Edrich and colleagues described the case of a burn patient who, after several skin grafts, required progressively larger doses of sedatives (midazolam 20 mg/h IV, diazepam 900 mg/day via jejunostomy tube, and propofol 300 mg/h IV) and opioid analgesics (fentanyl 70 mcg/h IV, hydromorphone 30 mg/h IV).¹³ The patient experienced unrelieved pain and persistent ileus with abdominal distention that caused respiratory compromise. A continuous infusion of ketamine 2.7 mg/kg/h IV produced an opioid-sparing effect of more than 90% and pain ratings of 3 on a scale of 0 to 10. The patient denied any psychotomimetic effects. The quality of sedation improved, and within 24 hours

the ileus resolved. After one month ketamine was tapered over a two-day period, and a month later the patient was discharged to a rehabilitation hospital.

CHRONIC, NONMALIGNANT PAIN

Well-controlled research on the use of ketamine for chronic, nonmalignant pain is sparse; it's recommended as a third-line option when traditional analgesics (opioids, anticonvulsants, or antidepressants) fail.² A review of the cases of 33 patients with severe pain associated with complex regional pain syndrome who underwent continuous infusion of ketamine (starting dose 10 mg/h) revealed that 76% experienced complete pain relief, 18% partial relief, and 6% no relief.¹⁴ Repeat treatment after relapse in 12 patients resulted in complete relief in all 12, and 58% of these maintained complete relief for at least one year; 33% for more than three years.

Researchers conducted a randomized, double-blind study (N = 35) of opioids plus a single infusion of low-dose (0.6 mg/kg) ketamine compared with opioids plus placebo in patients with severe ischemic limb pain associated with peripheral vascular disease.¹⁵ Patients receiving ketamine experienced significant improvements in pain relief, general activity, and the enjoyment of life, compared with those who received placebo. And a case report describes success in reducing postamputation phantom limb pain in a 44-year-old woman by administering 21 IV ketamine infusions in a four-month period.¹⁶

Oral ketamine may provide satisfactory pain control at lower doses and with fewer adverse effects than parenteral ketamine.^{17, 18} Low-dose parenteral ketamine (starting dosage of 40 to 60 mg over 24 hours) was administered as an adjuvant to other analgesics in three patients with refractory neuropathic pain.¹⁷ The patients were subsequently switched to oral ketamine at doses 30% to 40% lower than the parenteral doses, and patients experienced sustained satisfactory pain control and "remarkably few side effects." Also, a case report described the effectiveness of oral ketamine (20 mg twice daily) in reducing severe pain and allodynia (pain resulting from a normally nonpainful stimulus) associated with multiple sclerosis in a 60-year-old woman.¹⁹ One year after the initiation of oral ketamine therapy, she was satisfied with treatment and rated her paroxysmal pain, persistent pain, and allodynia as mild in intensity and reported improvements in activity and sleep patterns.

The use of a topical ketamine gel to treat chronic neuropathic pain has been reported in five case studies (complex regional pain syndrome, postherpetic neuralgia, and radiculopathy).²⁰ Researchers reported a 53% to 100% reduction in patients' pain

scores and no adverse effects after application of topical ketamine. Doses ranged between 0.093 mg/kg and 9.33 mg/kg, which demonstrates the great individual variety in analgesic requirements. (Ketamine gel must be formulated by a compounding pharmacy; it's not commercially available in the United States.)

CANCER PAIN

Although most cancer pain can be treated successfully with nonopioid and opioid analgesics, ketamine may have a role in treating patients who have refractory, cancer-related, neuropathic pain or who experience intolerable drug-related or dose-limiting adverse effects at the end of life.^{5, 21} Single subanesthetic infusions of ketamine (0.25 and 0.5 mg/kg) were compared with placebo in a double-blind, crossover study of 10 cancer patients with neuropathic pain.²¹ All of the patients were also receiving morphine and were given the two different doses of ketamine and placebo. Mean pain intensities (as measured on a 0-to-10 scale) were reduced from 6.6 to 1.4 and 5.9 to 0.2 after administration of 0.25mg/kg and 0.5 mg/kg of ketamine, respectively, compared with essentially no change (mean, 6.5) after placebo administration. Pain relief from ketamine 0.25 mg/kg and 0.5 mg/kg was sustained over the 180-minute observation period, with a gradual increase in pain intensity noted (3.8 and 1.8, respectively, at 180 minutes). Those who received 0.5 mg/kg experienced greater relief than those who received 0.25 mg/kg. No adverse effects were reported after placebo administration; however, four patients experienced varying degrees of psychotomimetic effects with ketamine, which were easily reduced with IV diazepam administration. All patients reported increased sedation but no respiratory depression occurred with ketamine administration.

Kannan and colleagues used oral ketamine (0.5 mg/kg three times daily) in combination with oral morphine to treat nine patients with neuropathic cancer pain.²² All were taking the highest-tolerated doses of morphine, amitriptyline, and sodium valproate and reported pain ratings greater than 6 on a 0-to-10 scale when ketamine was started. Seven patients experienced a decrease of more than 3 points in the average pain score, four experienced nausea, and all but one reported sedation. Sedation lessened over two weeks in five patients; three patients withdrew from the study, two because of excessive sedation and one because of a "feeling of unreality." Other studies, audits, and case reports exist describing the synergism between ketamine and morphine and dramatic relief of severe neuropathic cancer pain with vari-

Low-Dose Ketamine: Clinical Considerations

Indications

- Procedural pain
- Postoperative pain (opioid-sparing analgesia)
- Chronic neuropathic pain (third-line analgesia)
- Intolerable, dose-related adverse effects of traditional analgesics

Dosing recommendations

Note: These are starting doses and must be titrated. The effective dosage range varies widely (such as 30–1,000 mg/day per os)¹; increase as needed, limiting only for adverse effects.²

- **Parenteral***: 0.2–0.8 mg/kg IV bolus for procedural pain (administer slowly over three minutes)³; 0.15–0.25 mg/kg IV for preemptive analgesia³; 0.1–0.2 mg/kg IV bolus or 0.5 mg/kg subcutaneous bolus for chronic pain²; continuous IV or subcutaneous infusion for chronic pain (initial dosing recommendations vary): 0.14–0.4 mg/kg/h¹ and 0.1–1.5 mg/kg/h⁴
- **Oral**: 4–6 mg/kg for procedural pain⁵; recommendations for initial dosing for chronic pain treatment vary: 10–25 mg/day⁴ or 0.5 mg/kg taken at bedtime¹

Adverse effects

- Psychotomimetic effects (titrate slowly and coadminister a benzodiazepine to reduce or avoid these effects)
- Hypotension
- Excessive sedation
- Nausea, vomiting
- Excessive salivation
- Apnea (with rapid IV administration)

Monitoring

Note: This protocol is also used in terminally ill patients, and monitoring should be adjusted accordingly.

- Check vital signs and levels of pain and sedation and look for adverse effects 15 minutes after IV dose and 30 minutes after oral dose and with any dose increase, then every two hours.
- Stop administration if systolic blood pressure is less than 85 mmHg, heart rate is less than 60 beats per minute, respiration is less than 10 breaths per minute, or intolerable psychotomimetic effects occur.

Other key points

- Be alert to the opioid-sparing effects of ketamine.
 - u Decrease the opioid dosage by 25% to 50% if increased sedation is detected in opioid-naive patients.
 - u Decrease opioid dosage by 50% at initiation of treatment for chronic pain, and then decrease by 25% every six to 12 hours, as tolerated. Watch closely for abstinence symptoms (such as diaphoresis, abdominal cramps, diarrhea, or rhinorrhea) and be prepared to rebolus with ketamine if necessary.²
- Discuss psychotomimetic effects with patients¹; tell them to expect dreamlike feelings during administration.²
- Injectable formulation must be used for oral administration. Warn patients that oral ketamine has a bitter taste that may be lessened by taking it with sweet juice or gelatin.⁵
- Subcutaneous administration can be irritating and requires frequent infusion site changes.¹

* The intramuscular route is discouraged for pain management.

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ous amounts of oral or continuous IV or subcutaneous ketamine infusions.²³⁻²⁵

ADVERSE EFFECTS

The most common and potentially disturbing adverse effect of ketamine is the psychotomimetic response, but this appears to be significantly affected by dose; subanesthetic doses have been

shown to produce less pronounced or no dissociative effects.¹⁷ The incidence of psychotomimetic adverse effects is greatest in adults, females, and patients with a history of psychosis or personality disorders.³ Interestingly, one study showed that low-dose ketamine (1 mg/kg) given intraoperatively to 70 patients with major depression improved their postoperative depressive state.²⁶

Ketamine increases muscle tone, and movements often seem purposeless. Slow IV administration (over three minutes) does not produce respiratory depression; however, apnea can occur if the drug is administered too rapidly.³ Other adverse effects include hypotension, nausea, vomiting, and increased intracranial and intraocular pressure. Gastric ulcer, hepatic damage, and memory impairment were reported in one patient on long-term oral ketamine treatment.¹⁸ The drug is contraindicated in patients with intracranial hypertension and should be used with caution in patients with seizure disorders.³

Ketamine has not been approved by the FDA for intraspinal use because of possible neurotoxicity related to its preservative.⁴ The preservative-free formulation is not available in the United States, and intrathecal (subarachnoid) administration is not recommended.^{1 t}



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