KETAMINE: To Use or Not to Use for Pain Management

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Ketamine has been in long and routine use as a dissociative anesthetic. More recently, new pharmacologic features of ketamine have been discovered that provide novel pain modification.

IT'S PLACE IN PAIN MANAGEMENT

It is well-established in human medicine that the use of adjunct medications, including ketamine, minimizes the use of PCA (patient-controlled analgesia) opioids, with a resulting decrease in incidence of adverse effects, such as postoperative nausea and constipation, which in turn, quickens discharge from the hospital.[1]

However, ketamine is not considered an analgesic drug. Rather, it appears to be protective against hyperalgesia and central hypersensitization in the postoperative setting.[2] These effects can be important in reducing immediate postoperative morbidity and persistent postoperative pain.

In humans, acute postoperative pain is followed by persistent pain in 10% to 50% of individuals after common operations, such as groin hernia repair, breast and thoracic surgery, and amputations. Chronic pain is severe in about 2% to 10% of these patients.[3]

While we do not have this kind of epidemiologic data in animals, there is little reason to doubt that they can experience severe or protracted pain.

WHAT RESEARCH SHOWS

Various studies in humans and rodent models utilizing ketamine via constant rate infusion (CRI) or transdermal patch revealed that actual pain scores are not lowered significantly; however, there are individual studies which demonstrate that the modality:[1,4-6]

- Reduces opioid consumption by 30%
- Improves rehabilitation after arthroplasty
- Reduces analgesic drug requirements after abdominal and gynecologic surgery
- Results in superior pain control compared to intermittent morphine for musculoskeletal trauma
- Provides dose-dependent analgesia for third molar extraction
- Demonstrates use as rescue analgesic in opioid-tolerant and opioid-hyperalgesic patients
- Possibly reduces phantom-limb pain postamputation.

Looking at the totality of human literature regarding the utility of ketamine as a pain-modifying agent, a recent systematic review revealed the following evidence-based conclusions:[7]

Level I Evidence (Meta-Analyses)

- Considered to have "preventive" effects on pain in acute postoperative period
- Opioid-sparing
- Safe
- Most effective as low-dose CRI for acute pain management

Level II Evidence (> One Properly-Designed Randomized Clinical Trial)

- Most effective as "antihyperalgesic," "anti-allodynic," or "tolerance-protective" treatment
- Effective as rescue analgesic for opioid-tolerant patients
- Reduces peripheral neuropathic and spinal cord injury pain
- Improves fibromyalgia symptoms
- Intranasal route reduces breakthrough chronic pain (cancer and noncancer patients)

APPLICATION IN VETERINARY MEDICINE

In a pair of clinical studies in dogs, one demonstrated a positive pain-modifying effect of CRI ketamine following forelimb amputation[8] and another recorded improved feeding behavior postmastectomy.[9] In the forelimb amputation study, the study group received a loading dose of ketamine followed by CRI ketamine for 18 hours postoperatively. The authors recorded significantly lower pain scores throughout the study period compared to the control group. Interestingly, the authors also found that the study group dogs were more active than the control group for up to 3 days after surgery. In the mastectomy study, the CRI ketamine was continued for only 6 hours postoperatively in the study group, but improved feeding behavior compared to the control group was observed for up to 20 hours in the postoperative period.

Indications

The question of which surgical patients should receive ketamine CRI is an open one:

- One subset of patients might be those at greatest risk for postoperative maladaptive pain (eg, fracture repair, aggressive soft tissue procedures).
- Alternatively, the modality could be incorporated into the transoperative balanced anesthetic and pain management protocol for most patients.

Potential Precautions

Historically, concerns have been expressed about the anesthetic use of ketamine in two populations of patients: those with central nervous system disease, especially seizures and increased intracranial pressure (eg, trauma, neoplasm), and in cats with hypertrophic cardiomyopathy. However, the clinical importance of these concerns with regard to subanesthetic CRI ketamine has not been established.

Administration

Boscan and his colleagues at University of California–Davis found that a plasma ketamine concentration of 2 to 3 mcg/mL elicited the most benefits with minimal adverse effects. This can be achieved in the dog by administering ketamine as a CRI at approximately 10 mcg/kg/min.[10]

Administering ketamine by CRI is easily accomplished by:

- Including 60 mg (0.6 mL of 100 mg/mL drug) per liter of crystalloid fluids
- Administering intravenous fluids at standard intra-operative rates of 10 mL/kg/hr, which deliv-

KETAMINE'S MECHANISM OF ACTION

At doses to induce a dissociative anesthetic state, ketamine binds to many receptors throughout the body, including mu-opioid, sigma-opioid, and N-methyl-D-aspartate (NMDA) receptors. NMDA and opioid receptors are closely aligned in many areas of the central nervous system, and interaction has been detected between them.[12] Recent work reveals that ketamine may also have dopaminergic effects.[13]

Ketamine appears to be one of the most potent NMDA antagonists found in clinical medicine, and this activity is demonstrable even at subanesthetic doses, resulting in a pain-modifying effect.

Historically, the focus of analgesia has been to diminish transduction (eg, local anesthesia, anti-inflammatories) and perception (eg, opioids), and indeed these remain crucial components of a multimodal approach to pain management. However, ketamine exhibits its subanesthetic action in the dorsal horn of the spinal cord, where enhancement of nociceptive inhibitory modulation and interruption of the feedback loop that results in exaggerated pain responses and perception takes place.

These additional components of pain management provided by ketamine expand the traditional roles of analgesia.

ers ketamine at 10 mcg/kg/min
- Continuing fluids postoperatively at standard maintenance rates of 2 mL/kg/hr, resulting in a ketamine CRI rate of 2 mcg/kg/min.

In order to rapidly achieve plasma levels, it is recommended that the CRI follow an initial ketamine IV bolus of 0.25 to 0.50 mg/kg. Ketamine CRI can be administered concurrently with CRIs of opioids, such as fentanyl, morphine, and/or lidocaine.[11]

Duration of Administration

The ideal duration of CRI ketamine is uncertain, although in the studies cited (both very aggressive surgeries with a high predictability for discomfort), it was continued for 20 (forelimb amputation) and 6 (mastectomy) hours. It is interesting to note that the pain-modifying improvements in the ketamine CRI groups in both studies extended even after discontinuation of the CRI—until the studies were completed (3 days and 20 hours, respectively).

WHY ADMINISTER KETAMINE?

The ideal veterinary patient, surgery, or procedure for which subanesthetic ketamine CRI is indicated has not been identified. However, while the most optimum situations for ketamine administration are not known at this time, the existing evidence suggests that ketamine has a potential role in perioperative pain management.

The evidence, however, is strong that ketamine CRI at subanesthetic doses:

- Is safe and anesthetic-sparing
- Improves anesthetic cardiovascular and respiratory parameters
- Improves analgesic effects of other drugs
- Helps prevent exaggerated and sustained pain states.

In summary, ketamine is one of the most potent drugs available for NMDA-blockade, which accounts for its efficacy as an inhibitor of central hypersensitization and hyperalgesia. Due to its low cost and high safety margin at subanesthetic CRI doses, it appears to be a useful adjunct to many surgical procedures, and may have future applications for the treatment of central or peripheral hypersensitization.

CRI = constant rate infusion;
NMDA = *N*-methyl-D-aspartate

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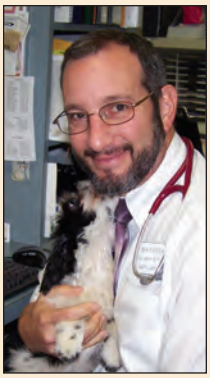

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