Ketamine: A Novel Approach with a Familiar Tool—Part 2 Clinical Application and Case Studies

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Ketamine is a unique player in the field of pain management and anesthesia and is the focus of new attention for the treatment of chronic pain conditions. There is growing evidence for the use of intermittent ketamine infusions and injections for chronically painful conditions, but details on dosing, route, frequency, duration of effect, and risks are still being explored. This variation in options for treatment as well as the non-uniformity of chronic pain conditions make designing clinical trials challenging and thus interpreting results in a clinically meaningful way even more murky. Patients who suffer from chronic pain syndromes often have significant psycho-emotional disturbances, numerous pain conditions/symptoms, complicating co-morbidities, and a wide variation in previous management strategies. Isolating a uniform patient population and determining a consistent treatment plan can be time consuming and unrewarding. There is also the complicating factor of appropriate outcome measures for assessing response, especially in veterinary patients. While significant data has been published on ketamine for the management of chronic and neuropathic pain, consistency in approach to treatments is rare. It is important to understand what we know about ketamine and its indications in chronic pain cases and the potential risks with its use. There is minimal to no published data in veterinary patients with chronic pain, though much of the preliminary human research is on lab animals. It is important to also recognize that while we can draw many similarities between humans and veterinary patients, their drug metabolism and response are not always the same. Taking these “grains of salt” into consideration is critical to designing an appropriate plan when managing chronic pain with ketamine.

Ketamine is found in almost all veterinary clinics and most in the field are familiar with its use in the perioperative setting at a minimum. As we have expanded intraoperative pain management, Ketamine is often incorporated into surgical constant rate infusion protocols and multimodal pain management plans for post-op recovery. Some practitioners are also using ketamine as part of a multimodal pain management of severe pain cases, a “pain vacation.” The use of ketamine as a sole agent for the management of chronic pain is uncommon at this point, despite our comfort with the medication and the growing evidence in human medicine. Ketamine offers an exciting, potentially new intervention, but unfortunately with

little guidance on application in the clinical setting. In order to apply this treatment in our hospitals we must draw on what data we have, primarily intraoperative and post-operative data and work within our comfort level and safety margin of the drug. At Red Sage, we are using ketamine as intermittent infusions as well as subcutaneous dosing in many of our challenging chronic pain cases with good success.

PATIENT SELECTION

Ketamine can be added to the pain management plan for many patients. In the human research, complex regional pain syndrome, spinal/back pain, chronic headache, mixed pain diagnoses, post herpetic neuralgia, phantom limb pain, fibromyalgia, and chronic ischemic pain are the most studied though many of these are not commonly recognized in our veterinary patients. There are likely many pain conditions that we have yet to officially describe in animals. Veterinary patients who suffer from chronic pain (lasting for longer than 3–6 months or beyond the resolution of the inciting injury or illness) or those who have been diagnosed with neuropathic pain resulting from direct injury to a part of the nervous system itself, are obvious candidates for ketamine treatments based on the current evidence and have shown good responses in our care. There are mixed results in patients suffering with cancer pain though certainly a selection of cancers can lead to chronic neuropathic pain as well. Cancer can complicate pain signaling, which may also alter the effectiveness of ketamine. In our patients with painful tumors like osteosarcoma, intramuscular hemangiosarcoma, transitional cell carcinoma, or those with painful metastasis, we have found relief in ketamine infusions. What may be more complicated is recognizing patients who may also be suffering from depression, anxiety, or other behavioral changes associated with chronic pain or other chronic diseases like cancer. Client interviews and patient observation can help, but often it is not until after treatment that we fully appreciate the true impacts of these effects. If there is suspicion of a significant emotional component, depression and withdrawal especially, ketamine should be strongly considered across many conditions.

When thinking about our veterinary caseload the most common chronic pain diagnoses include osteoarthritis and other musculoskeletal disease, intervertebral disc disease or other neuropathies, cervical myelopathy and neuropathies, lumbosacral disease, tendinopathies, and our patients dealing with cancer. Osteoarthritis is unfortunately common and is a large contributor to chronic pain and is often a major issue for quality of life and mobility in dogs and cats. Chronic

inflammatory and osteoarthritic pain can have similar impacts on the nervous system and neuropathic pain. Many of the patients we are treating at Red Sage have severe osteoarthritis and frequently in multiple joints. With its significant chronicity as well as the increasing number of tools to manage arthritis, these patients are living longer and dealing with the complexities of chronic disease and failing management strategies with time and disease progression. These are often rewarding patients to treat with ketamine. Patients who suffer with chronic neuropathic pain also frequent the rehab practice and offer compelling cases to incorporate ketamine. Those we have anecdotally seen the strongest responses in are those with significant and even intractable cervical pain and those with lumbosacral pain. This pain can be from a variety of etiologies, but often present as complicated and long-term pain cases.

When considering patient selection veterinary professionals also have the complicating issues of ease of intravenous access, tolerance of being in the hospital for 4–6 hours, and what are the owners' feelings/hesitations about ketamine treatments. If these are not compatible with the case, route of administration can be adjusted.

Side Effects/Cautions

Ketamine is very well tolerated and has a low and an incidence of long-term effects. Ketamine used as higher anesthetic doses can potentially disorientation, increased salivation, possible muscle spasm, tachycardia, hypertension, and occasionally head swaying. Ketamine was also previously thought to increase intracranial pressures though more recent studies including two large scales reviews have refuted that notation in human patients and it is no longer considered a contraindication to ketamine use in human hospitals. There are also some concerns with intraocular pressure (IOP), but again this has not held up in more recent human studies. A 2013 canine study did find increased IOP, but this was at a one-time IV dose of 20 mg/kg, which is far higher than what is recommended for chronic pain management. These risks may still be considered in patients with known elevated intracranial pressure or intraocular pressure, though they seem low especially at subanesthetic doses and should not limit ketamine use if strongly indicated for a patient.

Ketamine is generally considered to be cardiovascularly-sparing. There are not significant changes in cardiac output, stroke volume, and systemic vascular resistance. There can be a negative inotropic effect in critically ill human patients.

Heart rate can increase in some patients who receive ketamine, so any existing arrhythmias or other abnormal heart rhythms certainly call for closer monitoring during treatment. This is also true for patients who tend to be hypertensive as ketamine can raise blood pressure. There is some question on whether ketamine should be used in patients with a seizure history though it does not induce seizures and is in fact being used as a neuroprotectant and management tools in patients with refractory status epilepticus. Good communications with owners about these potentials and weighing risk and benefit are important for addressing adverse events if they happen. Many of these can be managed with dose adjusting. We have found that giving the bolus slowly over 2–5 minutes and gradually increasing the infusion rate improved the few patients with hypertension, increased heart rate, and dissociative effects.

There are some added considerations from humans who have abused ketamine recreationally. There is a long-term, dose-dependent hepatotoxicity. It also appears this hepatotoxicity is related to concurrent cocaine use in abuses of ketamine and may be related more to the combination than ketamine alone. These cases present with elevated liver values and tend to resolve with discontinuation of ketamine. Hemorrhagic cystitis is also possible and is typically sterile. This can occasionally persist beyond discontinuation of ketamine. We do not know if the same side effects occur in our veterinary patients and have not been reported in chronic pain patients but are worth considering with longer-term use (greater than 6 months–1 year).

Baseline blood work including a complete blood count, chemistry, and urinalysis are useful as screening tools for ketamine patients. Risks again are low, so this does not need to create a barrier to treatment. Ketamine is initially metabolized in the liver and undergoes biotransformation in the cytochrome P450 system into the primary metabolite norketamine which is excreted in the urine. Knowing this metabolic pathway other drugs that affect the CP450 pathway may need to be considered when dosing, though there is minimal published data on this. Baseline EKG as well as blood pressure are helpful for establishing baseline and normal for the specific patient and should be monitored intermittently through an infusion. Potentially consider rechecking blood work and monitoring urine in patients receiving numerous ketamine treatments.

Dosing Considerations

Considerations when designing a ketamine treatment include the route of administration, the total dose, the frequency of dosing, the duration of an infusion if IV or subcutaneous treatment, and the number of treatments. Many of these decisions will be based on pain severity, chronicity, patient tolerance, and previous responses to treatment. Based on recommendations from the American College of Anesthesiologists, a human patient should receive at least 80 mg of ketamine infused over at least 2 hours and assessment of patient response decides the frequency of the treatments. There do seem to be differences in pharmacokinetics between humans and dogs/cats, but this is a good place to start. Veterinary data is limited, but what exists can help guide initial dosing plans. There is a series of studies looking at ketamine as a sole agent in dogs who are awake and assessing nociceptive responses at various infusion doses. Normal dogs who received a constant rate infusion of ketamine after a 0.5 mg/kg bolus at 10 mcg per kg per minute had minimal side effects that were sort short-lived and harmless in the study period. Ketamine at these doses did not influence nociceptive withdraw (could not be recommended for surgical management alone), but interestingly there was an inhibitory effect on temporal summation, a measured increase in pain response to the same repeated noxious stimulus. Patients had up to an 81% reduction in temporal summation and decreased behavioral reactions scores. In human studies temporal summation is considered a model for central sensitization in chronic pain, supporting ketamine's impact on central sensitization. A clinical study looked at canine patients undergoing an amputation who received perioperative ketamine at 0.5 mg/kg intravenous bolus followed by 10 mcg per kg per minute during the surgical procedure and 2 mcg/kg/min in the postoperative phase. Lower pain scores were noted at both 12 and 18 hours postop and when clients were interviewed once patients had returned home those who had received ketamine received better scores especially when related to activity. It seems reasonable to take this as a starting point for infusion treatments starting with a bolus of 0.25–0.5 mg/kg and running the infusion between 2–10 mcg/kg/min will limit dysphoria but be effective in impacting chronic pain changes.

Duration of effect is also important to consider when planning treatment ketamine. The duration of effect will determine how often to give treatments and what owners can expect for a response. Duration will be influenced by many factors including route of administration as well as a dose, previous treatments, and underlying condition you are treating. In human patients being treated for depression the initial effects start within minutes or hours and can last from days to weeks. There is also evidence that serial IV ketamine infusions achieve a greater response rate without any increase in side effects/risks, but perhaps some

development of tolerance requiring increased dose. One study found that a ketamine infusion decreased visual analog scores in patients with intractable chronic pain when infusions were given every 3–4 weeks. In a mouse study, when ketamine was administered subcutaneously at 2 mg/kg daily for 7 days there was a significant decrease in nociceptive sensation space (complex regional pain syndrome model). Follow up studies in similar mice also found that infusions following a regimen where dose was gradually increased over treatments could reduce pain for over 10 weeks or longer which may indicate a disease modulatory role in this complex pain condition. This indicates that ketamine treatment can be disease modifying and thus some patients may not require as frequent management while others are more symptom modifying and may require more regular treatments.

In a study designed at Red Sage we started with a series of 3 infusion treatments that were 2 weeks apart and included a 0.25–0.5 mg/kg dose as a bolus followed by an infusion starting at 4–6 micrograms/kg/minute and increasing up to 8–10 micrograms/kg/minute depending on patient tolerance with rare adverse events or side effects. These patients included those suffering from chronic osteoarthritis pain, chronic pain associated with intervertebral disc disease at various locations, as well as cancer pain and other complex pain conditions. We have also used intermittent subcutaneous dosing at 0.25–5 mg/kg as needed in painful cases. There is also the option to use a subcutaneous pump to deliver an infusion of ketamine at home over 48 hours that can be programmed to deliver a specific dose.

Patient Assessment and Outcomes

To determine the effectiveness of treatment as well as fine tune dosing plans, establishing how to define a positive response is important. Because of the variety of ways ketamine can address chronic pain and associated anxiety and depression, concrete outcome measures sometimes fall short of capturing patient response. Assessing and quantifying pain in veterinary patients has proven challenging for even those most advanced in the field. A variety of pain scales as well as quality of life scales are available and offer potential tools for assessing responses to treatment. Are we looking for improvements in gait? Improvements with pain on palpation of an affected area? Owner reported improvement in perception of comfort or pain? Are there secondary changes in quality-of-life measures that also indicate an improvement, even if there is no improvement in lameness or physical exam finding? These may include things like desire to play, desire to go on walks,

playfulness, sleep patterns, level of interaction, and general attitude. Capturing these becomes much more challenging and requires intuitive owner reporting. Other factors considered often in human studies include the ability to return to work, the reduction of dependence on other medications, the ability to sleep and rest, and improvements in quality-of-life scales. Maintaining open communication with owners and encouraging them to not only look for changes in lameness and/or mobility, but also general changes in quality of life may improve assessment of response to ketamine treatments. This communication is also essential for understanding duration of effect and planning how often to administer ketamine. Use of pain scales and quality of life scales may help bring some of these indicators to light for owners and broaden the assessment of response.

Ketamine offers a relatively safe management tool for chronic pain in our veterinary patients with few barriers to its use. The dosing recommendations need optimization and continued research, but this is clearly challenging to establish in the field of pain management. When used in appropriately selected patients with good screening and monitoring ketamine can enhance our ability to manage and modify disease in our chronic pain patients with a tool most of us already have on the shelf.

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