Ketamine: Reinventing Chronic Pain Management

Jeannette Y. Wick, RPh, MBA, FASCP
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What Route?
To minimize adverse events associated with ketamine use, researchers are examining the use of administration routes other than intravenous. Oral ketamine, as an injectable liquid or a compounded product, is subject to hepatic first-pass metabolism and is less effective than parenteral doses. It also lacks a clear dose-response relationship.22,35 Some study results suggest that the oral route leads to few side effects.36 Topical formulations of ketamine or ketamine with other potential analgesics has been used for managing several painful conditions (eg, pelvic pain, pruritus) with mixed results.22,37-39

Managing Pain
Ketamine use in pain management evolved from its perioperative use. Perioperative pain is expected, but may have physical or psychological consequences that delay rehabilitation and prolong hospitalization.1 Most surgeons use opioids to treat postoperative pain and supplement with regional anesthesia, other analgesics, and adjuvant agents as needed.1,23,40 Some patients respond poorly or incompletely to opioids; ketamine may help these patients.26,27,41

In low doses, NMDA-receptor antagonists can provide analgesia and circuitry opioid-related tolerance, hyperalgesia, and allodynia.10,23,40 Randomized, placebo-controlled, double-blind clinical trials (RCTs) have found that perioperative subanesthetic doses of ketamine added to opioid analgesia improved pain scores and reduced opioid consumption by approximately 30% to 50%. Ketamine was given as an intermittent low-dose intravenous bolus or a continuous infusion. It reduced opioid-related nausea and vomiting and added no additional significant adverse effects.42,43

Ketamine can also be given with morphine patient-controlled analgesia, contributing a morphine-sparing effect. Patients with chronic neuropathic pain, opioid dependence or tolerance, and acute hyperalgesia seem to benefit more.42,43 Low-dose ketamine administered before the surgical incision can lead to better analgesia for 24 hours after surgery.1 Most studies report no significant increase in psychomimetic adverse effects when ketamine is added to morphine.42,43

Sickle Cell Crisis and Chronic Noncancer Pain
Acute sickle cell disease creates severe pain with a neuropathic element. Several published guidelines recommend using opioids as first-line treatment, but some patients are unresponsive to even high opioid doses. Rapidly escalating opioid doses may induce acute tolerance and opioid-induced hyperalgesia.29,44 Case studies (but no RCTs) indicate that adding a low-dose ketamine infusion to opioids can improve pain in sickle cell disease.44 Usually, NMDA receptors activate continually only after a severe, sustained painful stimulus allows sufficient glutamate release. This is why ketamine may be useful as an adjuvant in several types of chronic central and peripheral neuropathic pain (Table 2).23,45,46

Several of ketamine’s properties may prevent chronic pain from developing:

- Dampening of nociception
- Prevention or attenuation of hyperalgesia, allodynia, and tolerance
- Attenuating central sensitization and windup phenomenon from repeated noxious stimuli when previously nonpainful stimuli become exaggerated and painful23,40

Clinicians have used short-term subanesthetic doses of ketamine to treat neuropathic pain.45 Scheduled infusions over several days can improve pain scores in patients with chronic pain; a few

### TABLE 2: CHRONIC PAIN CONDITIONS FOR WHICH KETAMINE USE HAS BEEN TESTED

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studies report pain relief persisting for weeks following treatment, indicating that ketamine may be disease modifying.46

Cancer Pain

Limited but increasing data support ketamine use in refractory cancer pain. Adding a small dose of ketamine to opioid therapy in a patient with opioid tolerance, called burst therapy, can improve pain management.12,47 Patients on high-dose opioids whose cancer pain has a neuropathic component may respond to oral ketamine.48 Adding a small dose of ketamine to patient-controlled morphine seems to improve pain management, and some researchers are testing a ketamine mouthwash for mucositis.49,50

Endnote

Large, well-designed RCTs are needed to confirm the analgesic role of ketamine. Most studies suggest, and experts believe, that ketamine use should be reserved for patients in whom opioids, anticonvulsants, or antidepressants have failed.3,36 Because pain management is an off-label use for ketamine, clinicians should consult with field experts for dosing recommendations.

Ms. Wick is a visiting professor at the University of Connecticut.

References