

Pain Management in the ER/ICU

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Introduction

The recognition and treatment of pain is an incredibly important part of the hospitalized veterinary patient's regimen. Patients that do not have their pain addressed might suffer longer hospitalization times or face increases in morbidity and mortality from pain. Pain is known to elicit a sympathetic response worsening or inciting shock states which promote decreased wound healing and decreased organ perfusion. The veterinary technician is invaluable in assessing and reporting findings to the veterinarian. The veterinary technician, in conjunction with the veterinarian, can discuss and implement a multi-modal approach to managing pain in critically ill patients.

Pain Physiology and Pathophysiology

Pain is typically thought of as an adaptive response to prevent injury. If you stick your arm over a fire, it hurts so you can pull away and minimize tissue damage. However, severe injury, or failure to treat pain can cause detrimental physiologic effects, beyond the positive effects of self-preservation. In the periphery, specialized nerves, called nociceptors, exist and transmit pain signals to the spinal cord and to the brain. The free nerve endings, which terminate in soft tissue, have various receptors that can be activated in response to thermal, chemical, or mechanical noxious stimuli. For example, an acid burn will stimulate different fibers than a laceration. The first step in the pain process is transduction, where nerve endings convert stimuli into electrical signals. The two main nerve fibers (each with separate ability to transmit various stimuli) are the A-delta and C fibers. The A-delta fibers tend to fire faster, sending quicker signals to the spinal cord. The C-fibers tend to have a slower ability to reach their threshold. Thus, pain that is felt immediately upon exposure to noxious stimuli (crushing, pinching, tearing) is transmitted through A-delta fibers. Pain that is felt with a bit of a pause, cold temperature, etc is transmitted across C-fibers. Another important point is that there are various A-delta and C nerve fibers contain endings that typically do not transmit pain signals (initially) but can be "woken up" and recruited in severe circumstances. The next step in the pain process is transmission; after the nociceptors have converted the stimulus to energy it is sent to the spinal cord for initial processing. The signal travels through the nerve fibers to the dorsal part of the spinal cord. As discussed earlier, C-fibers are 10x slower than A-delta fibers in their transmitting speed. After pain signals reach the spinal cord, modulation occurs. Here, the spinal cord either dampens or increases the pain signal according to various neurotransmitters or chemicals that are activated/deactivated in the spinal cord. The majority of pain signals that make it to the spinal cord and are sent on are mediated by glutamate, a neurotransmitter. Glutamate acts on the AMPA, KAI, and neurokinin (NK) receptors and stimulates a response by sending the signal up the spinal cord to the brain. The NMDA receptor (upon which ketamine exerts its effects) is responsible for amplifying pain signals, whether they are incredibly strong or not. The NMDA receptor is thought to be important in prolonged/amplified pain states. A neurotransmitter called Substance P activates the NMDA receptor. Finally, GABA receptors, when activated, tend to inhibit signals from crossing into the spinal cord to be processed. There are other important neurotransmitters involved in modulation of signals in the dorsal horn of the spinal cord. These include: serotonin, norepinephrine, and opioid receptors. Serotonin, norepinephrine and opioid receptors, when activated, inhibit excitation of neurons, thus agonists of these drugs have analgesic properties. The last, and final, step of the pain pathway is perception. Perception occurs in multiple parts of the brain and is then perceived as an unpleasant sensation associated with real or perceived tissue damage. Pain can be categorized in various different ways: disease or anatomy related (pancreatic, etc), location (superficial, visceral, deep), duration (acute, chronic) or intensity (mild, moderate, or severe). These often require some objective input from the patient, so categorizing these in veterinary patients can be challenging.

A few other important concepts in pain management in the acute patient include: Allodynia, sensitization, windup, and referred pain. Allodynia refers to an exaggerated reaction to a stimulus that is normally not painful. This can occur due to an exaggerated pain response where the pain threshold of nociceptors is lowered.

Sensitization and windup are the result of peripheral and central physiochemical changes that occur during tissue damage and the inflammatory response. Peripherally, inflammatory mediators and cells can reduce the threshold of normally high-threshold nociceptors, and awaken "sleeping" nociceptors causing an exaggerated pain response. Central sensitization (windup) occurs as another mechanism for an exaggerated pain response, and because this occurs in the spinal cord, can result in severe pain that lasts much longer than the initial tissue insult. Repeated signaling to the spinal cord activates excitatory neurotransmitters which activate various receptors (NMDA, notably) and secure open-channels for pain stimuli to pass through. It appears that central sensitization can be responsible for allodynia. Referred pain is pain in a body part that is not affected by tissue damage. This might occur in a limb that was not amputated (phantom limb pain), or pain in limbs where the source of the pain is in the abdomen, for example.

Pain Pharmacology

Drugs used in the treatment of pain are best described by their effects on the pain pathway. Major classes of drugs used for pain in the acute setting include: opioids, NSAIDS, alpha-agonists, NMDA-antagonists, and local anesthetics.

Opioid medications act peripherally (transduction) and centrally (modulation) on opioid receptors. There appear to be three sub-types of receptors: mu, kappa, and delta. There are various types of opioid drugs including agonists, antagonists, and partial agonists/agonist-antagonist drugs. The below table summarizes these drugs.

Drug	Primary receptor	Secondary receptor	Level of pain appropriate for	Duration of action	Species	Routes to be administered
Morphine	Mu	NA	Moderate-Severe	Up to 4 hours	Cat, Dog	IV, IM, SQ-IV Can cause histamine release
Hydromorphone	Mu	NA	Moderate-Severe	Up to 4 hours	Cat, Dog	IV, IM, SQ
Oxymorphone	Mu	NA	Moderate-Severe	Up to 4 hours	Cat, Dog	SQ, IM, IV
Fentanyl	Mu	NA	Moderate-Severe	Single injection up to 30 minutes	Cat, Dog	IV- CRI
Buprenorphine	Mu (partial agonist)	NA	Mild-moderate	Up to 6 hours	Cat, Dog	SQ, IM, IV
Methadone	Mu	NMDA antagonist	Moderate-severe	2-6 hours	Cat, Dog	SQ, IM, IV
Butorphanol	Kappa	Mu	Mild-Moderate	1-6 hours (Dogs typically 1 hour or less)	Cat, Dog	SQ, IM, IV
Tramadol	Mu agonist	Serotonin/ Norepinephrine reuptake inhibitor	Mild-moderate	Twice-four times daily dosing	Cat, Dog	PO
Naloxone	Mu antagonist		Reversal agent	NA	Cat, Dog	IV

The second class of important analgesic drugs are the non-steroidal anti-inflammatory drugs (NSAIDS). These drugs have a potent ability to slow/stop inflammatory processes which are responsible for pain signaling. Although tissue damage may exist, if the inflammatory cascade can be prevented, pain signals will not be transduced. NSAIDS work on transduction of pain, working locally to prevent cytokine release, cell recruitment, and other inflammatory signs. They do have some significant side-effects and their use in critical patients are limited. Examples include: carprofen, meloxicam, aspirin, etodolac, piroxicam, deracoxib, firocoxib, tepoxalin, and ketoprofen.

Next, alpha-agonists, such as dexmedetomidine, can act in the spinal cord to prevent modulation of pain signals through agonizing norepinephrine at the alpha-receptors in the dorsal horn. Alpha-agonists tend to have severe cardiopulmonary effects, even at low doses, and so their use in critical patients is also limited. However, they remain an important part of the pain arsenal in dealing with anesthetic delirium, or as a continuous rate infusion for sedation with desired analgesic effects.

Local anesthetics are the next major class of analgesic drug to discuss. These drugs, ending in -caine, are Na⁺-channel blockers. Influx of Na⁺ ions into the neuron is responsible for the creation of an action potential in the nerve. The action potential propagates and the signal travels along the neuron to the spinal cord. Blocking Na⁺ influx would stop the action potential and prevent transmission of the painful stimulus. Examples include: lidocaine, bupivacaine, proparacaine, and tetracaine. A summary of these drugs is found below.

Drug	Duration of action	Routes administered	Notes
Lidocaine	60-120 minutes	Local, SQ/Intradermal, IV	Can provide effective adjunctive analgesia as a CRI Reduce dosages in cats****
Bupivacaine	180-480 minutes	Intrathecal, Intrapleural, NOT IV	Only to be used
Proparacaine	Variable	Topically (ocular)	

Finally, the adjunct drug that might be used in analgesia in the critically ill is ketamine. Ketamine functions as an NMDA-antagonist, preventing or stopping exaggerated pain signals from passing through these channels to the brain (windup). Ketamine does not have analgesic properties on its own. Rather, it seems to potentiate the effects of other drugs (opioids notably) by blocking NMDA-receptors and lowering the needs for the other analgesic drug (opioid) by itself.

Assessment of Pain

Assessing pain in small animals in the ICU can be somewhat difficult. There has been a lot of research into physiologic and behavioral responses to pain. This research has allowed the veterinary professional to better assess and categorize pain states in animal patients. While it might seem somewhat intuitive that a patient who was hit by a car and growls is painful, the veterinary community didn't always see things that way. The best recommendation is to implement a comprehensive pain scale in the hospital and use that when assessing pain in your patients. A commonly used chart is the Colorado State University pain scales found here:

- Canine: ivapm.evetsites.net/refid.20468/refDownload.pml
- Feline: ivapm.evetsites.net/refid.20467/refDownload.pml

Behaviors associated with pain can be found in the following charts:

Canine pain behaviors		
Anxiety	Decreased desire for interaction	Submissiveness
Reluctance to move	Whimpering/Howling/Growling	Guarding
Aggression	Anorexia	Self-mutilation

Feline pain behaviors		
Hiding	Decreased desire for interaction	Hissing/spitting
Reluctance to move	Excessive licking/grooming	Attempting to escape
Lack of grooming/unkept coat	Tail flicking	Crouching

Vitals alone (blood pressure, heart rate) have been found to be poor predictors of pain. Many animals with normal vital signs are in pain. Approaches to a patient for a pain assessment might include:

- Observation of the animal in the cage
- Observing the patient interacting with another staff member
- Taking vital signs: HR, RR, Temp, Mentation, BP
- Attempting to elicit a painful response: palpating incision or limb/organ affected
- Observing quality of life: eating/drinking, coat, ambulation

Once the assessment is complete, the decision is made to institute analgesic therapy or modify current therapy, if it is inadequate.

Treatment of Pain

Treating a patient with acute pain involves a multi-modal approach. The first step is to assess the pain and make judgments as to the level of pain, location, and analgesic therapy that is appropriate. This involves thinking of where the pain occurs, what stimuli is causing it, and if there is a windup component.

Options for treating pain in the ICU include: injections of analgesic medications, continuous rate infusions of analgesic medications, use of local anesthetic blocks near site of pain, epidural injection and catheter placement, transdermal patches, continuous infusion of analgesics into pain site ("soaker catheters), and non-allopathic interventions such as acupuncture and/or physical therapy.

An example of a multi-modal approach to analgesia in a thoracotomy patient:

Pre-medication:

Hydromorphone (pure u opioid) + Midazolam

Induction:

Fentanyl (pure u opioid) + Lidocaine (Na-channel blocker) + Ketamine (NMDA antagonist) + Midazolam

Intra-operatively:

Fentanyl + Lidocaine + Ketamine CRI

Intercostal block (local anesthesia)

Post-operatively:

Bupivacaine infusion into thoracostomy tube

FLK CRI

+/- NSAID

References available upon request.