MANAGING ACUTE PAIN
Bernie Hansen DVM MS DACVECC DACVIM (Int. Med)
Associate Professor, NCSU College of Veterinary Medicine
bernie_hansen@ncsu.edu

The role of pain and endogenous opioids in critical illness

Acute pain is an expected complication of injury and critical illness that requires attention and care from the clinician. It influences the integrated behavioral, hemodynamic, metabolic, and immune responses (collectively known as the stress response) that restore homeostasis and ensures survival following serious injury. This adaptive response is mediated by the neuroendocrine response to tissue injury and downstream complications such as blood loss, infection, and surgical interventions. Tissue injury, hypovolemia, and hypotension elicit immediate responses by the autonomic nervous system and the hypothalamic-pituitary axis. The sympathetic nervous system releases catecholamines from the adrenals and target organs; these products mediate increased vigor and rate of cardiac contraction, arterial vasoconstriction to organs capable of surviving on limited energy resources (skin, muscle, bone), and constriction of capacitance veins (e.g., mesenteric veins in the dog) to direct circulation to tissues with high energy requirements. Energy substrates (glucose, amino acids, and lipids) are mobilized from the liver, gut, muscle, and adipose tissue. The hypothalamus increases its release of corticotrophin-releasing hormone, vasopressin, and oxytocin, and the pituitary gland responds with increased production of ACTH, glucocorticoids, and beta-endorphin. In addition to pituitary release of beta-endorphin, many tissues release the related opioid peptides enkephalins and dynorphins. These peptides bind with different affinities to three G protein-coupled opioid receptors: mu, delta, and kappa. Ligand activation of these receptors initiates a wide range of responses depending on the target cell type.

Opioids and the circulation

The interactions between endogenous opioids and the cardiovascular and immune systems have been the subject of much research interest since observations in the 1970’s that the opioid antagonist naloxone can ameliorate hemodynamic instability in hemorrhagic shock.1 The mechanisms for improved hemodynamic stability following naloxone treatment are incompletely understood, but include enhanced catecholamine release2 and enhanced target tissue response to catecholamines3. Animal models of trauma demonstrate that circulating concentrations of beta-endorphin increase following crush injury or lipopolysaccharide administration4, and numerous clinical studies in humans demonstrate elevated plasma concentrations of beta-endorphin that positively correlate with severity of illness. This endogenous opioid release has been traditionally associated with a benefit (analgesia), and the antinociceptive properties of the stress response have been repeatedly demonstrated in experimental animal and human models of stress and pain. Although these findings may well be properly interpreted as a ‘good’ consequence of opioid activation, other opioid-mediated cellular responses are not clearly beneficial and may impair circulatory responses to injury. For example, endogenous opioids released from cardiac myocytes decouple contraction from excitation5, an effect that may protect the heart from hypoxic and ischemic injury but also impairs circulation during stress. Administration of opioid drugs produces similar effects on the cardiovascular system. Precocaine with morphine increases parasympathetic control of the circulation in humans6, consistent with observations in animal models7 (and veterinary observations in dogs) of slower heart rates and significant reduction in blood pressure following administration of opioids.

In spite of the evidence suggesting that opioids mediate earlier decompensation from hemorrhage, and meta-analysis level evidence for improved mean arterial pressure in humans with shock syndromes8 treated with opioids antagonists, there is currently no clinical trial confirmation that therapy with naloxone improves the outcome from severe injury or other causes of shock syndrome. However, the likelihood that endogenous and exogenous opioids mitigate the resuscitation goal of maintaining adequate blood pressure and perfusion in shock syndromes should be kept in mind when used to treat patients with both pain and shock syndrome.

Opioids and inflammation

The postinjury inflammatory response to injury is an essential step toward tissue repair and maintenance of immunocompetence in the face of compromised tissue integrity. This response is a complex integration of neuroendocrine and cellular responses that must be carefully matched to stimulus intensity. Tipping the balance of pro- and anti-inflammatory responses too far towards inflammation yields immediate tissue injury; too far towards immunosuppression results in host susceptibility to
infection and delayed tissue injury culminating in multiple organ failure. This latter situation is commonly observed as the "two-hit" model of injury, wherein a patient suffering initial injury is unable to mount a successful response to secondary sepsis later on and succumbs to multiple organ failure. Depending on the model, timing, route of administration, concentration, tissue location, and stimulus, both endogenous and exogenous opioids can affect the immune response in ways that are either pro- or anti-inflammatory. However, the bulk of evidence is that at clinically relevant dosages opioid analgesics are on balance immunosuppressive, a finding that has stimulated interest in sorting out the impact of this effect on patients already immunosuppressed or at risk of serious infection.

Metabolic effects of opioids

Opioids modulate other metabolic responses to injury in ways that may be detrimental in the face of severe injury. Immediately following surgical injury, previously healthy dogs mobilize energy substrate via increased proteolysis in the gut and develop hyperglycemia secondary to reduced glucose clearance. Administration of opioids produces hyperglycemia in normal animals, and hyperglycemia in illness is attended by elevated plasma concentrations of endorphin and cortisol. Hyperglycemia is correlated with illness severity, and glycemic control during acute illness has been widely adopted as a therapeutic strategy in critical care. If opioid therapy interferes with this goal, reliance on opioids for analgesia may complicate overall patient management and could interfere with recovery.

Potential benefits of acute pain management

Despite growing concerns about the pharmacological effects of opioids and concern that uncalibrated interference with the stress response adversely affects outcomes in patients with critical illness, achieving adequate analgesia is considered to be an essential component to patient management following injury or during other critical illness. Although definitive studies of the impact of analgesia on long-term global outcome measures are lacking, many smaller clinical studies in humans suggest that inadequate analgesia is associated with increased thromboembolism, pneumonia, agitation/delirium, catabolism, immunosuppression, chronic pain, longer hospitalization, and mortality (for a review, see Malchow RJ and Black IH).

Potential adverse consequences of analgesic therapy in critical illness

In addition to the potential for opioids to cause problems such as immunosuppression and hyperglycemia, other well-known complications of therapy yield the potential for causing harm in the injured patient. Perhaps the most serious of these in humans are over-sedation, hypotension, and respiratory depression. In the years since the 1991 adoption of Pain Management Standards by the Joint Commission on Accreditation of Healthcare Organizations, routine implementation of mandatory analgesic therapy has been implicated as a direct cause of patient deaths in trauma centers throughout the United States. Although the frequency of this complication is low (46 of 2,282 patients with an overall mortality rate of 38%) this trend does highlight the potential to cause harm with more aggressive application of analgesia. Although non-anesthetized companion animals appear to be comparatively resistant to severe respiratory depression, a number of side effects including opioid-induced reflux esophagitis, urine retention, hypotension, and hyperthermia have been observed clinically and experimentally. Non-opioid agents also hold the potential for harm, for example epidural bupivacaine may destabilize patients with sepsis, nonsteroidal anti-inflammatory drugs may cause gastrointestinal or renal injury, and alpha-2 agonist drugs produce hypotension and reductions in cardiac output that may compromise ill patients. Agents that produce excess sedation may prevent animals from effectively guarding their airway, predisposing them to aspiration injury.

Treatment

The concept of "multimodal" analgesia in trauma or critical illness should be broadened to include both pharmacological and nondrug treatments to relieve pain. To minimize reliance on drug therapy for analgesia we make every effort to provide attentive nursing care that minimizes movement-associated pain, sedation just adequate to promote overnight sleep, and distraction (with toys, owner visits, and locating patients in areas of activity) during periods of wakefulness. Despite concerns over their potential for side effects, opioids remain a key component of care for acute pain in dogs and cats in our intensive care unit. Fentanyl has become our most frequently used analgesic due to its comparatively low cost and the ability to titrate its effects rapidly. Whenever possible and where indicated we reduce opioid requirements with concurrent treatment with nonsteroidal anti-inflammatory drugs, regional/local
anesthesia, and continuous infusion of ketamine (1-2 mcg/kg/min in dogs and cats), lidocaine (2 mg/kg/hour in dogs only) and dexmedetomidine (.25 – 3 mcg/kg/hour for dogs and cats, when sedation is desired). Regional and local anesthetic agents are used whenever practical, particularly for intra- and postoperative analgesia. Tramadol provides little analgesic benefit, particularly after 1-2 days, and should generally have no role in acute care. Nonsteroidal anti-inflammatory agents are begun as injections (using either carprofen or meloxicam) as soon as the patient appears hemodynamically stable and the risk of gastrointestinal injury is judged to be low. For dogs at risk of renal or gastrointestinal complications, acetaminophen 10-15 mg/kg q 8h may be used.

Once the patient is judged able to transition to oral therapy and is moved from the intensive care unit it is treated with continued nonsteroidal anti-inflammatory agents and tramadol. Occasionally, local or regional anesthesia is maintained with wound, nerve, or epidural catheters for several days during the transition from intensive care to a general hospital ward. Although tramadol is a relatively weak analgesic and has not been formally evaluated as therapy for pain from injury, work in dogs and cats suggests that it provides meaningful analgesia for experimental pain or for pain and hyperalgesia following surgery27-29. If the animal was successfully maintained on intravenous fentanyl, another option is to add treatment with a fentanyl patch and overlap the two by 8-24 hours. The intravenous infusion is then discontinued and the animal observed and the pain score is re-evaluated in 4-6 hours. If there is no worsening of pain they are maintained on the patch. Because the patch fails to provide adequate analgesia to many animals we routinely use oral therapy unless owner compliance is expected to be a limitation.

Common complications

Opioids

Despite the potential concerns for circulatory and impairment of the immune response opioids remain the mainstay treatment for acute pain. Complications that are the most readily apparent include blunted cardiovascular responses for patients in shock, excessive sedation, gastroparesis, and dysphoria. As mentioned above, delaying opioid treatment until an animal in shock has been reasonably stabilized in the first minutes of resuscitation is usually all the consideration necessary for cardiovascular complications. Sedation is often a desirable goal of therapy, particularly within the first 24-48 hours of acute injury and especially overnight when the goal may be to promote sleep. When excessive, sedation can compromise that patient’s ability to guard its airway and put it at risk for aspiration injury, particularly if gastroparesis and esophageal reflux develop. Common strategies to minimize this include a) administration of the agent as a continuous rate infusion to avoid the peaks and valleys of sedation associated with intermittent administration, b) choosing the lowest dose necessary to provide meaningful relief of pain, c) adding nonopioid treatments to achieve a multi-modal effect, d) positioning the animal’s head in an elevated position on towels or blankets, and e) decompressing the stomach with an indwelling nasogastric tube or gastrotomy tube. Concurrent administration of prokinetic agents such as cisapride sometimes appears to lessen trouble with large gastric residual volume. Dysphoria is most often seen in otherwise vigorous dogs following major surgery, and in some cases may be difficult to differentiate from pain-induced distress. In general, dogs with opioid-induced dysphoria cannot be calmed by distraction and incremental doses of opioid either do not help or actually make their behavior worse. If this is suspected, partial reversal with either naloxone (0.25-0.5 micrograms/kg at a time IV and repeated every 1-2 minutes until the desired response is reached) or butorphanol (0.1 mg/kg IV) may be used, followed by a vacation from the opioid for minutes to hours depending on the agent and a subsequently slower infusion rate when it is re-started.

Nonsteroidal anti-inflammatory agents

The notorious complications of gastrointestinal and kidney injury precludes use of these drugs in animals with seriously compromised circulation until that condition is resolved. However, it is unusual for this circumstance to persist for more than a few hours and we generally add these drugs to therapy with opioids within 24 hours following injury or surgery. Because COX-2 agents may delay intestinal healing following surgery of the gut it may be prudent to avoid these agents in the immediate postoperative period.30 Similarly, nonsteroidal anti-inflammatory drugs have modest effects on delayed healing of fractures; although this is likely not an issue in the first hours to days post repair it is prudent to avoid them for long-term analgesia in dogs at risk for nonunions.31

Alpha-2 agonist drugs

Aside from sedation, the primary complication of treatment with dexmedetomidine or other alpha-2 agonist drugs is depressed cardiovascular function. The drugs reliably increase peripheral vascular
resistance and reduce heart rate and cardiac output. In general, the reduction in cardiac output is commensurate with the degree of sedation and is not problematic, but animals with unmet circulatory needs may be further compromised by treatment. The increase in peripheral vascular resistance precludes use of these agents in animals with left heart disease. Although administration as a continuous rate infusion of 0.5 – 3 mcg/kg/hour likely has significant impact on circulation, clinically this method appears to provoke less severe and unpredictable side effects than intermittent injection.

References