

**THE ANALGESIC EFFECTS OF EPIDURAL KETAMINE IN DOGS WITH A
CHEMICALLY INDUCED SYNOVITIS**

A COMPARISON BETWEEN PRE – OR POST – INJURY ADMINISTRATION

by

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The objective of this study was to determine if administering epidural ketamine before or after the induction of a sodium urate crystal synovitis provides analgesia in dogs.

In Part I, sixteen dogs were anesthetized with propofol (4 mg kg^{-1} intravenously). A sodium urate crystal synovitis was induced in the right stifle and allowed to develop for 12 hours. These dogs were again anesthetized with propofol and an epidural injection at the lumbosacral space of either ketamine (2 mg kg^{-1}) or placebo (saline containing not more than 0.1 mg ml^{-1} benzethonium chloride) was performed. Analgesia was measured with a force platform and a numerical rating scale (NRS). Assessments were performed before and at 12, 14, 16, 18, 20 and 24 hours after the induction of synovitis. Vertical ground reaction forces were significantly decreased and numerical rating scale scores of total pain were significantly increased after the induction of synovitis in all dogs ($p < 0.05$). No significant differences in ground reaction forces or total pain scores were measured between the ketamine and the control groups at any assessment period.

In Part II, synovitis was induced in the right stifle as described in Part I. Epidural injections at the lumbosacral space followed immediately. Analgesia was assessed at 2, 4, 6, 8, and 12 hours after the epidural injection and the induction of synovitis. Dogs that received ketamine had significantly lower NRS scores two hours after treatment ($p < 0.05$). NRS scores did not differ between the two treatment groups at any other evaluation. Vertical ground reaction forces did not significantly differ between treatment groups at any assessment period.

Results of this study indicate that ketamine, when administered epidurally at a dose of 2 mg kg^{-1} after the induction of a chemical synovitis, does not provide a significant level of analgesia. However, administration of ketamine immediately before the induction of synovitis resulted in a significantly decreased subjective pain score at two hours, but not at later evaluation periods.

Dedicated to my family: Douglass, Ollie, Harrison, and Margo

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LIST OF ABBREVIATIONS

NRS	Numerical Rating Scale
NMDA	N-methyl-d-aspartate
CNS	Central Nervous System
AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
GABA	gamma-aminobutyric acid
PAG	Periaqueductal gray matter
ATP	Adenosine triphosphate
NSAID	Nonsteroidal anti-inflammatory drug
VAS	Visual analogue score
PMN	Polymorphonuclear lymphocytes
PVF	Peak vertical force
I	Impulse area
CP	Conscious proprioception

INTRODUCTION

Conventional therapy for treating pain in veterinary species usually consists of intermittent parenteral administration of traditional analgesics such as opioids and nonsteroidal anti-inflammatory drugs. Unfortunately, inadequate levels of analgesia and periods of breakthrough pain are commonly seen. In an effort to resolve these deficiencies, more resources are being devoted to the study of acute pain and the cellular mechanisms responsible for the establishment of painful states.

As a painful stimulus travels through the body, changes occur within the nervous system that result in a state of hypersensitivity. Once these changes occur, there is a reduction in the stimulus intensity needed to initiate pain and responses to painful stimuli are exaggerated (Lamont et al. 2000). This altered processing of stimuli is thought to be a result of several mechanisms including: an expansion of receptive fields that respond to noxious stimuli, a decrease in the dorsal horn neuron response threshold, and an increase in the magnitude of the dorsal horn's response to painful stimuli (Woolf & Chong 1993, Coderre et al. 1993). The change in excitability of the dorsal horn neuron is attributed in part to the removal of the magnesium blockade on the N-methyl-d-aspartate (NMDA) receptors found within the dorsal horn. With the blockade removed, these receptors are available for activation by the excitatory neurotransmitter glutamate, and exaggerated responses to painful stimuli ensue (Muir 2002).

Techniques to prevent or modify these changes in the central nervous system (CNS) have received increasing attention. In particular, antagonism of the NMDA receptor appears to be useful in preventing the development of hyperexcitable states in

the CNS (Woolf & Chong 1993). NMDA receptor blockade has been shown to not only prevent the induction of central sensitization (Woolf & Chong 1993, Guirimand et al. 2000) but also to diminish or abolish it once it is established (Jones M. W. et al. 2001, Kristensen et al. 1992). As a result of this antagonism, overall pain is decreased (Jones M. W. et al. 2001, Forman 1999).

Selective NMDA antagonists are not available for clinical use. However, several drugs are approved for clinical use that have significant NMDA receptor antagonist activity (Lodge & Johnson 1990). Ketamine, an injectable anesthetic that is commonly used in many species, is a noncompetitive NMDA receptor antagonist (Liu et al. 2001, Jones M. W. et al. 2001). Investigations into the analgesic actions of this drug have been promising. Dogs undergoing forelimb amputation had significantly lower pain scores and were more active after receiving an intravenous constant rate infusion of ketamine in the perioperative period (Wagner et al. 2002). Additionally, epidurally administered ketamine decreased wound sensitivity in horses (Redua et al. 2002), and resulted in a reduction of minimum alveolar concentration in halothane anesthetized ponies (Doherty et al. 1997).

Furthermore, pre-emptive (before tissue injury) administration of ketamine has been shown to prevent central sensitization and provide analgesia well beyond ketamine's duration of action. Amarpal et al. (1999) demonstrated that ketamine given epidurally to dogs before fracture repair decreased post-operative pain for up to 15 days as compared to dogs receiving saline, while neuropathic pain behaviors in rats were

significantly reduced for 2 weeks after the pre-emptive administration of intrathecal ketamine (Burton et al. 1999).

The purpose of this study was to further evaluate the analgesic efficacy of epidurally administered ketamine and to determine if the timing of administration in relation to injury alters the analgesic effect. This was evaluated using a chemically induced synovitis model.

LITERATURE REVIEW

The Pain Pathway

The physiologic process that results in the perception of pain involves the transduction, transmission, and modulation of neural signals that originate in response to noxious stimuli (Lamont et al. 2000). Thought of in its simplest form, the pathway that a noxious stimulus travels to the brain can be thought of as a chain of three neurons (Figure 1). The first order neuron begins in the periphery and travels to the dorsal horn of the spinal cord. Here it synapses with the second order neuron which crosses the spinal cord and ascends to the brain. A second synapse occurs within the thalamus, and the third order neuron projects into the cerebral cortex (Lamont et al. 2000, Muir & Woolf 2001).

Transduction

Nociceptors are specialized nerve endings found in skin, periosteum, bone, joint capsules, pleura, muscles, tendons, viscera, and arterial walls (Lamont et al. 2000). They are divided into two categories: A-fiber mechanoheat and C-fiber mechanoheat

nociceptors. When a noxious stimulus is present, the nociceptors are activated which results in the depolarization of the receptor. This depolarization is converted into a nerve impulse that travels from the periphery to the central nervous system via the axon of the receptor neuron (Lamont et al. 2000, Muir 2002).

Transmission

Ascending axons of the receptors are classified in the same manner as nociceptors. A δ fibers are thinly myelinated large diameter axons capable of transmitting impulses quickly (Lamont et al. 2000). They are responsible for the generation of “first pain” (sharp, well localized, transient pain). C-fibers are smaller unmyelinated axons that therefore conduct impulses more slowly. These fibers contribute to “slow pain” which can be characterized by a more diffuse burning sensation that persists after the termination of noxious stimuli (Lamont et al. 2000).

Both types of afferent nerve fibers extend axons that synapse with neurons located in the dorsal horn of the spinal cord. The dorsal horn of the spinal cord is organized in layers or laminae of functionally distinct cells that form columns (Muir 2002). These columns extend the length of the spinal cord (Figure 2). The majority of A δ fibers form synapses in lamina I, while most C fibers travel to lamina II (Muir 2002). Here the axons may form synapses with one of three types of dorsal horn neurons: (1) interneurons, which may be excitatory or inhibitory and contribute to local modulation of the afferent signals; (2) propriospinal neurons, which are involved in reflex activities; or (3)

projection neurons, which are involved in the projection of afferent signals to supraspinal centers such as the midbrain and cerebral cortex (Lamont et al. 2000).

Communication between afferent axons and dorsal horn neurons depends upon the release of both excitatory and inhibitory neurotransmitters that are produced, stored, and released from the terminal ends of the afferent axons and dorsal horn neurons (Muir & Woolf 2001). Input from both types of fibers (A δ and C) results in the release of the excitatory neurotransmitters, glutamate and aspartate. These neurotransmitters are produced, stored, and released from the terminals of the afferent nerve fibers and the dorsal horn neurons. Glutamate binds to α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate, and N-methyl-D-aspartate (NMDA) receptors. These receptors are ligand-gated sodium and calcium channels. Therefore, once glutamate is bound to the receptor, the neuronal membrane is depolarized by the influx of positive ions (Muir & Woolf 2001). In addition, a variety of other neuropeptides capable of eliciting depolarization of the dorsal horn neurons are released (by C fibers in particular). These neuropeptides include substance P, vasoactive intestinal peptide, neurotensin, and cholecystokinin (Muir & Woolf 2001). The magnitude of neurotransmitter release is proportional to stimulus intensity. Intense stimulation (either thermal or mechanical) results in increased release of glutamate and substance P which potentiates the generation of action potentials that ascend the spinal cord to higher processing centers (Lamont et al. 2000).

Projection and Perception

Afferent nociceptive information is transmitted from the dorsal horn of the spinal cord to supraspinal centers through projection neurons that follow one of several pathways. These pathways include: (a) the spinothalamic, (b) spinoreticular, (c) spinomesencephalic, and (d) postsynaptic dorsal column tracts (Lamont et al. 2000). While all of these tracts are involved in nociceptive transmission to some degree, their relative importance appears to vary considerably between species (Muir & Woolf 2001).

In many species, the spinothalamic tract is the most prominent pathway in the spinal cord and serves a principal role in pain transmission. The spinothalamic tract originates from the axons in several dorsal horn laminae (I, V, VI, and VII), and from there it travels rostrally through the white matter of the spinal cord to the thalamus (Lamont et al. 2000). Here information is integrated and relayed to the somatosensory cortex as well as cortical association areas including the limbic system. These pathways appear to involve the sensory – discriminative aspects of pain as well as the motivational component of pain (including the determination of purposeful behavior) (Muir & Woolf 2001).

Areas of the brainstem also contribute to the perception of pain through the action of the reticular system and the periaqueductal gray matter (PAG) (Lamont et al. 2000). Reticular neurons modulate motivational aspects of pain through projections to the medial thalamus and limbic system, while the periaqueductal gray matter exerts its effect on pain perception through projections to the hypothalamus and thalamus (Lamont et al. 2000).

Signaling between ascending spinal tract projections and the thalamus and cerebral cortex is still not completely understood. It is thought that glutamate and aspartate are the principal excitatory neurotransmitters, while gamma-aminobutyric acid (GABA), glycine, and the monoamines (norepinephrine, serotonin, dopamine) function to inhibit transmission of noxious stimuli (Lamont et al. 2000).

Descending Modulation

While the perception of pain involves the ascension of signals from the periphery to the brain, it is important to note that the transmission of painful stimuli can be modified by inhibitory signals that descend the three-neuron chain. Further study has shown that the transmission of pain is subject to inhibitory influences on four levels: (1) the cortical and thalamic structures (2) the PAG (3) the medulla and pons (4) the spinal cord dorsal horn. The most important of these four appear to be the PAG and the dorsal horn of the spinal cord (Lamont et al. 2000).

Stimulation of the PAG results in outflow of opioid peptides that inhibit the transmission of painful stimuli both at the level of the brain and at the dorsal horn of the spinal cord (Lamont et al. 2000). This outflow of opioids is thought to be mediated by the release of the inhibitory neurotransmitter GABA from an interneuron (Lamont et al. 2000). Additionally, dorsal horn neurons have also been shown to contain dense concentrations of GABA as well as glycine, serotonin, norepinephrine, and the endogenous opioid peptides (Lamont et al. 2000). Release of these neurotransmitters will effectively block transmission of noxious stimuli to supraspinal levels, thereby reducing the degree of pain perception.

Types of Pain

This traditional view of the pain pathway is conceptually easy to understand and has laid the foundation for a more comprehensive understanding of pain. However, it must be understood that the preceding description of physiologic pain can rarely be applied to clinical pain. In most clinical situations, the noxious stimulus is rarely transient and is usually associated with inflammation and nerve injury. In this setting, the classic pathway of three neurons leading from the periphery to the central nervous system becomes less relevant and dynamic changes are evident in both the peripheral and central nervous systems. This pain can be thought of as pathological pain, or clinical pain, that can be further classified by its tissue of origin and duration (Lamont et al. 2000).

Somatic pain is usually described as sharp, well localized, and constant. It results from injury to bone, joints, muscle, and skin (Gaynor 2002). This is in contrast to visceral pain that tends to be described as gnawing, cramping, or aching that is not localized to a well-defined area. Visceral pain is associated with stretching, distention, or inflammation of thoracic or abdominal organs (Gaynor 2002). Lesions in the nervous system can result in neurogenic pain which is usually described by humans as a shooting or burning pain (Gaynor 2002).

When considering the duration of the clinical pain, all three types of pain can be classified as acute or chronic. Acute pain typically has a specific onset, and while it can be present for hours to several months, it usually subsides before the completion of healing (Lamont et al. 2000). Chronic pain persists beyond the normal course of the injury and is usually present for longer than three months (Lamont et al. 2000).

Nervous System Plasticity

Both acute and chronic pathologic pain can produce dramatic changes within the nervous system that result in profound alterations in response to painful stimuli. These changes occur both in the peripheral and central nervous systems and are referred to as “hypersensitivity, wind-up, or sensitization.” Peripherally there is a reduction in the threshold of nociceptor activation while centrally spinal neurons will become more responsive to noxious stimuli (Lamont et al. 2000).

Peripheral Sensitization (Figure 3)

Damaged cells and afferent nerve fibers release a number of sensitizing substances in response to noxious stimuli. Substance P, neurokinin A, histamine, prostaglandins and calcitonin gene-related peptide are released and promote vasodilation and the recruitment of inflammatory cells to the surrounding tissues (Muir & Woolf 2001). In addition, hydrogen ions, potassium ions and adenosine triphosphate (ATP) leak from damaged and inflammatory cells to induce enzymes including proteases, cyclooxygenase-2, and nitric oxide synthase (Muir & Woolf 2001). These mediators continue to amplify the inflammatory response within the surrounding tissues. Together, all of these substances form a “sensitizing soup” that acts synergistically to lower the response threshold for A δ and C fibers to mechanical, thermal, or chemical stimulation (Lamont et al. 2000). This lowering of the response threshold results in an exaggerated response to noxious stimuli (hyperalgesia) and a reduction in the stimulus intensity that is required to initiate pain (Lamont et al. 2000).

Central Sensitization (Figure 4)

In addition to the hyperalgesia associated with tissue damage, neighboring areas not subjected to tissue injury are also sensitized (zone of secondary hyperalgesia) (Muir & Woolf 2001). Furthermore, seemingly innocuous stimuli are capable of eliciting a response from afferent fibers (allodynia) (Gaynor 2002). These hypersensitivities can not be fully explained by changes occurring at the periphery in response to noxious stimuli, and it is now recognized that they are a result of changes in dorsal horn neuron excitability (Melzack et al. 2001).

Bombardment of the dorsal horn neuron by synaptic action potentials generated by A δ and C fibers eventually result in a summation of action potentials and progressively increasing and longer lasting depolarizations of the dorsal horn neuron (Lamont et al. 2000). This “wind-up” of the dorsal horn neuron is mediated by NMDA and possibly tachykinin receptors (Muir & Woolf 2001). Activation of these receptors results in an influx of calcium and activation of intracellular signaling cascades including protein kinase C, nitric oxide synthase, protein kinase A, and calcium calmodulin-dependant kinase (Muir & Woolf 2001). These signaling cascades facilitate receptor function and expression of receptors on the cell surface. For example, activation of the γ isoform of protein kinase C induces phosphorylation of membrane receptors and ion channels resulting in increases in neuronal excitability (Muir & Woolf 2001). Additionally, protein kinase activation in response to substance P increases the efficacy of the NMDA receptors by rendering them less susceptible to magnesium blockade (Muir & Woolf 2001).

These changes in the NMDA receptors in the dorsal horn neuron result in a threshold reduction, an increase in responsiveness, and in the recruitment of novel inputs (Flecknell & Waterman-Pearson 2000). These novel inputs are received from A β fibers, which are large myelinated neurons that are associated with specialized low threshold peripheral mechanoreceptors (Muir 2002). Under normal circumstances, these fibers are responsible for the sensation of touch or vibration, but not pain. However, once the dorsal horn neurons have been sensitized by noxious stimuli, activation of A β fibers will increase the receptive field and contribute to the pain response (Muir & Woolf 2001).

Abolishing or diminishing perceived pain by interruption of the pain pathway described above has been the crux on which traditional analgesic therapies have been based.

Analgesia

Traditional analgesic therapies

Intermittent dosages of analgesic agents have been applied in the perioperative period to accomplish pain relief. The most commonly relied upon of these agents are opioids, local anesthetics, and nonsteroidal anti-inflammatory drugs.

Exogenously administered opioids act upon the endogenous opioid pathway to provide analgesia. Specific opioid receptors are found in the periphery, spinal cord, and brain (Pascoe 2000) these receptors are coupled to G proteins which may activate K⁺ and Ca⁺² channels or exert effects on adenylyl cyclase (Uhl 1999). Of these receptors, the mu and kappa receptors are the most clinically important (Lamont et al. 2000). Opioid

administration produces analgesia by (1) inhibiting the transduction of noxious stimuli at the periphery, (2) modulating the spinal cord response to pain, and (3) reducing the perception of pain in the supraspinal centers (Lamont et al. 2000) (Figure 5).

Local anesthetics prevent transmission of painful signals by blocking sodium channels (Gaynor & Mama 2002). This blockade prevents the influx of sodium ions and therefore cell depolarization. Modulation of the pain response at the level of the spinal cord is also seen with systemic administration of these drugs (Lamont et al. 2000) (Figure 5).

It has been postulated that nonsteroidal anti-inflammatory drugs (NSAID) provide analgesia by both peripheral and central actions. Peripherally, the analgesic action of these drugs is attributed to the inhibition of cyclooxygenase and lipoxygenase leading to the prevention of prostaglandin synthesis and prevention of the sensitization of the nociceptor (Lamont et al. 2000). There is also considerable evidence that NSAIDs act within the spinal or supraspinal levels (Cherng et al. 1996). While the exact site and mechanism of action remains unclear, it is thought that inhibition of prostaglandin synthesis at the level of the spinal cord as well as modulation of cellular and intracellular processing is involved (Cherng et al. 1996) (Figure 5).

Multiple routes of administration exist for analgesic agents. Local anesthetics may be administered topically or injected locally. Additionally, recent studies have shown that constant rate intravenous infusions of lidocaine may be beneficial in managing clinical pain states (Lamont et al. 2000). The opioid analgesics may be given

via oral or parenteral, intra-articular, and transdermal routes. The NSAIDs are commonly administered by oral ingestion or injection.

Unfortunately, the administration of opioids, local anesthetics and NSAIDs is not without side effects. Local anesthetic administration can be associated with hypotension, while opioid analgesics can depress the respiratory system, result in dysphoria, as well as urine retention when given epidurally (Lamont et al. 2000). Detrimental side effects resulting from the administration of NSAIDs are well documented and can include coagulopathies, vomiting, gastric ulceration, and renal disease (Flecknell & Waterman-Pearson 2000). In an effort to reduce the occurrence of these side effects, different routes of administration have been investigated. In particular, epidural administration of analgesics has been evaluated.

Epidural Analgesia

Experimental dogs first received epidural analgesics in 1885; however, the technique was not widely accepted for clinical use in dogs until 1958 (Jones R. S. 2001).

Administration of analgesics into the epidural space places the drug in close proximity to their site of action either near the receptors located in the dorsal horn of the spinal cord or nerves as they enter and leave the spinal cord (Torske & Dyson 2000). For this reason, binding to specific receptors is maximized, allowing lower total doses to produce similar analgesia to systemically administered drugs. Due to the reduction in dosage, administration of drugs by the epidural route may potentially reduce or prevent the development of the detrimental side effects previously discussed. Onset of action and duration of action are dependent on the drug's lipid solubility and pK_a (Torske & Dyson

2000). Drugs with high lipid solubility will have a rapid onset of action with short duration while the converse is true of drugs with low lipid solubility.

Epidural injections in the dog are usually performed at the lumbosacral space (Figure 6). The technique is relatively simple to perform and does not require specialized equipment. The animal must remain still for the duration of the procedure; therefore, these injections are usually performed with the animal under general anesthesia or chemically restrained. Once anesthetized, the animal is placed in sternal recumbency and an area over the lumbosacral space is clipped and aseptically prepared. The lumbosacral space is located by placing the thumb and middle finger on the wings of the ilium. The index finger of the same hand is then used to locate the lumbosacral space just caudal to the seventh lumbar vertebra. A 20 or 22 gauge spinal needle is then inserted on midline at an angle that is perpendicular with the skin. The needle is advanced slowly into the epidural space. Proper location of the needle can be confirmed by the use of the hanging drop technique (Torske & Dyson 2000). Once the spinal needle has been inserted through the skin of the animal, the stylet is removed and a drop of sterile saline is placed in the hub of the needle. The needle is then advanced through the ligamentum flavum and into the epidural space. At this time, the subatmospheric pressure in the space draws the saline into the needle. After confirming needle placement, the drug can then be administered with little to no resistance felt on injection.

Contraindications for the injection of drugs epidurally include coagulopathies and sepsis (Torske & Dyson 2000). During needle insertion, it is possible to puncture or lacerate any of the numerous small blood vessels that pass through the epidural space

resulting in ongoing hemorrhage in an animal with a bleeding disorder. This hemorrhage may result in increasing pressure within the spinal canal that can result in paresis or paralysis (Torske & Dyson 2000). Any type of skin infection or dermatitis on the skin that overlies the lumbosacral space or sepsis is also a contraindication for the performance of an epidural injection. The potential risk of introducing infectious material into the spinal canal outweighs the benefits of providing analgesia in this way.

The use of opioids epidurally for analgesia has been reviewed (Jones R. S. 2001). Opioids act on receptors found in the dorsal horn of the spinal cord to produce analgesia. They are thought to work presynaptically by preventing the release of substance P and postsynaptically by hyperpolarizing the cells (Jones R. S. 2001). Therefore, they are able to provide analgesia without effecting motor function. Epidurally administered opioids have been shown to provide analgesia for both visceral and somatic pain that can persist in the dog for 10 to 24 hours (Torske & Dyson 2000). Side effects of epidural opioids include pruritis, nausea, vomiting, urinary retention, and respiratory depression (Jones R. S. 2001).

Local anesthetics are also used epidurally. Their mechanism of action is thought to be the result of three mechanisms. Local anesthetics may diffuse into the paravertebral areas and block nerves distal to their dural sheaths. Additionally, the drugs may diffuse across the dura and into the subarachnoid space where they act directly on the nerve roots or the spinal cord (Torske & Dyson 2000). As the drug is absorbed sympathetic nerves are blocked first, followed by sensory and finally motor nerves. Diaphragmatic function is not impaired unless the drug spreads cranially to the third through fifth cervical

vertebrae (Jones R. S. 2001). Arterial hypotension has been reported with epidural injection of local anesthetics (Torske & Dyson 2000).

The epidural use of NSAIDs has also been evaluated. These drugs are believed to act centrally at the spinal cord and perhaps supraspinally (Cherng et al. 1996).

Administration of these drugs epidurally has been shown to provide analgesia in dogs (Karnik 2003). However, gastrointestinal side effects such as ulcers have been seen after repeated administration (Gallivan et al. 2000).

The administration of analgesic drugs (either systemically, locally, or epidurally) traditionally occurs during the operative or postoperative period. This method, however, is not always effective at controlling clinical pain. Therefore, with further elucidation of the pain pathway and the mechanisms involved in the development of hypersensitivity, investigators have studied the effect of timing of drug administration on the degree of analgesia produced. Particularly the effect of pre-emptive analgesic administration or administration before actual tissue injury has been investigated.

Pre-emptive analgesia

Pre-emptive analgesia involves the administration of an analgesic drug in order to prevent the establishment of altered nociceptive processing that results in an increase in pain perception (Kissin 2000). This concept was first proposed by in 1913 by Crile (Woolf & Chong 1993). The theory was based on his clinical observations that when regional anesthetic blocks were used in combination with general anesthesia, the development of painful scars was decreased. Interest in the idea was renewed after a

series of animal studies conducted by Woolf and others in the 1980's elucidated the mechanisms of action of central sensitization (Kissin 2000).

However, experimental and clinical studies have produced conflicting results. The pre-emptive intrathecal administration of an NMDA receptor antagonist in rats before formalin injection (a peripheral model of inflammation) decreased nociception (Berrino et al. 2003). Additionally, the pre-emptive administration of pethidine (a mu receptor agonist) to dogs undergoing ovariectomy resulted in the prevention of allodynia and a reduction in wound hyperalgesia (Lascelles et al. 1997). Conversely, intrathecal morphine or bupivacaine did not exert a pre-emptive effect when given to rats in a model of postoperative pain (Brennan et al. 1997).

Despite the positive preliminary studies involving the pre-emptive administration of analgesics, the reduction in postoperative pain appears to be of uncertain clinical significance (Kissin 2000). However, as the discovery of the receptors, chemical mediators, and intracellular signaling cascades involved in central sensitization becomes more clear, renewed interest is emerging for the evaluation of other possible analgesic agents. Investigators, focusing on the role that the NMDA receptor plays in central sensitization, are investigating the role of NMDA receptor antagonists in the prevention of "wind-up" pain.

NMDA receptors and analgesia

Nociceptor activation and bombardment of the dorsal horn of the spinal cord results in the release of glutamate, an excitatory neurotransmitter that binds to NMDA receptors. Once activated, the NMDA receptors allow the influx of calcium and sodium

ions and intracellular signaling cascades are triggered that result in the sensitization of the dorsal horn (Muir & Woolf 2001).

Investigators have shown that NMDA receptor antagonism produces antinociception. Berrino et al (2003) demonstrated that the intraperitoneal administration of NMDA receptor antagonists produced analgesia in rats in the formalin test, while the inhibition of glutamate release or NMDA receptors attenuated pain in both acute and chronic models (Fundytus 2001). The NMDA receptor antagonist, CPP, abolished neurogenic “wind-up” pain after intrathecal administration (Kristensen et al. 1992). Other mechanisms for the analgesia provided by NMDA receptor antagonists have been reported. Forman (1999) reports that in addition to the direct effects on the cellular cascades, NMDA receptor blockade inhibits nitric oxide synthase that results in opioid mediated analgesia. Additionally, it appears that dopamine receptors that are coupled to adenylyl cyclase are also activated which will also produce analgesia (Forman 1999).

Ketamine

Unfortunately, selective NMDA antagonists are not available for clinical use. However, several drugs are approved for clinical use that have significant NMDA receptor antagonist activity (Lodge & Johnson 1990). Ketamine, an injectable anesthetic that is commonly used in many species, is a noncompetitive NMDA receptor antagonist (Liu et al. 2001, Jones M. W. et al. 2001). It is a congener of phencyclidine, and it occurs as a white, crystalline powder (Plumb 1995). Anesthesia is characterized by profound amnesia and catalepsy (Muir et al. 2000). Psychosomatic effects such as hallucinations,

agitation, and fear have been reported in humans and appear to occur in veterinary species receiving large doses (Muir et al. 2000).

Pharmacokinetic studies performed after intravenous and epidural administration reveal that ketamine follows a two compartment open model when administered intravenously and an extravasal two-compartment model when given epidurally (Pedraz et al. 1987). After intravenous injection, peak plasma levels of ketamine are seen within 1 hour and rapidly decline. The maximum plasma concentration of ketamine after epidural administration was measured at 0.38 ± 0.27 hours, with an implied plasma half-life of 4.82 ± 2.30 hours (Pedraz et al. 1987). The liver metabolizes the drug principally by demethylation and hydroxylation. The metabolites and unchanged ketamine are then excreted in the urine (Plumb 1995).

Investigations into the analgesic actions of this drug have been promising. (Schmid et al. 1999) Schmid (1999) provides a review of the use and efficacy of low-dose ketamine in the treatment of acute pain. In humans, ketamine has been shown to decrease central sensitization and pain especially in those patients with clinical pain that is difficult to treat with traditional analgesics. Fibromyalgia patients receiving intravenous ketamine showed reduced pain intensity and increased pressure pain tolerance as compared to patients receiving placebo (Graven-Nielsen et al. 2000). Additionally, patients with critical limb ischemia showed significant pain relief after a single intravenous infusion of ketamine (Mitchell & Fallon 2002). Opioid tolerance, which leads to the need for increasing doses of opioid analgesics, can be reversed by the administration of “small-dose” ketamine (Eilers et al. 2001). Long term treatment with

ketamine has also been reported with positive results (Kelpstad et al. 2001). However, not all studies regarding the analgesic efficacy of ketamine in humans have produced positive results. The addition of ketamine to morphine for patient controlled analgesia after major abdominal surgery provided no benefit to patients postoperatively (Reeves et al. 2001). Information in veterinary species is limited, but some evidence exists regarding the analgesic benefit of ketamine. Dogs undergoing forelimb amputation had significantly lower pain scores and were more active after receiving ketamine in the perioperative period (Wagner et al. 2002).

The pharmacokinetic study performed by Pedraz et al (1987) demonstrated that epidural ketamine not only had a longer plasma half life, but also had less systemic effects than ketamine administered by the intravenous route. For these reasons, and to deliver the drug in close proximity to NMDA receptors while minimizing the potential for adverse side effects, the analgesic action of epidurally administered ketamine has also been studied. Beltrutti et al (1999) provides a review of the epidural and intrathecal administration of ketamine in humans. However, just as with systemic administration, conflicting results are reported.

Epidurally administered ketamine in veterinary species appears to produce more consistently positive results. Epidural and intrathecal administration of ketamine produced analgesia in the dog (Baha & Malbert 1991, Martin et al. 1996, Rao et al. 1999) and provided perineal analgesia in the horse, goat, and cow (Aithal et al. 1996, Aithal et al. 1997, Gomez De Segura et al. 1998). Additionally, epidurally administered ketamine

decreased wound sensitivity in horses (Redua et al. 2002), and resulted in a reduction of minimum alveolar concentration in halothane anesthetized ponies (Doherty et al. 1997).

The timing of ketamine administration has also been investigated. Hoping to maximize the analgesic effects by preventing or reducing central sensitization, investigators have studied the efficacy of pre-emptive administration. It appears that pre-emptive (before tissue injury) administration of ketamine prevents central sensitization and provides analgesia well beyond ketamine's duration of action. Amarpal et al. (1999) demonstrated that ketamine, given epidurally to dogs before fracture repair, decreased post-operative pain for up to 15 days as compared to dogs receiving saline; while neuropathic pain behaviors in rats were significantly reduced for 2 weeks after the pre-emptive administration of intrathecal ketamine (Burton et al. 1999). Additionally, dogs that received ketamine before ovariohysterectomy required significantly less rescue analgesics, had lower pain scores, and delayed wound hypersensitivity as compared to those dogs that received ketamine postoperatively (Slingsby & Waterman-Pearson 2000).

Few studies exist that describe the safety of epidurally administered ketamine. Repeated intrathecal injections of preservative free ketamine in the rabbit resulted in no significant histopathologic changes as compared to control (Borgbjerg et al. 1994). Infusion of ketamine containing the preservative benzethonium chloride through an epidural catheter for seven days lead to a focal lymphocytic vasculitis in the medullary tissue, nerves, and leptomeninges near the catheter site. No other histological changes were noted and no clinical signs or neurologic deficits were observed (Stotz et al. 1999).

While these studies are promising, it is difficult to determine how effective the administration of ketamine will be in veterinary patients. This difficulty arises from the challenges of pain assessment.

Evaluation of Analgesia

It is well documented that animals respond to noxious stimuli and pain with both behavioral and physiologic responses (Firth & Haldane 1999). However, pain management in veterinary species is still hindered by the lack of any validated method to assess pain and/or response to treatment.

Pain scoring systems

Various scales have been developed for the assessment of pain in veterinary species although none have gained wide spread acceptance. These range from simple descriptive scales to slightly more complex numerical rating scales. The simple descriptive scale usually has four to five degrees of severity, for example: no evidence of pain, mild pain, moderate pain etc. This type of scale is straightforward and easy to use, but does not allow for small changes in pain to be measured (Muir et al. 2000). The visual analogue scale (VAS) is widely used in human pain assessment. The VAS is a line usually 10 cm in length with only the limits at either end described (0 meaning no pain, 100 mm meaning the worst pain imaginable). An observer marks anywhere along the line where he believes the perceived pain falls. This technique has been used in many veterinary studies (Lascelles et al. 1997, Slingsby & Waterman-Pearson 1998). This method of pain assessment is subject to a great deal of observer variability, however, and the observer must be trained in the scale's use (Firth & Haldane 1999).

While researchers like Holten et al. (1998) have shown that physiologic factors such as heart rate, respiratory rate, and pupil size are not useful indicators of pain in hospitalized dogs, others have shown that a combination of physiologic and behavioral parameters can be useful in assessing pain (Firth & Haldane 1999, Hellyer & Gaynor 1998, Holton et al. 1998). A numerical rating scale (NRS) combines both physiologic and behavioral categories. A numeric score is given to the different categories and then summed to yield an overall score. This total score is used to base analgesic therapy (Mathews 2000). This type of scale has been used in veterinary studies (Firth & Haldane 1999, Conzemius et al. 1997, Hellyer & Gaynor 1998) and shown to have excellent agreement between evaluators (Firth & Haldane 1999).

Efforts to establish more objective measures of pain have led to the development of tools such as the force platform.

Force platform

The force platform is a specialized device that measures ground reaction forces. Ground reaction forces are those external forces that are generated between an object (such as an animal's paw) and the ground (Gurevich et al. 1994). As an animal places a paw on the force plate, the plate will move in proportion to the forces placed on it. Transducers located under the force plate, are triggered by the applied force and send signals to a computer. This computer will convert the amount of movement of the force plate into forces. These forces represent the summation of truncal and limb forces transmitted through one limb to the ground (Decamp 1997). Three ground forces are generated by the force plate: vertical (F_z), craniocaudal (F_y), and mediolateral (F_x).

Impulse area, or the area under the curve, is also measured in all three directions (Decamp 1997). Of the forces measured, the vertical ground reaction forces most directly measure weight bearing and are used most often as objective measures of limb function (Figure 7) (Decamp 1997).

The force plate has been used in previous studies as a measurement of analgesic and surgical success as well as return to function. Millis et al (2002) and Cross et al. (1997) used the force plate to evaluate the success of an NSAID in preventing lameness in a synovitis model in dogs. While Jevens et al. (1996) and Bubenik et al. (2002) used the platform to objectively evaluate pain and lameness and by extension, pain, after different surgical procedures.

While the pain assessment scales discussed above and the force platform aids researchers in the assessment of analgesia provided by different therapies, it is important to note that the overall assessment of pain in veterinary species remains very subjective.

Animal Models of Pain

Accurate assessment of analgesic therapy success in the laboratory is not only dependent on the subjective evaluations of an observer, but also the use of a reproducible, consistent model for pain.

Investigators have developed animal models for different types of pathologic pain states. Neurogenic pain models have involved lesions of the trigeminal system (Anderson et al. 1971) as well as dorsal root sections (Basbaum 1974). More recently investigators have been able to model neurogenic pain by placing loose ligatures around

the sciatic nerve (Bennett & Xie 1988). The sutures are absorbable, therefore making the process self-limiting.

Models for acute pain have also been described. Formalin injection of the dorsal or plantar aspects of the fore- or hind paws of rats results in brief and relatively mild pain for the animals. These injections are associated with easily recognizable pain behaviors such as guarding or flinching of the affected limb that can be easily quantified for study (Dennis & Melzack 1979).

The polyarthritic rat model for pain has been used as a model for chronic pain (Butler 1990). Polyarthritis is induced in rats by the injection of killed *M. butyricum* in an inert medium subcutaneously at the base of the tail. In the acute phase, severe inflammation develops with swelling of the tibiotarsal joints, hind limbs, the distal tail, and often carpal joints (Butler 1990). These rats become listless, lose weight, and have a productive cough, bloody urine, and conjunctivitis (Butler 1990). Obviously, from this description, these rats have a mixture of widespread autoimmune inflammation and metabolic abnormalities, all of which can influence changes in the peripheral and central nervous system thereby clouding the assessment of analgesic efficacy.

Sodium urate crystal synovitis model for pain

Newer, limited animal models have been developed that allow more specific observation or stimulation of the pain pathway (Butler 1990). Of these models, the sodium urate crystal model has proven to be very useful. In this model, sodium urate crystals are injected into a joint. Once there, crystal induced inflammation ensues and within 2 to 4 hours, peak synovitis occurs (Schumacher et al. 1974). The pathogenesis of

this crystal induced inflammation is complex and dependent on several factors. First, the protein binding of the crystals is important. Sodium urate crystals have positively charged ions at their surface that are available for binding to negatively charged groups such as proteins and cell membrane phospholipids (Fam & Schumacher 1988). The inflammatory cells and the phagocytosis of crystals as well as the chemotactic factors and inflammatory mediators also play an important role in the development of this synovitis (Fam & Schumacher 1988). Of these mediators, prostaglandin E is thought to play a major role (Carlson et al. 1986). The pathogenesis of crystal induced synovitis is described in Figure 8. Histopathologic studies of the synovium and synovial fluid reveal an increase in monocyte/macrophage and mast cell densities followed by an influx of polymorphonuclear lymphocytes (PMN) after crystal injection (Schumacher et al. 1974). Peak concentration of these cell types occurs at 2 and 24 hours after injection respectively (Schiltz et al. 2002). Studies of the synovium of dogs injected with sodium urate crystals weekly for four weeks show that a chronic inflammatory state, characterized by a thickening of the synovial membrane and infiltration of inflammatory cells, will occur (Schumacher et al. 1974). However, a single intra-articular injection of urate crystals does not appear to cause any clinically evident long-term effects (Cross et al. 1997). This is in contrast to other models for pain such as the transection of cranial cruciate ligaments that will induce chronic degenerative changes in the affected stifle.

The urate crystal model for synovitis has been used as a model for pain in several studies (Cross et al. 1997, Millis et al. 2002, Rumph et al. 1993). Peak effect is observed two to four hours after intra-articular injection of a urate crystal suspension and clinical

lameness can be observed for 24-72 hours (Fam & Schumacher 1988). Because the lameness is transient, the urate model is useful for simulating an acute lameness such as that associated with surgery or musculoskeletal disorders.

AIMS OF STUDY

The purpose of this study was to further evaluate the analgesic efficacy of ketamine and to determine if the timing of administration in relation to injury alters the analgesic effect. Ketamine, administered epidurally to dogs before or after the induction of a chemically induced synovitis, was evaluated.

MATERIALS AND METHODS

This study was conducted in two parts under a protocol approved by the Virginia Polytechnic Institute and State University Animal Care and Use Committee. A time line of events occurring in both parts of the study can be seen in Figure 9.

Sodium urate crystal preparation

A sterile sodium urate crystal suspension (10 mg ml⁻¹) was prepared using a modification of a previously described method (Cross et al. 1997, Millis et al. 2002, Rumph et al. 1993). Sodium urate crystals (2,6,8 trihydroxypurine, Sigma-Aldrich Corporation, St. Louis, MO, USA) were mixed with sterile water using a mechanical stirrer for up to 12 hours. The resulting suspension was placed in an ultrasonic vibrator for sixty minutes and then placed into multi-dose vials and autoclaved (120°C for 10 minutes). Before being used, the pH of the suspension was adjusted to 7.0 –7.2 by either

the addition of hydrochloric acid (hydrochloric acid, Sigma-Aldrich Corporation, St. Louis, MO, USA) or sodium hydroxide (sodium hydroxide, Sigma-Aldrich Corporation, St. Louis, MO, USA).

Part I

Sixteen mixed breed dogs of either sex and weighing between 13 and 30 kg were used. Prior to beginning the protocol, the dogs were determined to be healthy by physical, orthopedic, and neurologic examination. Dogs were housed in separate concrete runs and provided food and water ad libitum throughout the study. Leash training and acclimation to the force plate lab was conducted daily for two weeks.

On the day of study, the right cephalic vein was catheterized with an over the needle intravenous catheter (20 gauge 1.88 inch) (Angiocath, Becton Dickinson, Sandy, UT, USA). Anesthesia was induced with propofol (PropoFlo, Abbott Laboratories, North Chicago, IL, USA) and titrated to effect (approximately 4 mg kg⁻¹ intravenously). Once induced, the dogs were placed in lateral recumbency and the area over the right stifle was clipped and aseptically prepared. One milliliter of a sterile solution containing 10 mg of sodium urate crystals was injected by lateral parapatellar injection as previously described (Cross et al. 1997, Millis et al. 2002, Rumph et al. 1993). Intra-articular injection was confirmed by aspiration of synovial fluid. The dogs were then allowed to recover and returned to their runs.

The synovitis was allowed to develop for twelve hours. After intravenous catheter placement, the dogs were again anesthetized with propofol (approximately 4 mg kg⁻¹ intravenously). The dogs were placed in sternal recumbency and the area over the

lumbosacral space was clipped and aseptically prepared. An epidural injection was then performed using a 20 gauge, 2.5 inch spinal needle (Spinal Needle Quincke type point, Becton Dickinson, Franklin Lakes, NJ, USA). Placement of the needle into the epidural space was confirmed by the hanging drop technique (Torske & Dyson 2000). At this time, the dogs were randomly assigned to one of two treatment groups. Dogs in the ketamine group received ketamine (Ketaset, Fort Dodge Animal Health, Fort Dodge, IA, USA) at a dose of 2 mg kg^{-1} (20 mg ml^{-1}), while dogs in the control group received an equal volume ($1 \text{ ml } 10 \text{ kg}^{-1}$ of body weight) of a control solution. The control solution consisted of saline containing not more than 0.1 mg ml^{-1} of benzethonium chloride (diisobutylphenoxyethoxyethyl-dimethylbenzylammonium chloride, Sigma-Aldrich Corporation, St. Louis, MO, USA), the preservative used in ketamine. The investigator was blinded to the group assignments. Dogs were allowed to recover fully from the brief anesthetic period during which subjective observations of the recovery were noted.

Evaluations using both the force platform and the numerical rating scale (NRS) were conducted prior to the induction of synovitis (time 0), 12 hours after the injection of sodium urate crystals (preceding the epidural injection), and then at 14, 16, 18, 20 and 24 hours after the injection of urate crystals (Figure 9). At each evaluation period 5 to 6 ml of blood was withdrawn from the dog for serum ketamine analysis. This blood was placed in a collection tube containing no anticoagulants and allowed to clot. It was then centrifuged at 12000 rpm for five minutes and the serum drawn off. The serum was then placed in a freezer (-20° C) for later analysis with gas chromatography. After all

evaluations were completed, all dogs received 10-15 mg kg⁻¹ of etodolac (Etogesic, Fort Dodge Animal Health, Fort Dodge, IA, USA) by mouth once daily for two days.

Part II

The second part of this study was designed to determine the analgesic action of epidural ketamine given prior to the induction of a sodium urate crystal synovitis. The protocol was conducted after the completion of Part I and was approved by the Animal Care and Use Committee of Virginia Polytechnic Institute and State University.

Sixteen mixed breed dogs of either sex weighing between 14 and 28 kg were used. Dogs were determined to be healthy and housed as in Part I. Leash training and acclimation to the force plate lab was conducted once daily for one week.

Similar to Part I, the right cephalic vein was catheterized, and anesthesia was induced with propofol (approximately 4 mg kg⁻¹ intravenously). Intra-articular injection of the right stifle with 10 mg (1ml) of a sodium urate crystal suspension was then performed as previously described. Immediately following injection of urate crystals, the dogs were placed in sternal recumbency, and an epidural injection was performed by a blinded investigator. Again the dogs were randomly assigned to one of two treatment groups. Dogs in the ketamine group received ketamine at a dose of 2 mg kg⁻¹ (20 mg ml⁻¹), while dogs in the control group received an equal volume (1 ml 10 kg⁻¹ of body weight) of the control solution. As the dogs recovered from the brief anesthetic period, subjective observations of the recovery were made and recorded.

As in Part I, evaluations using both the force platform and the numerical rating scale (NRS) were conducted. Assessments occurred before the induction of synovitis and

epidural injection (time 0) and then at 2, 4, 6, 8, and 12 hours after the induction of synovitis and epidural injection (Figure 9). Blood samples were withdrawn as in part I. After all evaluations were completed, all dogs received 4.4 mg kg^{-1} of carprofen (Rimadyl, Pfizer Animal Health, Exton, PA, USA) by mouth once daily for two days.

Pain Scoring

An investigator, unaware of treatment group assignment, using the numerical rating scale seen in Table 1, assigned subjective pain score. Interactive behavior was evaluated by looking through a window into the room that contained the run in which the dog was housed, and then while the investigator approached the dog's run. All other parameters were evaluated after the dog was walked to the force plate laboratory.

Range of motion was evaluated using goniometry. The dog was placed in left lateral recumbency and the goniometer was placed on the lateral side of the limb with the affected stifle held at a natural angle. The limb was then slowly flexed until the dog resisted further flexion. The degree of flexion was noted, and the limb was then extended until the dog resisted. The two resulting angles were summed to yield a total range of motion measurement. This measurement was compared to the baseline value and a score was assigned according to the percentage of change.

Tolerance was measured in newtons with a digital force gauge (DFG70, Omega Engineering Inc., Stamford, CT, USA). The gauge was applied to the lateral parapatellar region of the affected stifle with a steady rate of pressure until the dog exhibited avoidance behavior (turning of head or withdrawing of limb) or 50 newtons of force was

applied. This was performed three times in quick succession and the mean of the three measurements was calculated.

The scores for all seven parameters were then summed to yield a total pain score. Any animal receiving a total pain score of 11 or greater was rescued from the protocol and administered 1 mg kg⁻¹ morphine (morphine sulfate, Elkins Sinn Inc., Cherry Hill, NJ, USA) subcutaneously.

Force plate evaluation

Dogs were led at a trot over a centrally mounted force plate in a 15 m runway. A valid force plate trial consisted of ipsilateral right fore and hind limb strikes occurring entirely on the force platform, with no contralateral limb footstrike. For this study, the dogs were required to maintain a trotting gait with forward velocity of 1.7-2.0 m s⁻¹ with an acceleration of ± 0.5 m sec⁻². Trials were video recorded from two perpendicular views for further evaluation. Trials were discarded for distracting head motion or gait alteration. The first five valid trials were used in data analysis.

Of the ground reaction forces measured by the force plate, two were selected for evaluation. Peak vertical force (PVF), the maximum force that a dog would exert on the limb, and impulse area (I), the amount of force exerted on the limb multiplied by time in seconds, was determined for each trial. All values were normalized as a percent of each dog's body weight. If, at the time of the evaluation, the dog would not bear weight on the affected limb or if the dog was unable to move over the force plate with the required velocity and gait, a value of 0 was recorded.

Statistical Analysis

Force plate and numerical rating scale data obtained in Part I was analyzed using repeated measures analysis of variance to determine if a time, treatment effect, or a treatment by time interaction was present. The numerical rating scale data obtained in Part II was analyzed in the same manner. Due to the number of evaluations for which force plate data was not obtainable in Part II, the force plate data was treated as a categorical response. Dogs that were bearing weight on the affected limb were assigned a score of 1. Dogs that did not bear weight on the affected limb were assigned a score of zero. This data was analyzed with a repeated measures analysis using a generalized estimating equations approach. Significance was set at $p < 0.05$

RESULTS

Part I

All dogs completed the study. Force plate data (PVF and I) are represented graphically in Figures 10 and 11. In both groups, peak vertical force was significantly decreased 12 hours after the injection of sodium urate as compared to baseline. Significant decreases in impulse area were also observed between baseline and the time 12 evaluation in both groups. No significant treatment effect or treatment by time interaction occurred at any evaluation period after the epidural injection.

The NRS scores (total pain) of both groups were significantly increased at the time 12 evaluation as compared to baseline (Figure 12). But again, no significant treatment effect or treatment by time interaction occurred at any other time.

Rear limb ataxia and conscious proprioception (CP) deficits as well as ptialism and nystagmus were observed in three dogs following epidural injection. In two of these dogs, these clinical signs resolved within 60 minutes. However, rear limb ataxia and CP deficits persisted for approximately 150 minutes in the third dog. All three of these dogs received ketamine epidurally. None of the control dogs exhibited similar clinical signs after epidural injection.

Part II

The NRS scores are represented graphically in Figure 13. Dogs that received ketamine had significantly decreased pain scores as compared to the control dogs at 2 hours. The dogs receiving the control solution had significantly higher pain scores at 2 hours as compared to baseline. Significant differences between treatment groups were not seen at any other evaluation time.

Due to the number of evaluation periods for which force plate data was unobtainable (dogs would not bear weight on the limb, or move over force plate with proper gait) in this study, the force plate data was treated as a categorical response. The force platform results are seen in Figure 14. No significant differences in the number of dogs that would bear weight on the affected stifle were demonstrated between treatment groups at any evaluation.

Observations recorded after the epidural injection are summarized in Table 2. As in Part I, the most common clinical signs observed were hind limb ataxia and rear limb conscious proprioception deficits. All eight of the dogs listed in Table 2 received

ketamine epidurally. And again, no dogs receiving placebo exhibited similar clinical signs.

The results of the serum ketamine analysis for Part I are shown in Table 3. Due to the apparent spurious results (ketamine levels detected in dogs receiving placebo) this data was not analyzed statistically. Additionally, the analysis of the serum obtained from dogs in Part II has not been performed.

One dog that had received placebo was rescued from the protocol at 2 hours due to a NRS score of 12. Data obtained from this dog was not used in the analysis.

DISCUSSION

A significant decrease in pain score was observed in dogs receiving 2 mg kg^{-1} of ketamine epidurally before the induction of a sodium urate crystal synovitis. The reduction in pain scores as compared to those dogs receiving placebo was seen only at the evaluation performed 2 hours after the epidural injection. Epidural ketamine administered to dogs twelve hours after the induction of a sodium urate crystal synovitis did not provide measurable levels of analgesia.

The analgesic properties of ketamine appear to be mediated by action on a number of receptor systems. Ketamine will bind stereospecifically to opioid receptors (Finck & Ngai 1982, Forman 1999, Hustveit et al. 1995) as well as cholinergic receptors (muscarinic and nicotinic) (Scheller et al. 1996, Hustveit et al. 1995). Additionally, ketamine may activate the monoaminergic descending inhibitory system (Crisp et al. 1991) and produce local anesthetic effects by blockade of sodium channels (Yaksh 1996).

All of these interactions may result in analgesia, but recently ketamine's action at the NMDA receptor has been the focus of study.

NMDA receptors are involved in the development and maintenance of central sensitization in response to tissue injury and pain. Ketamine, by noncompetitively binding at the NMDA receptor, prevents the influx of calcium ions into the cells of the dorsal horn neuron. This blockade of ion flux prevents depolarization of the neuron, transmission of painful stimuli, and the development of central sensitization (Beltrutti et al. 1999). This ability to prevent the establishment of central sensitization, known as pre-emptive analgesia, may account for the lower pain scores seen in the dogs receiving ketamine before the induction of synovitis as compared to those receiving the drug after the development of the synovitis.

The concept of pre-emptive analgesia is controversial at best. The idea, first introduced by Crile (Kissin 2000) and then furthered by animal studies conducted by Woolf (1993), asserts that analgesic techniques initiated before noxious stimuli will prevent the development of hypersensitive pain states. Additionally, pre-emptive administration of analgesic can potentially confer benefits long after the duration of action of the administered drug (Shafford et al. 2001, Moiniche et al. 2002, Kissin 2000).

Whether ketamine produces pre-emptive analgesia is still not clear. It has been argued that ketamine can not provide pre-emptive analgesia because binding to the NMDA receptor can only occur when the receptor has been opened by painful stimuli (Arendt-Nielsen et al. 1995). A clinical study in human patients undergoing abdominal surgery further showed that pre-emptive ketamine did not reduce pain or post-operative

opioid use (Kucuk et al. 1998). In contrast, others have demonstrated that pre-emptive ketamine administration can significantly reduce pain for weeks (Amarpal et al. 1999, Burton et al. 1999). While this study provides evidence that epidurally administered ketamine produces a reduction in pain scores for a short period of time when administered before the induction of a synovitis, it is possible that the design of this study (particularly the model for pain) may have limited our ability to draw clear conclusions regarding the analgesic efficacy of epidurally administered ketamine.

The urate crystal model for synovitis has been used as a model for pain in several studies (Cross et al. 1997, Millis et al. 2002, Rumph et al. 1993). Peak synovitis is observed two to four hours after intra-articular injection of a urate crystal suspension and clinical lameness can be observed for 24-72 hours (Fam & Schumacher 1988). The inflammatory reaction induced within the joint is thought to be mediated by prostaglandin E₂. Histopathologic studies reveal an increase in monocyte/macrophage and mast cell densities followed by an influx of polymorphonuclear lymphocytes (PMN) after crystal injection. Peak concentration of these cell types occurs at 2 and 24 hours after injection respectively (Schiltz et al. 2002). Studies of the synovium of dogs injected with sodium urate crystals weekly for four weeks show that a chronic inflammatory state, characterized by a thickening of the synovial membrane and infiltration of inflammatory cells, will occur (Schumacher et al. 1974). However, a single intra-articular injection of urate crystals does not appear to cause any clinically evident long-term effects (Cross et al. 1997). Because the lameness is transient, the urate model is useful for simulating an acute lameness such as that associated with surgery or musculoskeletal disorders.

All dogs in this study developed a clinically evident lameness that resolved within 48 hours. This is similar to what has been reported by others (Cross et al. 1997, Millis et al. 2002, Rumph et al. 1993). However, the degree of lameness developed by the dogs in this study was much more severe than that seen in other studies. Millis (2002) injected 10 mg of sodium urate crystals to produce a partial weight-bearing lameness so that force plate data could be gathered for most dogs. The same dose of urate crystals in this study produced a non weight-bearing lameness that made force plate evaluation impossible for many evaluation periods. The difference in the severity of our model as compared to that reported by others using the same dose and method of crystal preparation can not be readily explained. However, this difference must be taken into consideration when making conclusions regarding the analgesic efficacy of ketamine. It is possible that the severity of the pain model used in this study prevented the acquisition of force plate data that may have shown small differences between treatment groups in both part I and II of this study.

Additionally, the severity of the model in this study may have necessitated a higher dosage of ketamine in order to demonstrate significant levels of analgesia. However, the dosage of 2 mg kg^{-1} used in this study was similar to dosages that provided analgesia in other studies (Slingsby & Waterman-Pearson 2000, Martin et al. 1996, Gomez De Segura et al. 1998). In these studies, analgesia was achieved quickly yet was only maintained for relatively short periods of time.

Pharmacokinetic data conducted in dogs shows that epidurally administered ketamine is rapidly absorbed into the systemic circulation with peak plasma levels

occurring within 45 minutes of administration. Plasma levels decline rapidly during the first hour after administration; however, ketamine concentrations in excess of $1 \mu\text{g ml}^{-1}$ are seen up to six hours after epidural administration. During this time, concentrations of two biotransformation products (norketamine and dehydroxyketamine) increase with peak plasma concentrations seen as much as three hours after administration (Pedraz et al. 1987). Therefore, despite the fact that Segura et al (1998) demonstrated dose dependant analgesia, the lack of measurable differences in this study may be a consequence of ketamine's short duration of action. Slingsby et al (2000) noted that multiple and frequent doses of ketamine may be needed in order to provide adequate levels of analgesia to dogs in the post operative-period. This study bears similar findings. No significant level of analgesia was demonstrated in Part I of this study (post synovitis administration), while only short-lived analgesia was achieved in dogs that received ketamine before the induction of synovitis. It is possible that, because the dogs in this study were allowed to recover fully from the brief anesthetic period and therefore not evaluated with the force platform or the NRS until two hours after the epidural injections were performed, the peak analgesic effects of ketamine occurred before the first evaluation. From these findings, it is thought that frequent administration of ketamine (beginning before noxious stimuli occur) would be needed to provide adequate analgesia in this model. Delivery of ketamine via a constant rate infusion (rather than increasing the dose), as Wagner et al (2000) demonstrated, may have been more effective in providing detectable levels of analgesia of longer duration in this model.

Delivery of ketamine via a constant rate infusion may increase the likelihood of side effects such as ptialism and psychosis. In an attempt to avoid these side effects, and to target the NMDA receptor specifically, treatments were administered epidurally in this study. Eleven of the sixteen dogs (3/8 in Part I and 8/8 in Part II) that received ketamine exhibited clinical signs that are associated with systemic administration of ketamine, however. This was likely due to the rapid redistribution of ketamine into the systemic circulation. Therefore, a single epidural dose of ketamine at 2 mg kg^{-1} may not provide substantial benefit over systemic administration with a constant rate infusion.

CONCLUSIONS

Results of this study demonstrate that the administration of 2 mg kg^{-1} of ketamine epidurally to dogs before the induction of a chemical synovitis significantly reduces pain scores for a brief period of time. The same dose of ketamine given epidurally to dogs after the development of a chemically induced synovitis does not provide significant analgesia. Further study involving different models of pain and different administration techniques are warranted to further elucidate the analgesic efficacy of ketamine.

LITERATURE CITED

- Aithal HP, Amarpal K, Singh GR (1996) Clinical effects of epidurally administered ketamine and xylazine in goats. *Small Rumin Res* 24, 55-64.
- Aithal HP, Singh GR, Mogha IV et al. (1997) Epidural ketamine and xylazine for hindquarter surgery in ruminants: A study on 35 clinical cases. *Indian Vet J* 74, 625-626.
- Amarpal K, Aithal HP, Singh GR et al. (1999) Preemptive effects of epidural ketamine for analgesia in dogs. *Indian Vet J* 76, 300-303.
- Anderson LS, Black RG, Abraham J et al. (1971) Neuronal hyperactivity in experimental trigeminal deafferentation. *Journal of Neurosurgery* 35, 444-452.
- Arendt-Nielsen L, Petersen-Felix S, Fischer M (1995) The effect of N-Methyl-D-aspartate antagonist (ketamine) on single and repeated nociceptive stimuli: a placebo controlled experimental human study. *Anesth Analg* 81, 63-68.
- Baha F, Malbert CH (1991) Effect of ketamine given by intrathecal route in dogs. *Revue-de-Medecine-Veterinaire* 142, 283-285.
- Basbaum AI (1974) Effects of central lesions on disorders produced by multiple rhizotomies in rats. *Experimental Neurology* 42, 490-501.
- Beltrutti DP, Trompeo AC, Di Santo S (1999) The epidural and intrathecal administration of ketamine. *Curr Rev Pain* 3, 458-472.
- Bennett GJ, Xie Y-K (1988) A peripheral neuropathy in rat that produces disorders of pain sensation like those seen in man. *Pain* 33, 87-107.
- Berrino L, Oliva P, Massimo F et al. (2003) Antinociceptive effect in mice of intraperitoneal N-methyl-D-aspartate receptor antagonists in the formalin test. *Eur J Pain* 7, 131-137.
- Borgbjerg FM, Svensson BA, Frigast C et al. (1994) Histopathology after repeated intrathecal injections of preservative-free ketamine in the rabbit: A light and electron microscopic examination. *Anesth Analg* 79, 105-111.
- Brennan TJ, Umali EF, Zahn PK (1997) Comparison of pre-versus post-incision administration of intrathecal bupivacaine and intrathecal morphine in a rat model of postoperative pain. *Anesthesiology* 87, 1517-1528.

- Bubenik LJ, Johnston SA, Smith MM et al. (2002) Evaluation of lameness associated with arthroscopy and arthrotomy of the normal canine cubital joint. *Vet Surg* 31, 23-31.
- Burton AW, Lee DH, Saab C et al. (1999) Preemptive intrathecal ketamine injection produces a long-lasting decrease in neuropathic pain behaviors in a rat model. *Reg Anesth Pain Med* 24, 208-213.
- Butler S (1990) In *Animal Pain: ethical and scientific perspectives*(Ed, Kuchel TR RM, Burrell J) ACCART, Barossa Valley, Adelaide, pp. 50-55.
- Carlson RP, Chang J, Datko LJ et al. (1986) Questionable role of leukotriene B4 in monosodium urate (MSU)-induced synovitis in the dog. *Prostaglandins* 32, 579-585.
- Cherng CH, Wong CS, Ho ST (1996) Spinal actions of nonsteroidal anti-inflammatory drugs. *Acta Anaesthesiol Sin* 34, 81-8.
- Coderre TJ, Katz J, Vaccarino AL, et al. (1993) Contribution of central neuroplasticity to pathological pain: A review of clinical and experimental evidence. *Pain* 52, 259-285.
- Conzemius MG, Hill CM, Sammarco JL et al. (1997) Correlation between subjective and objective measures of postoperative pain in dogs. *J Am Vet Med Assoc* 210, 1619-1622.
- Crisp T, Perrotti JM, Smith DL (1991) The local monoaminergic dependency of spinal ketamine. *Eur J Pharmacol* 194, 167-172.
- Cross AR, Budsberg SC, Keefe TJ (1997) Kinetic gait analysis of meloxicam efficacy in a sodium urate-induced synovitis model in dogs. *Am J Vet Res* 58, 626-631.
- DeCamp C (1997) Kinetic and kinematic gait analysis and the assessment of lameness in the dog. *Vet Clin North Am Small Anim Pract* 27, 825-840.
- Dennis SG, Melzack R (1979) Comparison of phasic and tonic pain models. In: *Advances in pain research and therapy*. Bonica JJ (eds). Raven Press, New York.
- Doherty TJ, Geiser DR, Rohrbach BW (1997) The effect of high volume epidural morphine, ketamine, and butorphanol on halothane minimum alveolar concentration in ponies. *Equine Vet J* 29, 370-373.
- Eilers H, Philip LA, Bickler PE et al. (2001) The reversal of fentanyl-induced tolerance by administration of "small dose" ketamine. *Anesth Analg* 93, 213-4.

- Fam AG, Schumacher HR (1988) Crystal-induced joint inflammation. In: CRC Handbook of Animal Models for the Rheumatic Diseases. Greenwald RA, Diamond HS (eds). CRC Press, Boca Raton, pp. 99-125.
- Finck AD, Ngai SH (1982) Opiate receptor mediation of ketamine analgesia. *Anesthesiology* 56, 291-297.
- Firth AM, Haldane SL (1999) Development of a scale to evaluate postoperative pain in dogs. *J Am Vet Med Assoc* 214, 651-659.
- Flecknell PA, Waterman-Pearson AE (2000) *Pain Management in Animals*, W. B. Saunders, New York, 255.
- Forman LJ (1999) NMDA receptor antagonism produces antinociception which is partially mediated by brain opioids and dopamine. *Life Sci* 64, 1877-87.
- Fundyus ME (2001) Glutamate receptors and nociception: implications for the drug treatment of pain. *CNS Drugs* 15, 29-58.
- Gallivan ST, Johnston SA, Broadstone RV et al. (2000) Clinical, cerebrospinal fluid, and histopathologic effects of epidural ketorolac in dogs. *Vet Surg* 29, 436-41.
- Gaynor JS (2002) Definitions of terms describing pain. In: Handbook of Veterinary Pain Management. Gaynor JS, Muir WW (eds). Mosby, St. Louis, pp. 60-62.
- Gaynor JS, Mama KR (2002) Local and regional anesthetic techniques for alleviation of perioperative pain. In: Handbook of veterinary pain management. Gaynor JS, Muir WW (eds). Mosby, St. Louis, pp. 261-280.
- Gomez de Segura IA, De Rossi R, Santos M et al. (1998) Epidural injection of ketamine for perineal analgesia in the horse. *Vet Surg* 27, 384-391.
- Graven-Nielsen T, Kendall SA, Henriksson KG et al. (2000) Ketamine reduces muscle pain, temporal summation, and referred pain in fibromyalgia patients. *Pain* 85, 483-491.
- Guirimand F, Dupont X, Brasseur L et al. (2000) The effects of ketamine on the temporal summation (wind-up) of the RIII nociceptive flexion reflex and pain in humans. *Anesth Analg* 90, 408-414.
- Gurevich L, Bennett WH, Anderson MA et al. (1994) A force plate display system for studying ground reaction forces in dogs. *Biomed Sci Instrum* 30, 81-6.

- Hellyer PW, Gaynor JS (1998) How I treat acute postsurgical pain in dogs and cats. *Compend Contin Educ Pract Vet* 20, 140-153.
- Holton L, Scott EM, Nolan AM et al. (1998) Relationship between physiological factors and clinical pain in dogs scored using a numerical rating scale. *J Small Anim Pract* 39, 469-474.
- Hustveit O, Maurset A, Oye I (1995) Interaction of the chiral forms of ketamine with opioid, phencyclidine, sigma and muscarinic receptors. *Pharmacol Toxicol* 77, 355-359.
- Jevens DJ, DeCamp CE, Hauptman J, et al. (1996) Use of force-plate analysis of gait to compare two surgical techniques for treatment of cranial cruciate ligament rupture in dogs. *Am J Vet Res* 57, 389-393.
- Jones MW, McClean M, Parsons CG et al. (2001) The in vivo relevance of the varied channel-blocking properties of uncompetitive NMDA antagonists: tests on spinal neurones. *Neuropharmacology* 41, 50-61.
- Jones RS (2001) Epidural analgesia in the dog and cat. *Vet J* 161, 123-131.
- Karnik P (2003) Personal communication, Hamilton SM, Blacksburg.
- Kelpstad P, Borchgrevink P, Hval B et al. (2001) Long-term treatment with ketamine in a 12-year-old girl with severe neuropathic pain caused by a cervical tumor. *J Pediatr Hematol Oncol* 23, 616-619.
- Kissin I (2000) Preemptive analgesia. *Anesthesiology* 93, 1138-1143.
- Kristensen JD, Svensson BA, Gordh T (1992) The NMDA-receptor antagonist CPP abolishes neurogenic "wind-up pain" after intrathecal administration in humans. *Pain* 51, 249-253.
- Kucuk N, Kizilkaya M, Tokdemir M (1998) Preoperative epidural ketamine does not have a postoperative opioid sparing effect. *Anesth Analg* 87, 103-106.
- Lamont LA, Tranquilli WJ, Grimm KA (2000) Physiology of pain. *Vet Clin North Am Small Anim Pract* 30, 703-728.
- Lascelles BDX, Cripps PJ, Jones A et al. (1997) Post-operative central hypersensitivity and pain: the pre-emptive value of pethidine for ovariohysterectomy. *Pain* 73, 461-471.

- Liu H-T, Hollmann MW, Liu W-H et al. (2001) Modulation of the NMDA receptor function by ketamine and magnesium: part I. *Anesth Analg* 92, 1173-1181.
- Lodge D, Johnson KM (1990) Noncompetitive excitatory amino acid receptor antagonists. *Trends Pharmacol Sci* 11, 81-86.
- Martin DD, Tranquilli WJ, Olson WA et al. (1996) Analgesic action of epidural ketamine injection in isoflurane-anesthetized dogs. *Vet Surg* 25, 184.
- Mathews KA (2000) Pain assessment and general approach to management. *Vet Clin North Am Small Anim Pract* 30, 729-755.
- Melzack R,Coderre TJ, Katz J et al. (2001) Central neuroplasticity and pathological pain. *Ann N Y Acad Sci* 933, 157-74.
- Millis DL, Weigel JP, Moyers T et al. (2002) The effect of deracoxib, a new COX-2 inhibitor, on the prevention of lameness induced by a chemical synovitis in dogs. *Compend Contin Educ Pract Vet* 24, 7-18.
- Mitchell AC, Fallon MT (2002) A single infusion of intravenous ketamine improves pain relief in patients with critical limb ischemia: Results of a double blind randomised controlled trial. *Pain* 97, 275-281.
- Moiniche S, Kehlet H, Dahl JB (2002) A qualitative and quantitative systematic review of preemptive analgesia for postoperative pain relief. *Anesthesiology* 96, 725-741.
- Muir WW (2002) Physiology and pathophysiology of pain. In: *Handbook of veterinary pain*. (eds). Mosby, St. Louis, pp. 13-45.
- Muir WW, Hubbell JAE, Skarda RT et al. (2000) *Handbook of Veterinary Anesthesia*, Mosby, St. Louis, 574.
- Muir WW, Woolf CJ (2001) Mechanisms of pain and their therapeutic implications. *J Am Vet Med Assoc* 219, 1346-1356.
- Pascoe PJ (2000) Opioid analgesics. *Vet Clin North Am Small Anim Pract* 30, 757-772.
- Pedraz JL, Lanao JM, Calvo MB et al. (1987) Pharmacokinetic and clinical evaluation of ketamine administered by i.v. and epidural routes. *Int J Clin Pharmacol Ther Toxicol* 25, 77-80.
- Plumb DC (1995) *Veterinary Drug Handbook*, Iowa State University Press, Ames,

- Rao KNM, Rao KV, Makkena S et al. (1999) Ketamine as an epidural anaesthetic in dogs. *Indian Vet J* 76, 61-61.
- Redua MA, Valadao CAA, Duque JC (2002) The pre-emptive effect of epidural ketamine on wound sensitivity in horses tested by using von Frey filaments. *Veterinary Anaesthesia and Analgesia* 29, 200-206.
- Reeves M, Lindholm DE, Myles PS et al. (2001) Adding ketamine to morphine for patient-controlled analgesia after major abdominal surgery: A double-blinded, randomized controlled trial. *Anesth Analg* 93, 116-120.
- Rumph PF, Kincaid SA, Baird DK et al. (1993) Vertical ground reaction force distribution during experimentally induced acute synovitis in dogs. *Am J Vet Res* 54, 365-369.
- Scheller M, Bufler J, Hertle I et al. (1996) Ketamine blocks currents through mammalian nicotinic acetylcholine receptor channels by interaction with both the open and the closed state. *Anesth Analg* 83, 830-836.
- Schiltz C, Liote F, Prudhommeaux F et al. (2002) Monosodium urate monohydrate crystal-induced inflammation in vivo: quantitative histomorphometric analysis of cellular events. *Arthritis Rheum* 46, 1643-1650.
- Schmid RL, Sandler AN, Katz J (1999) Use and efficacy of low-dose ketamine in the management of acute postoperative pain: a review of current techniques and outcomes. *Pain* 82, 111-125.
- Schumacher HR, Phelps P, Agudelo CA (1974) Urate crystal induced inflammation in dog joints: sequence of synovial changes. *J Rheumatol* 1, 102-113.
- Shafford HL, Lascelles BDX, Hellyer PW (2001) Preemptive analgesia: Stopping pain before it begins. *Veterinary Medicine* 96, 478-492.
- Slingsby LS, Waterman-Pearson AE (1998) Comparison of pethidine, buprenorphine and ketoprofen for postoperative analgesia after ovariohysterectomy in the cat. *Vet Rec* 143, 185-89.
- Slingsby LS, Waterman-Pearson AE (2000) The post-operative analgesic effects of ketamine after canine ovariohysterectomy--a comparison between pre- or post-operative administration. *Res Vet Sci* 69, 147-152.
- Stotz M, Oehen H-P, Gerber H (1999) Histological findings after long-term infusion of intrathecal ketamine for chronic pain: a case report. *J Pain Symptom Manage* 18, 223-228.

Torske KE, Dyson DH (2000) Epidural analgesia and anesthesia. *Vet Clin North Am Small Anim Pract* 30, 859-874.

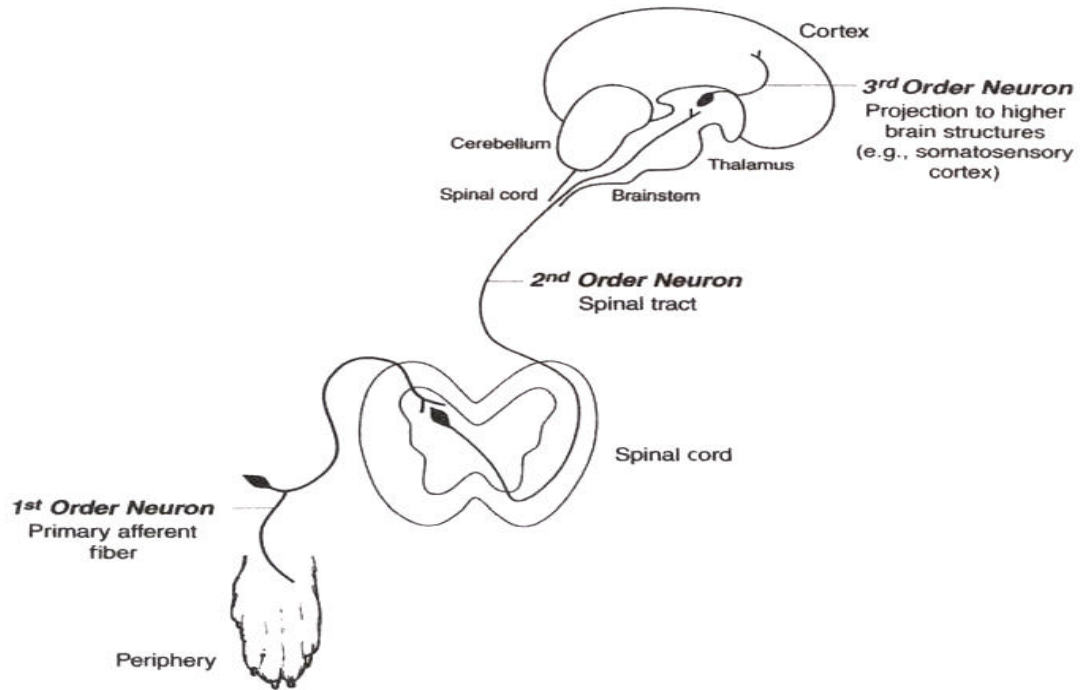
Uhl GR (1999) Neurochemical bases of drug abuse. In: *Basic Neurochemistry*. Seigel GJ, Agranoff BW, Albers RW, Fisher SK, Uhler MD (eds). Lippincott Williams and Wilkins, Philadelphia, pp. 1095-1107.

Wagner AE, Walton JA, Hellyer PW et al. (2002) Use of low doses of ketamine administered by constant rate infusion as an adjunct for postoperative analgesia in dogs. *J Am Vet Med Assoc* 221, 72-75.

Woolf CJ, Chong MS (1993) Preemptive analgesia--treating postoperative pain by preventing the establishment of central sensitization. *Anesth Analg* 77, 362-379.

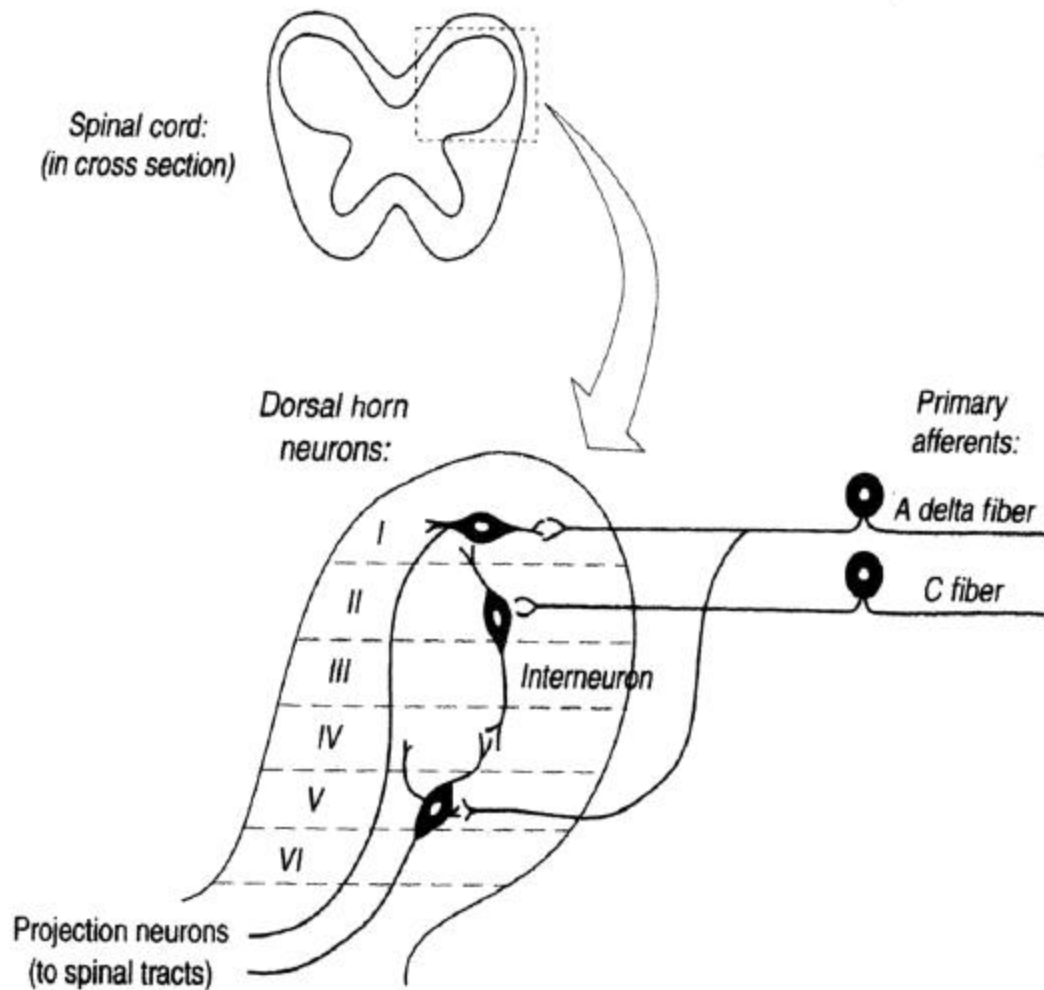
Yaksh TL (1996) Epidural ketamine: a useful, mechanistically novel adjuvant for epidural morphine? *Reg Anesth* 21, 508-513.

Figure 1. The pain pathway



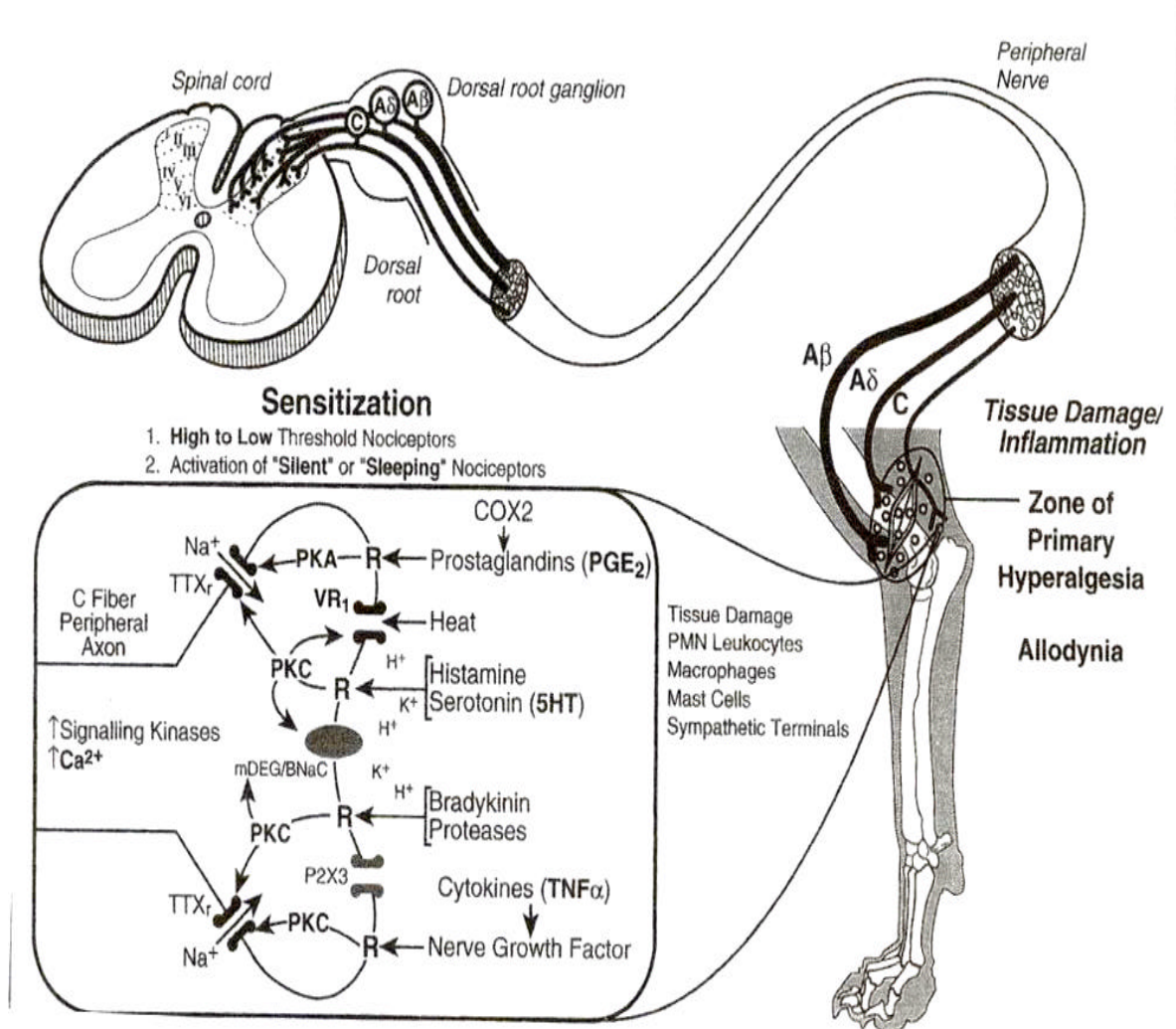
A schematic representation of the pain pathway as a chain of three neurons.
From: Lamont, L. A., W. J. Tranquilli, et al. (2000). "Physiology of pain." Vet Clin North Am Small Animal Pract 30(4): 703-728.

Figure 2. Spinal cord dorsal horn



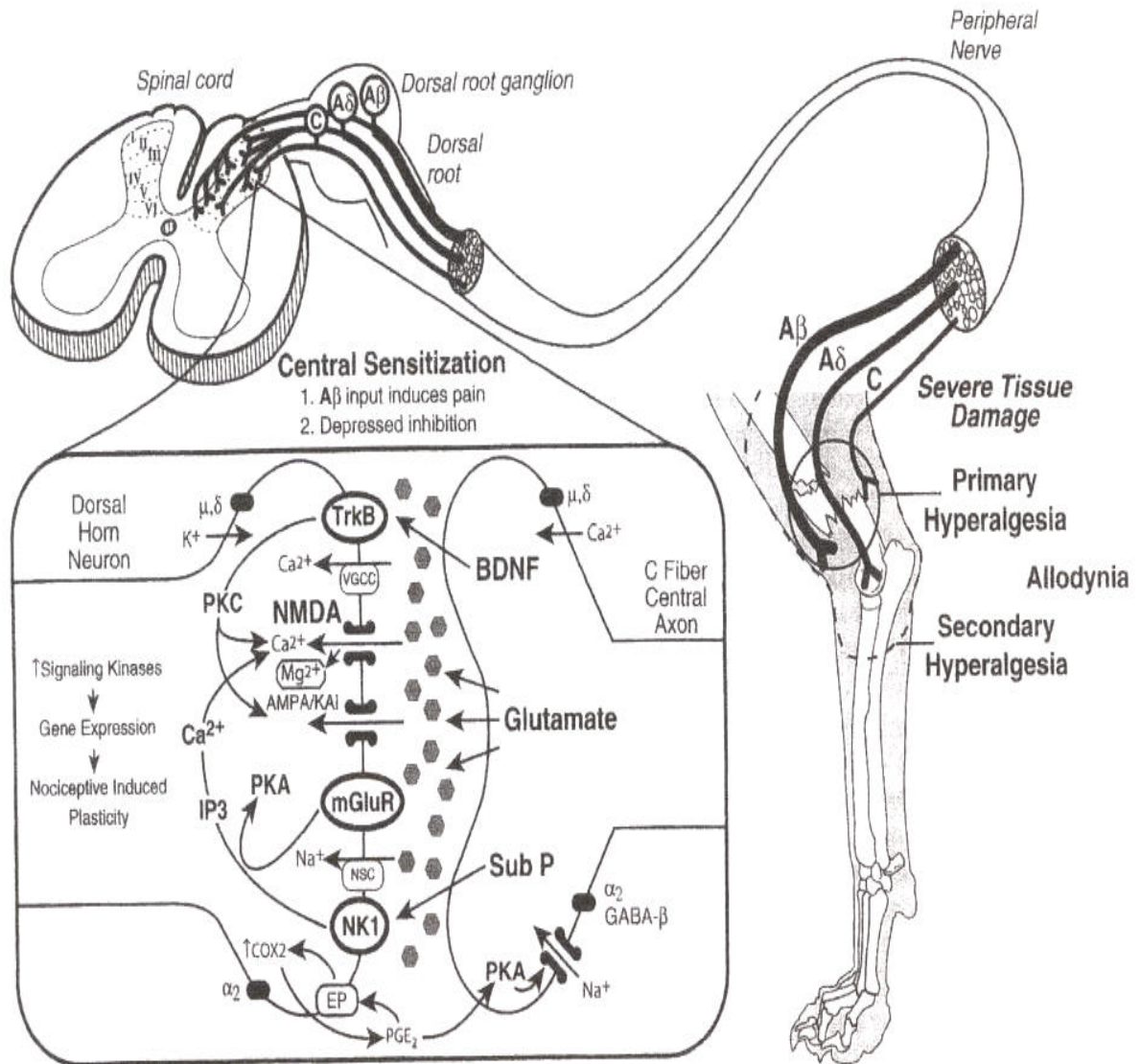
Laminar organization of the spinal cord dorsal horn. A delta fibers are shown entering in lamina I and V while C fibers enter at the second laminae. *From: Lamont, L. A., W. J. Tranquilli, et al. (2000). "Physiology of pain." Vet Clin North Am Small Animal Pract 30(4): 703-728.*

Figure 3. Peripheral sensitization



Structures and processes involved in peripheral sensitization. Tissue damage results in the release of sensitizing substances that increase the intracellular calcium concentration. This increase in calcium activates a number of intracellular signaling cascades. The product of these signaling cascades results in hyperalgesia and allodynia. R = receptor, PKC = protein kinase C, PKA = protein kinase A, TNF α = tumor necrosis factor α , VR₁ = vanilloid receptor, P2X₃ = purine receptor, TTX_r = tetrodotoxin resistant sodium channel, mDEG/BnaC = Degenerin/epithelial sodium channel. *From: Muir, W. W. and C. J. Woolf (2001). "Mechanisms of pain and their therapeutic implications." J Am Vet Med Assoc 219(10): 1346-1356.*

Figure 4. Central sensitization



Bombardment of the dorsal horn of the spinal cord with afferent signals results in temporal summation and depolarization resulting in wind up and central sensitization. BDNF = brain-derived neurotrophic factor, Sub P = substance P, IP3 = inositol triphosphate, COX2 = cyclooxygenase-2, EP = prostanoid receptor. *From: Muir, W. W. and C. J. Woolf (2001). "Mechanisms of pain and their therapeutic implications." J Am Vet Med Assoc 219(10): 1346-1356.*

Figure 5. Location of analgesic actions

Inhibit Perception

- *Anesthetics*
- *Opioids*

Modulation of Spinal Pathways

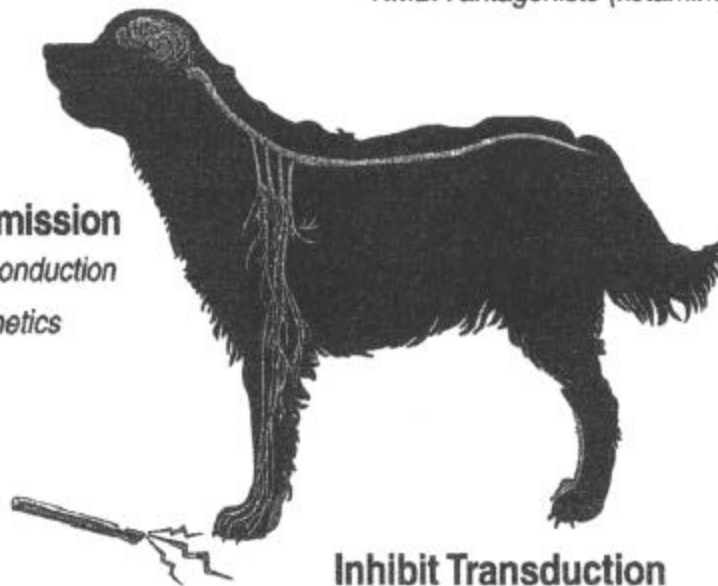
Inhibit central sensitization

- *Local anesthetics*
- *Opioids or α_2 -agonists*
- *NSAIDs*
- *NMDA antagonists (ketamine)*

Inhibit Transmission

Inhibit impulse conduction

- *Local anesthetics*



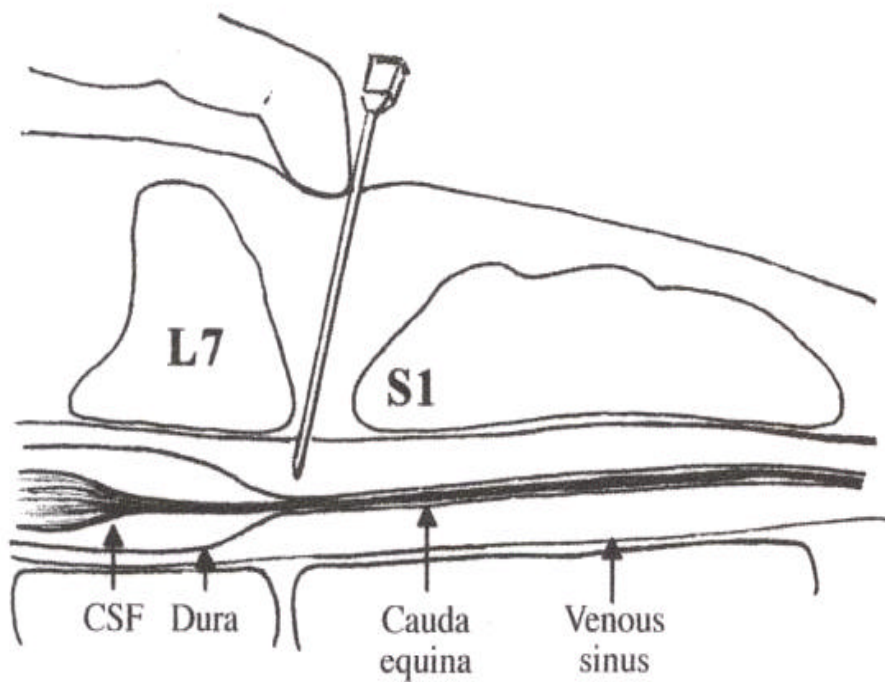
Inhibit Transduction

Inhibit peripheral sensitization of nociceptors

- *NSAIDs*
- *Opioids*
- *Local anesthetics*

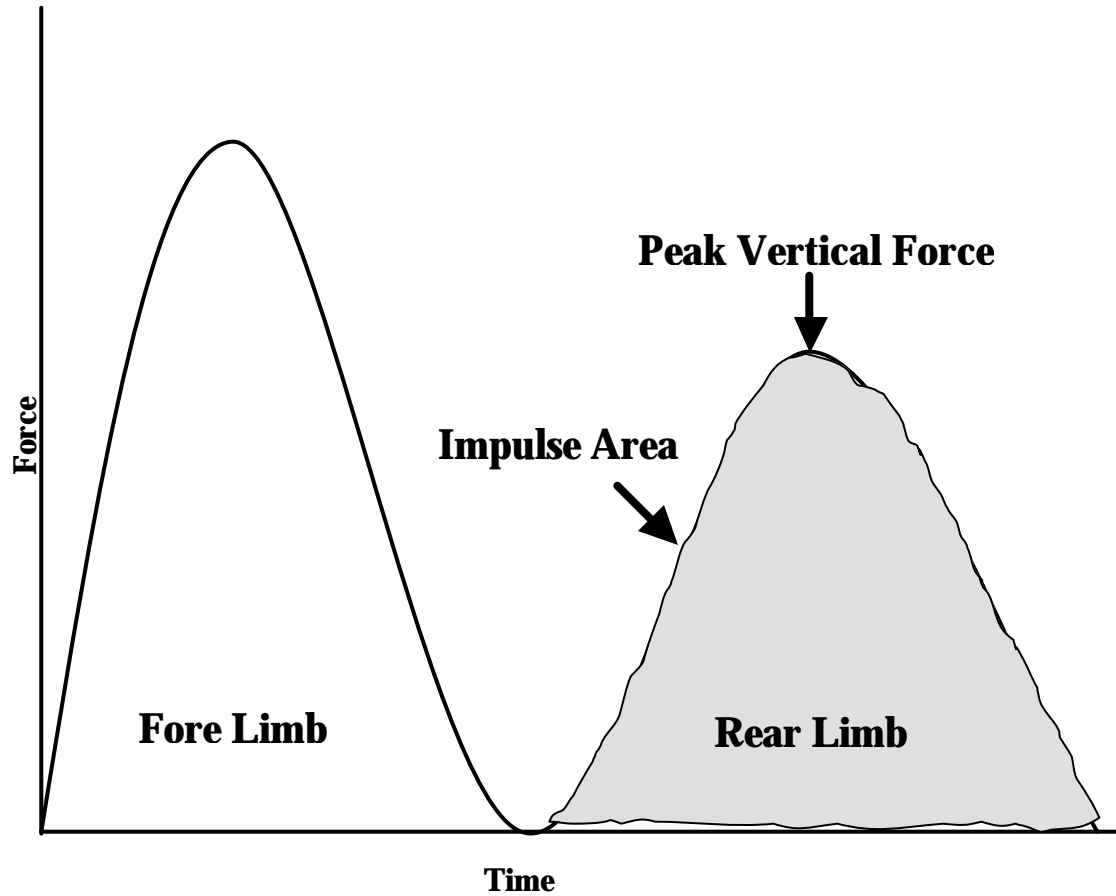
Sites of action of major classes of analgesic drugs. *From: Lamont, L. A., W. J. Tranquilli, et al. (2000). "Physiology of pain." Vet Clin North Am Small Animal Pract 30(4): 703-728.*

Figure 6. Epidural injection



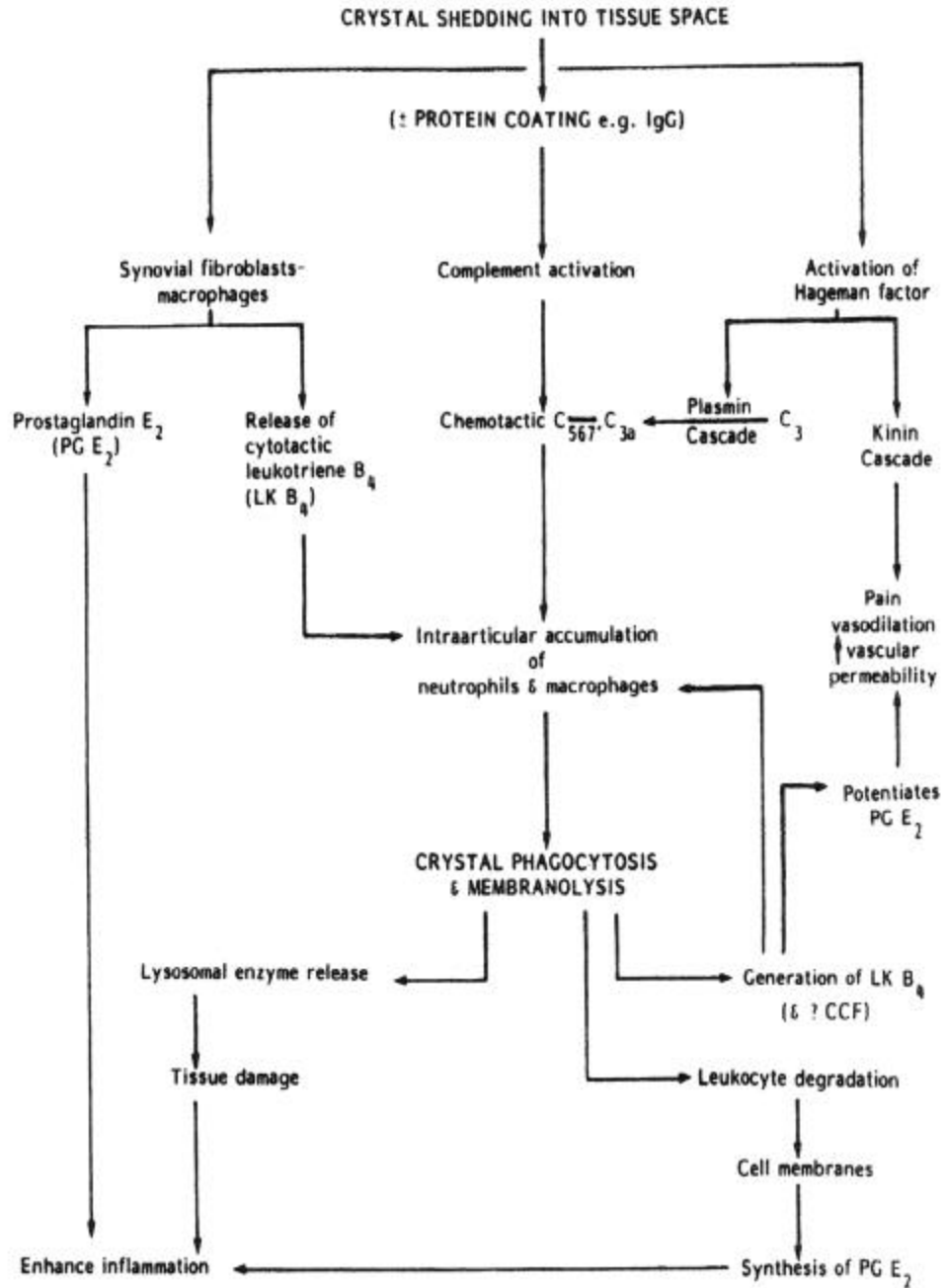
Proper needle placement between the seventh lumbar vertebra (L7) and the sacrum (S1) for epidural injection. CSF = cerebrospinal fluid. *From: Lamont, L. A., W. J. Tranquilli, et al. (2000). "Physiology of pain." Vet Clin North Am Small Animal Pract 30(4): 703-728.*

Figure 7. Force platform output



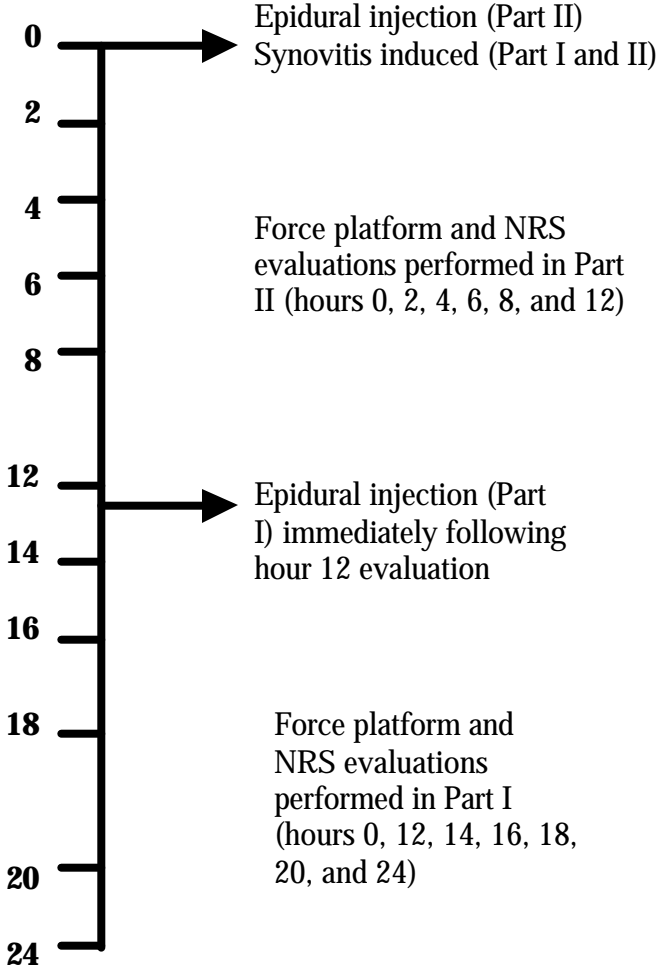
Graph generated by the force platform as an animal moves over the platform. The first rise in the curve represents the front limb striking the plate. The second rise in the curve represents the rear limb striking the plate. The two variables measured in the study are labeled. Peak vertical force generated by the hind limb is the maximum value of the curve. Impulse area is the amount of force placed on the hind limb over time (shaded area under the curve).

Figure 8. Pathogenesis of urate crystal synovitis



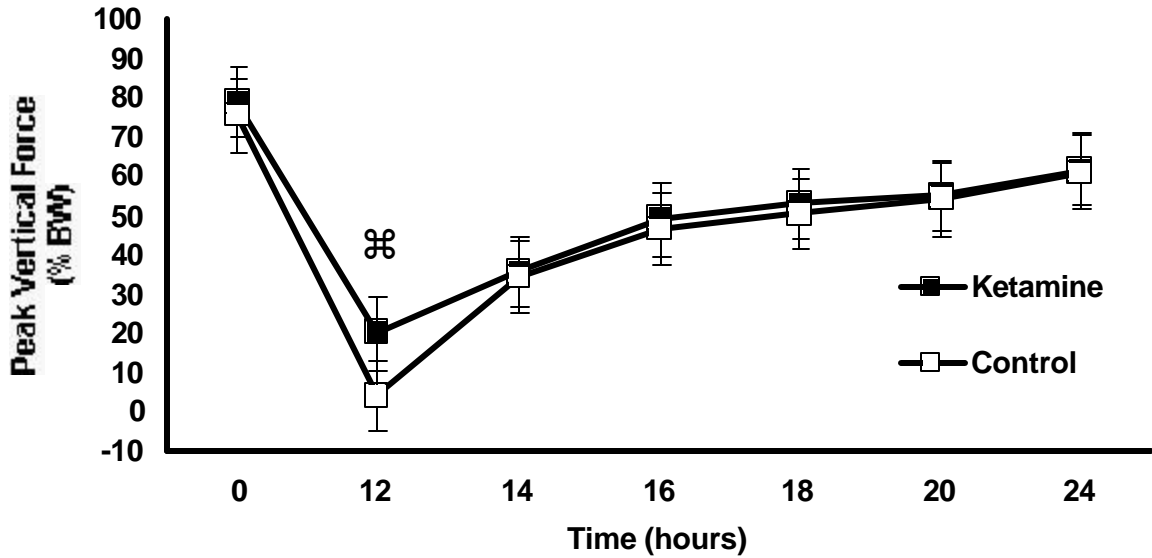
From: Fam AG, S. H. (1988). Crystal-induced joint inflammation. CRC Handbook of Animal Models for the Rheumatic Diseases. G. R. a. D. HS. Boca Raton, CRC Press. II: 99-125.

Figure 9. Timeline of study



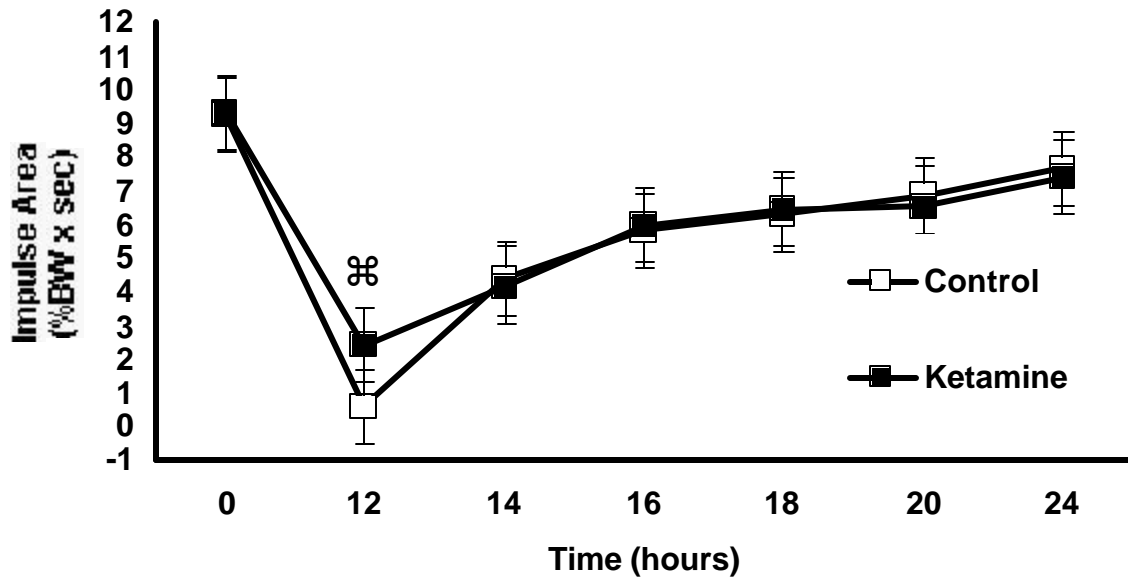
Timeline outlining when injections and evaluations were performed during each part of the study. Part I and Part II were conducted separately using different animals.

Figure 10. Peak vertical force



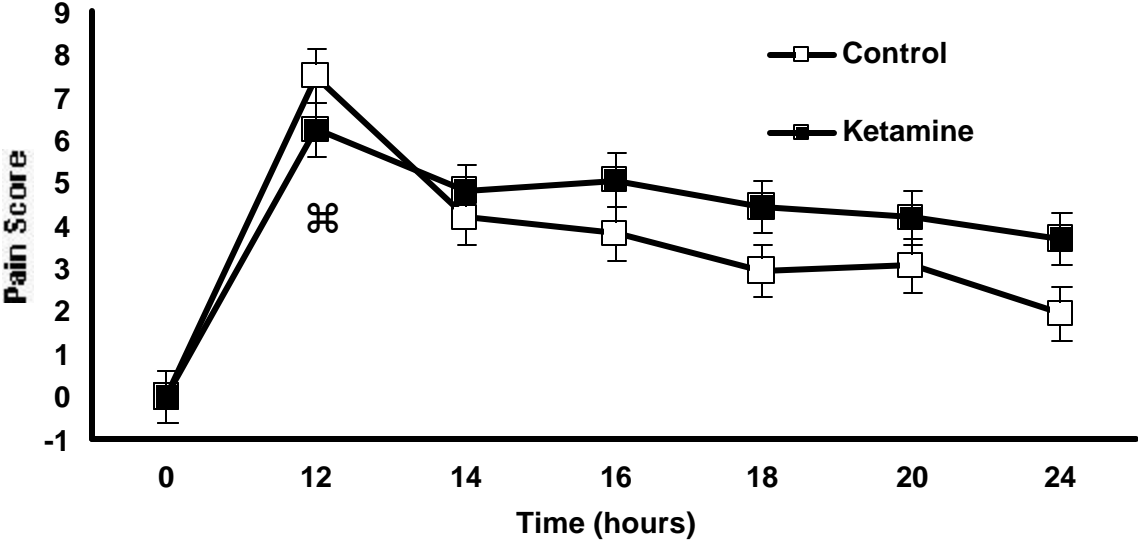
Peak vertical force of control and treated dogs expressed as a percentage of body weight (mean \pm SE) at baseline (time 0), prior to epidural injection (time 12) and then at intervals after the induction of synovitis. \otimes Indicates a significant change in both groups from baseline.

Figure 11. Impulse area



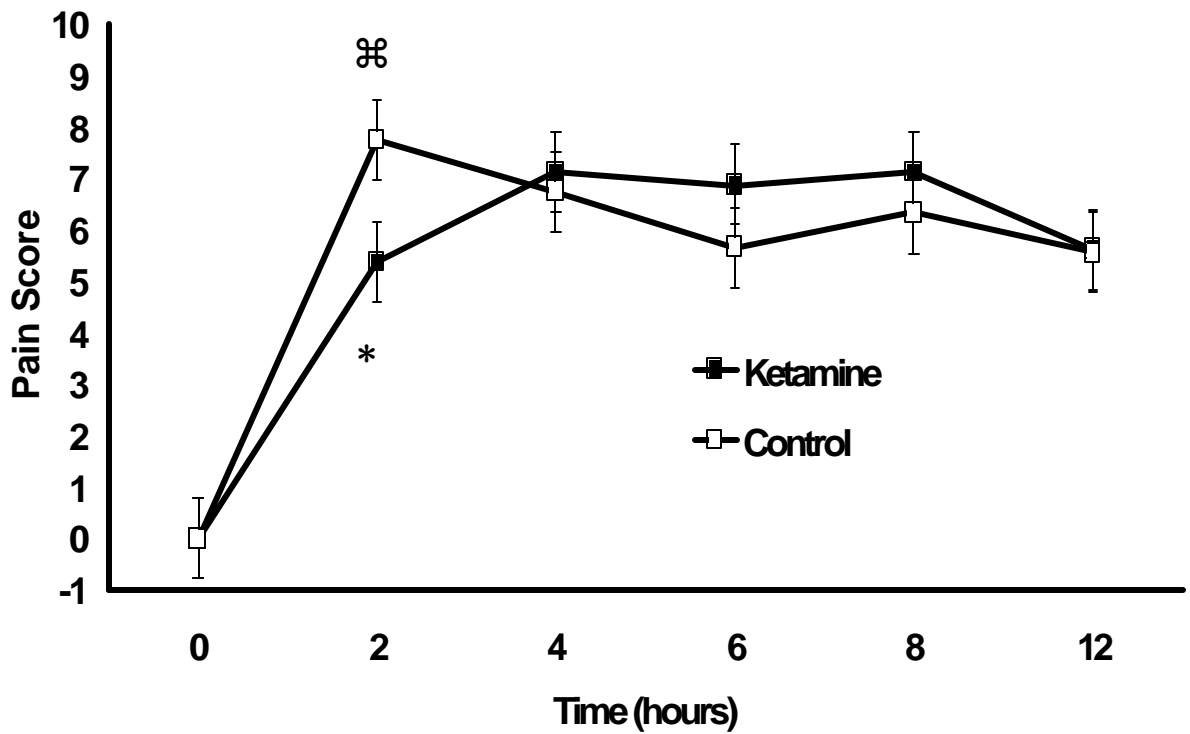
Impulse area of control and treated dogs expressed as a percentage of body weight x time (mean \pm SE) at baseline (time 0), prior to epidural injection (time 12) and then at intervals after the induction of synovitis. ‡‡ Indicates a significant change in both groups from baseline.

Figure 12. Total pain score



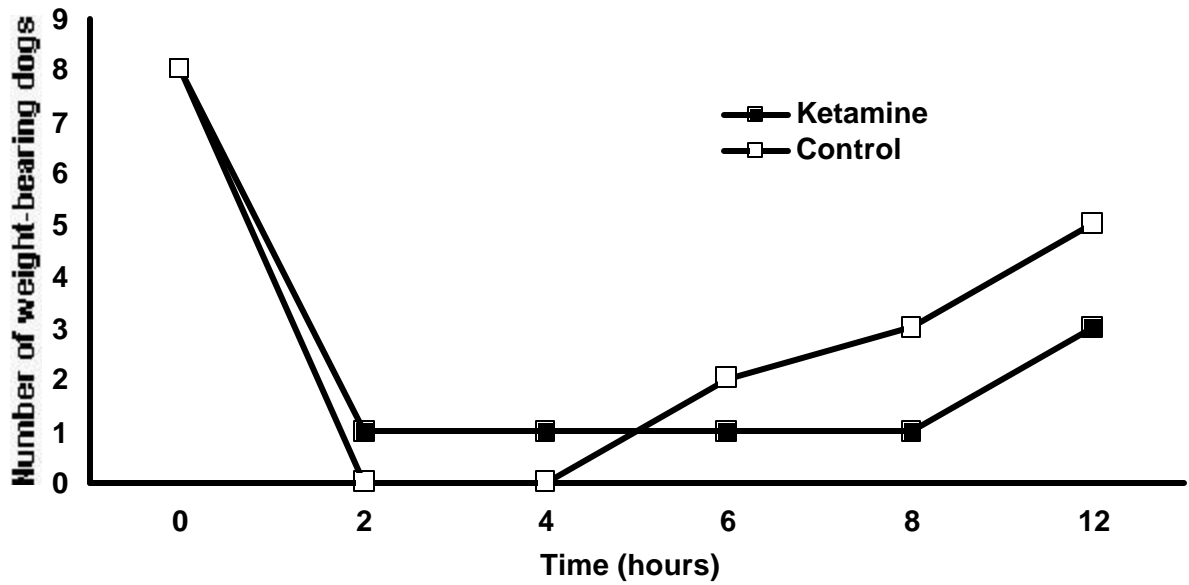
Total pain score of control and treated dogs (mean +/- SE) at baseline (time 0), prior to epidural injection (time 12) and then at intervals after the induction of synovitis. ** Indicates a significant change in both groups from baseline.

Figure 13. Total pain scores



Total pain score of control and treated dogs (mean +/- SE) at baseline (time 0), prior to epidural injection and induction of synovitis, and then at intervals after the injections. * Indicates a significant difference between treatment groups. ⌘ Indicates a significant difference in the control group from baseline.

Figure 14. Weight-bearing dogs



Number of weight-bearing dogs in control and treatment groups at baseline (time 0), prior to epidural injection and induction of synovitis, and then at intervals after the injections.

Table 1. Numerical Rating Scale

Observation	Score	Description
Heart Rate	0	0-15% increase from baseline
	1	16-30% increase from baseline
	2	31-45% increase from baseline
Respiratory Rate	0	0-15% increase from baseline
	1	16-30% increase from baseline
	2	31-45% increase from baseline
Vocalization	0	No vocalization
	1	Vocalization that responds to a calm voice
	2	Vocalization that does not respond to a calm voice
Interactive Behavior	0	Normal
	1	Not interactive when approached, looks at affected limb
	2	Not interactive when approached, not mobile, vocalizes when affected limb touched
	3	Aggressive when approached, extremely restless
Lameness	0	No lameness evident
	1	Lameness evident in affected limb
	2	Moderate lameness evident in affected lib, patient occasionally only toe-touches
	3	Patient will not bear weight on affected limb
Range of Motion	0	0-20% decrease from baseline
	1	21-40% decrease from baseline
	2	41-60% decrease from baseline
	3	Patient will not tolerate movement
Tolerance	0	0-20% decrease from baseline
	1	21-40% decrease from baseline
	2	41-60% decrease from baseline
	3	Patient will not tolerate touching of affected limb

Total Score (0 – 18)

Numerical rating scale for the assessment of analgesia provided by epidurally administered ketamine. Scale is modified from Hellyer, P. W. and J. S. Gaynor (1998).

Table 2. Observations made after epidural injection

Dog Number	Observation	Duration
701	Conscious proprioception deficits in both hind limbs	30 minutes
690	Hind limb paresis, conscious proprioception deficits in both hind limbs	45 minutes
682	Hind limb paresis; conscious proprioception deficits in both hind limbs,	150 minutes
	deficit in left rear limb present longer than right	(left hind limb)
695	Hind limb paresis/ataxia	30 minutes
667	Conscious proprioception deficits in both hind limbs	30 minutes
692	Hind limb paresis/ataxia	45 minutes
698	Hind limb paresis/ataxia, Conscious proprioception deficits in both hind limbs	180 minutes (Ataxia, CP deficits)
714	Rapid head movements from left to right	20 minutes (head motion)
	Hind limb paresis/ataxia	30 minutes

Table 3. Plasma levels of ketamine

Sample#	Time (h)	[Ketamine] (ppb)	Sample#	Time (h)	[Ketamine] (ppb)
472	0	ND	517	0	303
	2	ND		2	414
	4	ND		4	398
	6	ND		6	62
	8	ND		8	ND
	12	ND		12	1288
488	0	16	520	0	68
	2	28		2	50
	4	13		4	29
	6	13		6	117
	8	11		8	1745
	12	ND		12	2759
490	0	24	537	0	88
	2	419		2	88
	4	22		4	46
	6	1826		6	19
	8	144		8	15
	12	73		12	10
494	0	72	538	0	29
	2	64		2	498
	4	73		4	41
	6	18		6	337
	8	61		8	25
	12	16		12	27
509	0	8	545	0	238
	2	3		2	469
	4	9		4	ND
	6	6		6	ND
	8	ND		8	ND
	12	ND		12	49
512	0	ND	551	0	11
	2	ND		2	31
	4	ND		4	19
	6	ND		6	27
	8	ND		8	16
	12	ND		12	8
515	0	43	552	0	15
	2	276		2	22
	4	155		4	8
	6	830		6	7
	8	79		8	8
	12	ND		12	54
516	0	24			
	2	19			
	4	112			
	6	13			
	8	15			
	12	31			

ND = None Detected
 Dog numbers in bold type are dogs that received ketamine epidurally.

VITA

Stephanie Marie Hamilton was born February 12th, 1973 in Frankfurt, Germany to George and Ingeborg Hamilton. Her father's military career soon brought Stephanie and her three older brothers back to the United States, and the family eventually settled in Newport News, Virginia.

Stephanie graduated from Ferguson High School in 1991. She then earned a Bachelor of Science degree in biology from the College of William and Mary in 1995. During her time at William and Mary, Stephanie was employed as a veterinary assistant and participated in research involving filter-feeding fish. She was then accepted into the Doctor of Veterinary Medicine program at the Virginia – Maryland Regional College of Veterinary Medicine and graduated in 1999. After graduation, she worked as an associate veterinarian in a small animal practice in Martinsville, Virginia.

Stephanie returned to Blacksburg and the VMRCVM in July of 2000 to begin a residency in anesthesiology and pursue a Master's degree in veterinary medical sciences. After completion of her residency, Stephanie will begin a clinical instructorship at the VMRCVM.