Ketamine: A Novel Approach with a Familiar Tool—Part 1 Review of Ketamine and Chronic Pain

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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 in human medicine. There is growing evidence for the use of intermittent ketamine infusions and injections for chronically painful conditions, including complex regional pain syndrome, chronic headaches, and chronic back pain in humans. Ketamine acts as an NMDA receptor antagonist, as well as having an ability to alter brain and spinal cord neuroplasticity in patients with central sensitization related to chronic pain. Ketamine is showing efficacy in unexpected conditions proving there may be more to its underlying mechanisms of action yet to be fully understood. Ketamine is well known for its benefits in preventing pain and central sensitization in the acute and perioperative pain setting but has not been studied in the context of veterinary chronic pain. Because the parallels between chronic pain and central sensitization in humans and animals are strong, it is promising to think that ketamine infusions could be used to address chronic pain issues for veterinary patients.

CHRONIC PAIN

Chronic pain presents a growing challenge with an increasing rate of diagnosis in humans and there is a matching trend in our animal patients though our vocabulary and criteria for diagnosis remain anecdotal at best. Management is often challenging and unrewarding with weak overall response rates and significant adverse reactions or risk of addiction with other treatments in human medicine. Conditions like depression and anxiety which are intimately related to chronic pain syndromes complicate management. There is a perpetual need for effective, safe, and innovative tools to address the multifactorial and very individual condition. Chronic pain is technically defined by time, but also by specific changes in the nervous system and clinical/quality of life changes for the patient.

In human medicine, the clinical definition of chronic pain can be nebulous, which makes its application in veterinary medicine even more challenging. Chronic pain is defined by pain that persists for longer than 3–6 months often beyond the healing of the initial stimulus or lesion. Numerous chronic pain conditions in humans are associated with chronic stimulus that is persistent, constantly bombarding the

nervous system with pain signals after the initial problem has resolved but residual signaling, and effects remain. In both cases, there are characteristic changes in the nervous system. With these alterations, innocuous stimuli become painful (allodynia) and normal pain signals are amplified (hyperalgesia). These are two classic characteristics of chronic pain conditions and help with its recognition clinically. More recently anhedonia, the inability to feel joy or experience pleasure, has been considered as part of chronic pain syndromes.

Both allodynia and hyperalgesia can be traced to specific underlying changes in the peripheral and central nervous systems. Research also continues to explore the links in the nervous system between chronic pain and anhedonia (characteristic of mental illnesses like depression). Our understanding of these changes is constantly evolving, and new mechanisms are being elucidated, so this list is partial and expanding. Fundamentally, the chronification of pain results from the loss of inhibition in pain signaling pathways and the amplification of pain signals, leading to confusion and misperception of pain in the brain. The protective balance the nervous system can typically keep between inhibition and amplification falls victim to changes that prevent the normal regulation of pain signaling. One very well recognized change is the upregulation and phosphorylation of the NMDA receptor in various regions of the nervous system. The NMDA receptor is a glutamate receptor and ion channel that resides in the membrane of postsynaptic neurons in the spinal cord. This channel is typically closed with a magnesium plug, blocking the flow of cat ions thus keeping transmission in check. When bound by an agonist, the channel opens and allows for greater ion flow, thus increasing excitability of the postsynaptic neuron. This essentially “turns up the volume” on these neurons so pain signals are amplified. This “volume” is also increased by the activation of glial cells and immune cells within the spinal cord. This increased activity impacts the cytokine milieu shifting to a more proinflammatory and active state. Glial cells play a critical role at the level of the synapse regulating the amount and clearance of many critical neurotransmitters. They are typically quiet in acute pain/nociceptive transmission, but their involvement in signaling changes with central sensitization. Activation leads to dysregulation of this baseline clearance and modulation, changes in phenotypes of the glial cells and enhances release of pro-nociceptive factors.

In addition to these physiologic changes there are physical changes in the nervous system as well. There is loss (death) of inhibitory neurons and new growth and expansion of nociceptive neurons. This expansion and sprouting widens the receptive fields for pain and contributes to the loss of the differentiation between

nociception and other stimuli like pressure and temperature. This widened range increases the volume and type of pain signals to an already less inhibited system upstream. The sprouting can also occur within the spinal cord creating linkages between regions that typically do not communicate, further confusing the signals that will reach the brain. There are complex changes within the brain itself with both the processing and interpretation of the pain signals. These changes in processing relate closely to changes in behavior in the chronic pain patient leading to issues like learned helplessness, fatigue, depression, coping behaviors, and anxiety.

Pain processing in the brain is altered in chronic pain syndromes and is often responsible for the profound impact on quality of life. There are extensive networks within the brain that communicate with each other and help to modulate and organize the signals coming through the spinal cord from the periphery. Specific areas of the brain are responsible for descending inhibition, spatial perception and localizing of pain (somatotopic representation) and developing the emotions and full body response to pain. With the increased volume and confusion of signals from the periphery, these systems start to get crossed and abnormal synapses are formed. These pathologic changes in the spinal cord and brain are called maladaptive neuroplasticity. Short term plasticity, i.e., turning on of silent synapses and neurons temporarily, modification of thresholds to be protective, can be reversed, but as the pathology progresses there is cell death, shrinkage of the gray matter, and new neuronal sprouting that are less recoverable.

On the human side of medicine, there is significant focus on the well-being and quality of life of the chronic pain patient. Human patients suffering from chronic pain report depression, anxiety, insomnia, and withdraw from normal activities. There is a well identified interaction between anxiety, depression, and pain. These changes are intimately connected to the functional changes in the central nervous system. A biopsychological approach is being embraced more widely when diagnosing and designing treatment plans for these patients that incorporate not only the pathophysiology of chronic pain as a disease state, but also considers the individual patient and their psycho-emotional influences. These influences are unique to every patient and are typically related to personality, family life, social life, and other cultural influences. Owners of animal patients with chronic pain often describe similar changes in their pets, but a clear definition for these patients does not exist, so it is hard to quantify. It is a reasonable assumption that many of these changes in human patients also affect our veterinary patients. Pets have similar influences in their lives, personalities, work, human interactions, play, etc. I would

argue that veterinary professionals who embrace a patient-centered care approach recognize the value of these influences in developing a treatment plan in the chronic pain patient.

KETAMINE

Ketamine was first synthesized in the 1960s as the hunt was on for an inexpensive, injectable, easy to use, and safe anesthetic option for humans, primarily on the battlefield. Phencyclidine had proven effective, but also induced severe and prolonged psychedelic episodes. Initial studies on phencyclidine and subsequently the less potent and shorter acting ketamine, were performed on a variety of animal species, introducing its use in the laboratory animal setting. Ketamine was approved by the FDA for human use in 1970 as it was soon found that the psychedelic symptoms (hysteria, anxiety, panic, etc.) were far less common and less severe with ketamine, though not totally eliminated. Lower doses or "subdissociative" doses of ketamine, still provided analgesia with far fewer of the undesirable side effects. This analgesic efficacy at lower doses and ketamine's limited impact on the cardiovascular and respiratory system made it an ideal choice for cases of hemodynamic instability (trauma, shock) and in more fragile patient populations like geriatric, and pediatric/obstetric groups. The undesirable side effects are not as severe in animals and can be similarly limited with lower dosing and by combining ketamine with other medications. This allowed its popularity to grow quickly in veterinary medicine.

Ketamine is a racemic compound that contains both an S(+) isomer and R(-) isomer. The isolated S(+) ketamine is not available in the United States and the most common formulation available from Pfizer is a racemic mixture. The S(+) isomer has a higher affinity to the NMDA binding site and produces greater anesthetic/analgesic effects with less cardiac stimulation and cardiac excitement in human and rat studies. R(-) ketamine may play a more critical role in some of the antidepressant/neuroplasticity effects of ketamine. Ketamine is highly lipid and water soluble and readily crosses the blood brain barrier with a quick distribution time of 10–15 minutes accounting for its rapid anesthetic effects. It increases cerebral blood flow which varies by region of the brain. It can be given via numerous routes (IV, IM, oral, nasal, rectal, epidural). Bioavailability is high when given IV or IM, but weak when given orally or rectally. It has a high volume of distribution and a half life in humans of 2–3 hours. Ketamine is a cytochrome p450 dependent medication and is metabolized primarily in the liver and excreted in bile and by the kidneys.

There was a resurgence in interest in ketamine in the 1980s with a better understanding of its primary mechanism of action. Ketamine acts as a non-competitive antagonist binding the N-methyl-D-aspartate (NMDA) receptor. Ketamine's NMDA receptor antagonism is critical in both its analgesic and psychogenic effects. Ketamine's NMDAR antagonist reduces neuronal excitement and thus can influence neuronal plasticity in the pain perception pathways and potentially numerous other areas of the nervous system. The discovery of ketamine's activity at the NMDA receptor led to further applications of the drug in the management of central sensitization (wind up pain) and further exploration of other mechanisms of action including structural modification in the brain and spinal cord. Research is also exploring anti-tumor effects, anti-inflammatory effects, and neuroprotective effects of ketamine. It is a unique drug that potentially reaches numerous therapeutic targets.

Ketamine and Chronic Pain

Ketamine's potential to help address chronic pain was first developed in the palliative care setting in patients with chronic or neuropathic pain associated with a cancer diagnosis. A retrospective study at one palliative care center found patients treated with ketamine injections had a significant reduction of pain in the 1–10 scale and reduced their opioid intake by an average of 25%.[1] With the promise shown in these initial patients alongside the safety of sub-anesthetic/analgesic doses of ketamine, the applications became much further reaching. Researchers started exploring other challenging pain conditions like complex regional pain syndrome, fibromyalgia pain syndromes, migraines, chronic back pain, diabetic neuropathy, post-herpetic neuralgia, with convincing results and minimal adverse events. A retrospective study published in *Pain* in 2012 found that all patients in the study reported reduced pain after a series of ketamine infusions and lasting pain relief in 59–85% of the patients.[2] These positive results have been repeated many times and there is ongoing research to try to fully understand how and where ketamine is working in these patients and to determine ideal dosing and protocols for pain management as variation between studies is significant. The challenge with clinical trials is that often the underlying physiology remains unknown despite positive clinical effects.

Ketamine has the potential to impact the changes in the nervous system related to chronic pain in many ways. Ketamine's antagonism of the NMDAR helps stifle the increased volume of pain signals coming from the periphery, primarily at the level of the dorsal horn of the spinal cord. Allowing a recovery period and relief from

overload. This may explain the short-term relief from ketamine as this is its primary mechanism for the management of acute pain, but there seem to be sustained changes as well. Though its activity as a NMDA receptor antagonist is the most widely understood, there is also evidence that it acts on a variety of additional receptors and sites including opioidergic, muscarinic, and monoaminergic receptors. It has also been shown to reduce the occurrence of opioid induced hyperalgesia (mediated by glial cells) and reduce undesirable opioid side effects like nausea. Ketamine also impacts the function and integration of various regions of the brain and directly impacts neuroplasticity. Function MRI studies have demonstrated that ketamine activates areas of the brain that are responsible for descending inhibition and pain modulation over baseline in affected patients. Clearly ketamine affects the nervous system in many ways and provides a potentially far-reaching intervention.

It also cannot be ignored that there is an intimate connection between depression and chronic pain. Ketamine has gained significant popularity recently for its fast-acting antidepressant effects. These effects seem to be directly related to ketamine's ability to alter abhorrent synapses and "dendrite spikes" in the cortex of the brain. These spikes are increased in patients with depression and are associated with the abnormal synapses formed. It is postulated that ketamine may be rewiring circuits in the brain that are deranged in chronic conditions like depression. This may also play a role in the maladaptive neuroplasticity in chronic pain, though this has not been definitively confirmed. Ketamine also eliminates the behavior of learned helplessness in the laboratory setting, which is a common phenomenon in chronic depression as well as chronic pain. Despite not completely understanding all the underlying beneficial mechanisms of ketamine in our chronic pain patients, the potential for relief in a challenging condition is compelling. As we become more skilled at diagnosing and naming chronic pain in veterinary patients as well as incorporating a more biopsychological approach, ketamine will become a more commonly used tool.

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