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The Science and Art of Analgesia

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Introduction

Pain has been defined by the International Association for the Study of Pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" [1]. Pain is, by definition, a subjective experience and can be quite difficult to quantify. In fact, assessing pain in the veterinary patient is one of the biggest stumbling blocks to effective pain management. Although it was once thought that some pain persisting into the postoperative period was beneficial, encouraging immobility and, in turn, healing and recovery, we now know that postoperative pain may actually delay recovery due to a number of clinically significant negative side effects [2]. Immobility, for example, can retard bone healing and decrease pulmonary function. Catecholamine release stimulates the sympathetic nervous system, increasing myocardial work and oxygen consumption. Stress hormone release, inappetance and insomnia all lead to an overall catabolic state and lengthen the time required for wound healing. Last and most importantly, postoperative pain leads to patient suffering [3].

The Physiology of Pain

Pain perception is the result of at least four distinct physiological processes:

1. **Transduction** of a noxious stimulus (e.g., extreme heat or pressure, tissue damage) into an electrical message by nociceptors.
2. **Transmission** of the message from the nociceptor along the primary afferent sensory fibers to the spinal cord, and through the spinal cord and ascending relay neurons in the thalamus, reticular formation and brainstem to the somatosensory cortex.
3. **Modulation** of the message as it passes across synapses in the spinal cord, thalamus and other areas of the midbrain and brainstem.
4. **Integration** of the above series of electrochemical events with the unique psychology of the individual, resulting in the final experience of pain perception

The perception of pain is no longer viewed as a static process. Long-term changes occur within the peripheral and central nervous system following stimulation, which alter the body's response to further input.

Transduction

Peripheral nociceptors are comprised of small myelinated (A-delta) and unmyelinated (C polymodal) fibers that respond maximally to a variety of noxious mechanical, chemical and thermal stimuli. A-delta fibers found at cutaneous sites may also be classified as high threshold mechanoreceptors (HTMs) or mechanothermal nociceptors depending on whether or not they respond to pressure, thermal stimulation or both. A-delta fibers have relatively small receptive fields and are responsible for the initial, sharp, localized pain felt after a noxious stimulus. C-polymodal nociceptors (C-PMNs) found at cutaneous sites respond to noxious stimuli of mechanical, thermal and chemical (e.g., inflammatory mediator) origin, thus the term polymodal. C-PMNs have relatively large receptive fields and mediate the more diffuse, aching and prolonged pain experienced following the initial response [4,5].

Transduction in deep somatic tissue is similar to that in cutaneous tissues although the nociceptors respond to slightly different stimuli (i.e., some nociceptors are also responsive to muscle activity and joint extension in the noxious range). Visceral nociceptors are relatively insensitive to stimuli that are noxious to cutaneous receptors, but are sensitive to twisting, distension and ischemia. They generally have large overlapping receptive fields and can become sensitized in

response to inflammation.

The insult to the body that produces pain often results in inflammation and nerve injury. As part of the inflammatory response, a number of substances may be released peripherally at the site of tissue injury to increase transduction of the noxious stimulus (peripheral sensitization). These substances may be released by the nociceptor itself (substance P, neurokinin A, calcitonin gene-related peptide), or may be released from near-by damaged cells and infiltrating inflammatory cells (potassium, serotonin, bradykinin, histamine, nitric oxide, cyclooxygenase products of arachidonic acid metabolism such as prostaglandin E_2, and cytokines such as interleukin-1 and tumor necrosis factor). Release of these substances increases the excitability of sensory and sympathetic nerve fibers, causes vasodilation and extravasation of plasma proteins, and results in further release of chemical mediators from inflammatory cells. The net result is sensitization of the peripheral nociceptors such that low intensity signals not normally causing pain are perceived as painful (hyperesthesia), and an increase in the pain response to noxious stimulation (primary hyperalgesia) [6]. In addition, these changes spread to adjacent non-injured tissue (secondary hyperalgesia).

Transmission
Painful stimuli that are transformed into an electrical signal by nociceptors relay their information to the spinal cord through the primary afferent sensory fibers, which have their cell bodies in the dorsal root ganglion. Sodium channels in the nerve axons allow a wave of depolarization that carries the signal into the dorsal horn of the spinal cord. These nerves synapse in the dorsal horn with second order neurons, which relay the stimulus up the spinal cord to the brain. Application of local anesthetics that block these sodium channels stops the signal from reaching the dorsal horn and the brain.

Transmission to higher centers occurs primarily via the spinothalamic, spinoreticular, and spinomesencephalic tracts, leading to suprasegmental and cortical responses. Suprasegmental responses include increases in sympathetic tone and catecholamine release, hypothalamic stimulation with increases in metabolism and oxygen consumption, and an overall increase in "fight or flight" arousal mechanisms.

Modulation
The cell body of the nociceptor lies in the dorsal root ganglia. From the cell body, projections run both peripherally to the free nerve ending and centrally, entering the spinal gray matter and synapsing in the dorsal horn of the spinal cord. Here, the incoming information may be modified by inputs from both excitatory and inhibitory interneurons before the incoming information is relayed to higher centers in the brain.

A number of neurotransmitters are important for transmitting information across synapses in the spinal cord, including excitatory amino acids such as glutamate and aspartate, peptides such as substance P and neurokinin A, and cyclooxygenase products of arachidonic acid metabolism such as prostaglandin E_2 (PGE_2). For example, glutamate activates postsynaptic AMPA and kainite receptors, while substance P activates postsynaptic AMPA and neurokinin (NK) receptors. Within the dorsal horn neuron, arachidonic acid is released and metabolized via the cyclooxygenase (COX) pathway to PGE_2, which then acts in a feedback loop on excitatory interneurons to amplify the incoming message. Interestingly, while nonsteroidal anti-inflammatory drugs (NSAIDs) have traditionally been viewed as providing pain relief primarily by decreasing signs of inflammation and sensitization of pain receptors peripherally, we now know that the COX pathway is up-regulated at the level of the spinal cord, which suggests that NSAIDs may actually provide pain relief predominantly through this central effect [7].

Repetitive noxious stimulation, including that associated with surgery or trauma, results in a change in the response properties of the dorsal horn neurons such that neuronal activity of the dorsal horn cell progressively increases throughout the duration of the stimulus. This results in a decrease in the response threshold, an increase in the responsiveness of the cell once threshold is reached ("after-discharge"), and an increase in the receptive field of that neuron. This is known **as central hypersensitization or "wind-up"** and results is an increased perception of pain to a given stimulus [8].

Wind-up will occur in the absence of peripheral sensitization and is thought to be mediated, in part, by activation of the NMDA receptor within the spinal cord [9]. NMDA receptor antagonists such as ketamine can ameliorate central hypersensitization without altering the normal response of the dorsal horn cells to noxious stimulation. In addition, up-regulation of COX activity (especially COX-2 activity) occurs during wind-up. The resulting increase in production of PGE_2 causes amplification of the incoming nociceptive signal at the level of the spinal cord, further contributing to "wind-up".

Demonstration of this "wind-up" phenomenon is the basis for the increased interest in preemptive analgesia (that is, providing analgesics before inciting injury). preemptive analgesia, by reducing the initial acute pain response, may prevent (or at least limit) the changes associated with "wind-up." Evidence for "wind-up" may be found as long as a month after surgery [9]. To prevent wind-up, analgesics should ideally be started prior to surgery.

Activity within the spinal cord is strongly influenced by descending inhibitory pathways originating in higher centers of the

brain. Profound analgesia can be achieved by electrical stimulation of several areas of the central nervous system, including the periaqueductal grey matter (midbrain) and periventricular grey matter (lateral to the hypothalamus). These two areas are connected anatomically to each other and to the rostroventral medulla, another area with similar properties. Activation of these regions activates descending opioid, noradrenergic (acting via an alpha-2 receptor mediated mechanism) and serotonergic pathways, which inhibit incoming pain stimuli at the level of the dorsal horn. For example, small injections of morphine to discrete regions of the brain, as well as application of opioids directly to the spinal cord, can produce profound analgesia, indicating multiple sites of opioid action [10]. Similarly, activation of descending serotonergic and noradrenergic pathways lead to activation of inhibitory interneurons within the dorsal horn of the spinal cord which release endogenous opioids (endorphins, enkephalins, dynorphins) as their neurotransmitter.

Pain - Assessment

Assessing pain in our veterinary patients can be difficult, especially if the animal is in unfamiliar surroundings such as a hospital or in unfamiliar circumstances such as waking up from anesthesia. However, there are some basic steps to follow that can help in determining whether or not a patient needs analgesics.

1. **Anticipate pain severity**: Learning to anticipate when a patient will be painful is extremely helpful, since pain is much easier to manage if the patient is treated before they become painful and upset, than if they are treated afterward. Frequently, knowing the patients underlying disorder, whether or not a procedure has recently been performed on the animal and, if so, what type will guide the use of analgesics. Usually, analgesics are given before surgery to take advantage of preemptive analgesia (and minimize "wind-up").
   Certain procedures are considered "high pain" procedures (see below), and the need for profound analgesia should be anticipated. These include thoracotomies, proximal joint surgeries, many ophthalmologic procedures, aural surgery and any surgery involving extensive tissue trauma. In addition, an inexperienced surgeon may cause more tissue trauma, and consequently more pain, than an experienced surgeon would. Very young and very old patients, as well as critically ill patients, tend to be less tolerant of pain and the neurohormonal and autonomic changes associated with pain.
2. **Learn common and species-specific behavioral responses to pain** and be able to distinguish them from normal behavior exhibited in a veterinary clinical setting. Each species has behaviors that are demonstrated in the presence of pain. As an example, many dogs and cats are unwilling to sit or lie down in the presence of abdominal pain. Painful animals also retreat to the rear of the cage, and may appear disinterested in their environment. In contrast painful prey animals such as goats and sheep may appear relatively normal but be less interested in eating and do not ruminate as often as non-painful animals. It is important that when possible, animals be observed prior to a painful stimulus such as surgery so that both normal and unique individual behavioral characteristics (such as vocalization in nervous dogs) can be identified and distinguished from post surgical pain behaviors.
3. **Learn and practice regular assessment of pain**: Pain is a dynamic process and can change in severity depending on the presence of inflammation, the duration of action and route of administration of analgesics, and the physical activity and position of the patient. As such, patients should be assessed regularly after trauma or surgery for the presence of pain and if found, treated appropriately. In addition to patient observation as described above, pain assessment requires physical examination of the patient using gentle palpation of the affected area and assessment of cardiovascular and respiratory variables such as heart rate and respiratory rate. Pain scoring systems can be used to quantify pain and define a level of severity above which "rescue" analgesics will be given. Effective use of pain scoring systems requires education of both professional and support staff in order to reduce observer variability and create a common language for discussing and recording pain.

Pharmacologic Mechanisms of Intervention

Designing an Analgesic Drug Regimen

Understanding mechanisms of pain transmission and antinociceptive mechanisms allows a logical choice in prescribing analgesics for our patients. Current recommendations for pain management include the following:

1. **A preemptive approach**: Analgesic administration before, during and after a painful stimulus will minimize the effects of "wind-up".
2. **A mechanism-based approach**: Understanding pain pathways and the mediators responsible for transduction, transmission, and modulation allow a tailored approach to pain management for different underlying disease processes. For example, analgesia may be directed at minimizing inflammatory changes at the site of injury (e.g., by using a non-steroidal anti-inflammatory agent), at inhibiting transduction or transmission of the nociceptive signal (e.g., by using a local anesthetic), and/or at increasing descending inhibition (e.g., by using an opioid analgesic).
3. **A multimodal approach**: Selecting drugs from different analgesic classes, that influence different portions of the pain pathway, results in a synergistic, rather than a mere additive, effect and optimizes analgesia while minimizing drug side effects.

Specific Analgesic Drugs Families

Opioids

Opioids are frequently used for acute pain control in veterinary medicine, and are the mainstay of therapy in the perioperative period. Not only are opioids highly effective analgesics for moderate to severe pain, they may also be given pre-operatively to provide sedation and aid restraint. Opioids tend to be relatively sparing of the cardiovascular system and their use as a premedication allows for a decrease in the amount of other, more cardiovascularly depressant agents needed to provide anesthesia [11]. Opioids may be administered by epidural, intrathecal or systemic routes to inhibit pain transmission from the dorsal root to higher centers, and to modulate the perception of pain at the level of higher centers. Recent evidence suggests that there is also an up-regulation of peripheral opioid receptors (e.g., within the joint capsule) during chronic inflammatory states, and that local administration may provide analgesia [12].

Opioids produce analgesia by their actions on specific opioid receptors (mu, kappa, delta), mimicking the effects of the endogenous opioids (endorphins, enkephalins, dynorphins). These receptors vary in their pharmacological effects (although all three produce analgesia) and their distribution throughout the body. Pure opioid agonists (morphine, fentanyl, sufentanil, meperidine, methadone, hydromorphone and oxymorphone) bind to one or more opioid receptors subtypes [13], and provide the most profound analgesia for patients with moderate to severe pain. However, the side effects may also be pronounced, especially in the debilitated patient.

Opioid agonist-antagonists (butorphanol and buprenorphine) generally provide less analgesia than pure opioid agonists and are usually inadequate for any surgery with significant tissue trauma (e.g., most orthopedic procedures), but are advantageous in that their side effects also tend to be less severe. Therefore, their use may be preferred in certain situations. The submaximal analgesia and less severe side effects reflect the fact that these drugs have a "ceiling" on the maximal effect they cause. Despite additional drug administration, no improvement in analgesia can be achieved over that obtained from one maximal recommended dose. Administration of these agents may partially reverse the effects of previously administered pure agonists. This may be advantageous if the effect you are trying to reverse is sedation or respiratory depression. Unfortunately, it will also reverse some of the analgesia.

Side effects

1. **Sedation**: All of the opioids cause a certain degree of sedation. This may be helpful if an animal has not been able to sleep due to pain, stress, etc. However, overzealous use of opioids may cause the patient to become excessively sedate and unarousable.
2. **Excitement or dysphoria**: Many animals become excited during emergence from general anesthesia. This is especially true if they have received opioids during the anesthetic period. Vocalization in dogs does not necessarily equate with pain. Some breeds (e.g., Huskies, Dobermans, Labradors) appear especially susceptible to excitement and excessive vocalization after opioid administration. Cats (especially young, healthy cats) may get excited when given pure opioid agonists, but are less likely to get excited with butorphanol or buprenorphine. The excitatory effects of opioids in cats although inconsistent are usually dose dependent and to prevent this phenomenon cats are generally given doses 1/2 - 3/4 those administered to dogs. If your patient becomes excessively dysphoric or excited after receiving an opioid, a sedative such as acepromazine or diazepam may be required (remember…respiratory depression and hypotension may be exacerbated).
3. **Respiratory Depression**: Respiratory depression is one of the more serious complications of systemic opioid administration. All opioids cause respiratory depression, and cause a decrease in the responsiveness of the brain to CO_2. Respiratory depression may be exacerbated by concomitant administration of other drugs (e.g., diazepam). Opioids should be used judiciously at reduced dosages in patients where respiratory function is a serious concern (e.g., pneumonia, post-thoracotomy). Increased CO_2 as a result of respiratory depression also causes cerebral vasodilation and increased intracranial pressure. Therefore, opioids should not be used in patients with head trauma or intracranial lesions unless they are being ventilated. In addition, opioid-induced sedation may make neurologic assessment more difficult.
4. **Hypotension**: Most opioids are relatively sparing of the cardiovascular system, although they must be used with care, especially in debilitated patients. In addition, there are some differences between the various drugs. Most opioids may cause a vagally-mediated bradycardia that is easily treated with anticholinergics (e.g., atropine, glycopyrrolate). Oxymorphone, hydromorphone and fentanyl tend to provide the most cardiovascular stability of the opioids commonly used as analgesics in veterinary medicine. Both morphine and meperidine given IV may cause hypotension secondary to histamine release and vasodilation, especially in dogs. Meperidine also causes cardiac depression. Note: hypotension after opioid administration may be exacerbated by concomitant administration of other drugs (e.g., diazepam or acepromazine).
5. **Nausea and vomiting**: Opioids cause stimulation of the medullary chemoreceptor trigger zone to cause emesis. When used as a premedication, some opioids (e.g., morphine) are especially prone to causing vomiting. This is usually not as common when using opioids post-operatively, but occasionally it may be difficult to differentiate from other causes of vomiting (e.g., pancreatitis). If vomiting is a concern, butorphanol is a good alternative due to its anti-emetic properties.

6. **Hypothermia**: Opioids that are partial or full agonists at the mu receptor (e.g., buprenorphine and hydromorphone) reset the thermoregulatory center in the brain causing patients to tolerate heat loss without initiating compensatory mechanisms such as shivering. Immediately after receiving opioids, it is common for dogs to actively cool them selves to subnormal temperatures by panting. Patients receiving opioids must be insulated from environmental surfaces that promote cooling and they commonly require warm water blankets or forces air warmers to maintain body temperature above 100°F. Mild hypothermia (98 - 100°F) is not uncommon in alert patients on opioids and should not be a cause for concern. However, a body temperature below 100°F should always be corrected in severely depressed or unarousable patients.
7. **Urine Retention**: Opioids that are agonists at the mu receptor have been reported to cause dose related urinary retention (inability to urinate with a full bladder). Studies have demonstrated that fentanyl, buprenorphine, and to a lesser extent, morphine alter bladder sensations and increase the residual volume in the bladder after voiding for several hours after administration. This occurs because opioids inhibit the sacral parasympathetic outflow, especially after epidural administration and after large IV doses, resulting in an increased maximal bladder capacity and detrusor muscle relaxation. Animals being treated with agonist opioids should have their urine output and bladder size assessed regularly and a urinary catheter should be placed if urination is inadequate.

Treatment of Side Effects: If undesirable side effects should occur after opioid administration, the opioid can be reversed by giving naloxone at 0.01 - 0.02 mg/kg IM or slowly IV while closely observing the patient. It is important to provide cardiovascular and respiratory support if needed until the naloxone has had adequate time to take effect. Buprenorphine may be difficult to reverse and require up to 10X the naloxone dose required to reverse a full mu agonist such as morphine. Opioid reversal with naloxone will also remove the analgesia. Therefore, it is usually preferable to titrate the dose of naloxone by using smaller boluses (one-eighth to one-quarter of the usual dose) until the desired effect is achieved. Alternatively, small doses of butorphanol (0.05 - 0.1 mg/kg) may be titrated to reverse some of the sedative effect of a pure opioid agonist, while retaining some of the analgesia by enhancing the kappa effects.

Specific Opioids
The opioids are a diverse group of drugs that are classified together due to their affinity for the opioid receptors. The effects of each opioid are noted below along with unique aspects important to remember in the clinical use of each drug.

Morphine: pure mu opioid agonist
- provides excellent analgesia of relatively long duration (4 - 6 hrs after IM administration)
- provides good sedation
- commonly causes vomiting when used as a premedication, but this is seen less frequently when used postoperatively
- histamine release and subsequent hypotension is dose-dependent after IV administration
- may see pronounced excitement after rapid IV administration
- can be given as a constant rate infusion (CRI)
- Schedule II

Oxymorphone (Numorphan ®): pure opioid agonist
- good cardiovascular stability
- lasts 2 - 4 hours after IM administration
- relatively expensive at this time, not readily available
- least amount of dysphoria
- Schedule II

Hydromorphone (Dilaudid ®): pure opioid agonist
- cardiovascular effects similar to those of oxymorphone
- may see excitement when giving IV
- Schedule II

Meperidine (Demerol ®): pure opioid agonist
- can cause pronounced histamine release - DO NOT GIVE IV
- relatively short duration (45 minutes), therefore, not commonly used postoperatively
- structurally similar to atropine - less likely to cause bradycardia than the other opioids, antispasmodic?
- can cause myocardial depression
- Schedule II

Fentanyl: pure mu opioid agonist
- relatively short duration of action after IV administration due to redistribution (20 - 30 minutes), may be given as a continuous infusion
- provides good cardiovascular stability, although a pronounced vagally-mediated bradycardia may be seen
- profound respiratory depression at higher doses

- Schedule II

Butorphanol (Torbugesic ®, Torbutrol®): kappa agonist, mu antagonist
- side effects (e.g., excitement, respiratory depression, sedation) may be less severe than those seen with pure opioid agonist, but provides only mild to moderate analgesia (good visceral analgesia)
- duration of action reportedly 2 - 4 hrs, but recent reports suggest it only lasts 1 - 2 hrs
- low doses (0.05 - 0.1 mg/kg) may be used to partially reverse the effects of a pure agonist
- Schedule IV

Buprenorphine (Buprenex®): partial mu agonist, kappa antagonist (?)
- long duration of action (6 - 8 hours)
- provides good analgesia
- may be difficult to reverse with naloxone
- excellent lingual/mucosal absorption in cats
- Schedule III

Alternate routes of opioid administration
Alternative routes of opioid administration are being used with increasing popularity. Since systemic levels of the drug tend to be lower, side effects tend to be less severe.

1. Epidural administration of opioids
   The use of epidural opioids has gained increased favor over the last few years. Epidural administration in small animal patients is generally made in the lumbosacral space. Although Morphine is the most commonly administered epidural opioid, fentanyl, oxymorphone, butorphanol, and buprenorphine have also been proven effective when given epidurally.
   Morphine
   0.1 mg/kg of a 1 mg/ml preservative-free solution (e.g., DuraMorph®) may be administered as is or diluted to 0.2 or 0.3 ml/kg with sterile saline - delayed onset (2 - 8 hr), long lasting (24 hr)
   Morphine and bupivacaine
   0.1 mg/kg of a 1 mg/ml preservative-free solution (e.g., DuraMorph®) and 0.1 ml/kg of 0.5% bupivacaine. The bupivacaine begins to work within the first 30 minutes and lasts about 8 hours, while the morphine's peak effect occurs after 8 - 12 hours and lasts 24 hours
2. Intra-articular administration
   Intra-articular opioids may be useful during chronic inflammatory states (e.g., cruciate rupture) due to activation of peripheral opioid receptors within the joint (after tissue damage)
   Morphine
   0.1 mg/kg of a 1 mg/ml preservative-free solution (e.g., DuraMorph®) may be diluted to 0.3 ml/kg with sterile saline
3. Transdermal fentanyl patches
   Transdermal fentanyl patches marketed for use in human patients with chronic pain disorders are also used in veterinary patients. The respiratory depression caused by fentanyl is clinically significant when used in the post-operative period in humans and has led to death. However respiratory depression does not appear to be as severe in dogs. Other side effects that have also been reported include nausea, vomiting, inappetance, sedation and bradycardia. Excitement may be seen in cats.
   The patch must be applied (usually between the shoulder blades) for 12 - 24 hrs before therapeutic drug levels are achieved. There is considerable individual variation in drug absorption. Therefore, patients should be monitored both for analgesia and side effects. Some patients may require additional analgesics. If unacceptable side effects do occur, systemic drug levels decrease rapidly after the patch is removed. Patches at a dose of 2 - 4 micrograms/kg have been shown to provide therapeutic blood levels of fentanyl in dogs for up to 3 days and in cats for 4 days.

Local Anesthetics
Lidocaine and bupivacaine are amide local anesthetics frequently used in veterinary medicine as adjuncts to general anesthesia. These drugs act by blocking the sodium channel in the neuronal membrane, inhibiting action potential generation and propagation, and, when used topically, by local infiltration or for regional nerve blocks to block transduction and transmission of primary afferent signals. These agents also may be administered epidurally or intrathecally where they act to block transmission of the nociceptive signal from the dorsal root of the spinal cord to higher centers.

Local anesthetics are extremely useful for providing analgesia for pain arising in discrete locations. Routine use of these techniques in the postoperative period is often limited, however, because repeated infiltration can be technically difficult and may be painful in the awake patient.

The effects of bupivacaine (4 - 8 hrs) are of longer duration than those of lidocaine (1.5 - 3 hrs), so it is often preferred for postoperative analgesia. However, it also has a longer onset of action (15 - 30 minutes vs. 5 - 10 minutes, respectively). A combination of lidocaine and bupivacaine may be used when a more rapid onset of action is desired, although the total dose of each drug should be adjusted accordingly (e.g., use half of the calculated dose of each drug or 66% of one and 33% of the other).

Bupivacaine may be infiltrated around the intercostal nerves or given intrapleurally to provide analgesia after thoracotomy. For intrapleural administration, the animal is placed incision side down before the bupivacaine (1.5 mg/kg of a 0.5% preservative-free bupivacaine solution) is administered via the chest tube. The local anesthetic diffuses across the parietal pleura and allows repeated block of the intercostal nerves (e.g., every 4 - 6 hours). To reduce the pain on injection, 0.1 mEq of sodium bicarbonate may be added to 1 ml of the local anesthetic. Perineural drug infiltration is also useful for other painful procedures such as amputation.

Local anesthetics may be given intra-articularly (0.3 ml/kg of a 0.5% preservative-free bupivacaine solution for stifle surgery) at the time of surgery. Lidocaine may be given intravenously as an adjunct to other methods of analgesia. Bupivacaine, however, should never be given intravenously, due to a high incidence of cardiotoxicity. In addition, either lidocaine or bupivacaine may be used intraperitoneally to decrease inflammation and provide pain relief in some situations (e.g., pancreatitis).

These drugs may be administered epidurally or intrathecally. The site for epidural injection in small animal patients is usually the lumbosacral intravertebral space. This space is relatively easy to access in small animal patients, and the spinal cord generally ends at (cats) or cranial to (dogs) the lumbosacral junction, so an intradural (subarachnoid) puncture is uncommon. It is important to remember that when local anesthetics are used, sympathetic fibers will be blocked in addition to the sensory blockade. Therefore, vasodilation is commonly seen after epidural administration of local anesthetics, and may cause hypotension in hypovolemic patients. As the dose or concentration of local anesthetic is increased, progressively larger nerves (e.g., motor neurons) become blocked and the cranial extent of the block will increase. The sympathetic block will extend a couple of dermatomes cranial to the sensory block, potentially causing significant cardiovascular side effects. Local anesthetics are frequently given in combination with an opioid (e.g., bupivacaine with morphine-see above) to produce effective analgesia while decreasing the overall dose of local anesthetic given. Contraindications to epidural injection include hypovolemia and septicemia, coagulopathy, and local skin infection at the site of injection [14].

Local anesthetics can also be administered through a catheter implanted in the surgical site. These catheters, known as "soaker catheters", allow the administration of small amounts of local anesthetic within the surgical field after closure of the incision. A constant rate infusion of lidocaine (1 - 2%, 1.5mg/kg/hr), or intermittent administration of bupivacaine (0.5%, 1.5mg/kg) every 6 hours through the soaker catheter for the first 24 - 48 hours after surgery, in addition to low doses of systemic analgesics, provides excellent postoperative analgesia for highly invasive surgeries such as limb amputations and ear ablations, or surgeries with extensive tissue dissection such as mastectomy and removal of invasive tumors. These catheters can be made from red rubber catheters, as described by Hansen [15], or purchased from a veterinary manufacturer (Mila International, Florence, KY, www.milaint.com).

More recently, use of lidocaine patches has been advocated for pain arising from discrete locations. Patches (Lidoderm®, Endo Pharmaceuticals) currently available contain lidocaine (5%) embedded in a gel suspension (700 mg total) on a felt background, such that the patch may be cut to fit the affected area. The manufacturer recommends that the patch be applied for a 12 hour period and then removed for a 12 hour period to minimize systemic absorption of the local anesthetic.

Care must be taken when administering these drugs by any route, due to their relatively high systemic toxicity. Toxic cardiovascular and neurologic effects (i.e., convulsions) may be seen at doses relatively close to the effective dose. Arrhythmias and myocardial depression from local anesthetics, particularly bupivacaine, can be extremely difficult to treat. In dogs, the IV dose for lidocaine that produces seizures is 11 mg/kg, while for bupivacaine it is 3 - 5 mg/kg [16]. Cardiotoxic doses are slightly higher than the seizure dose. These agents rely on hepatic metabolism; therefore, adjustments should be made in patients with liver disease. In addition, half-lives are longer in cats and toxic doses are lower than for dogs. There are no available reversal agents.

Non-Steroidal Anti-inflammatory Agents (NSAIDs)

NSAIDs are effective analgesic adjuncts, especially in the face of tissue inflammation. New information and the availability of new drugs are changing the way that non-steroidal anti-inflammatory agents (NSAIDs) are being viewed as part of the multimodal approach to treating pain in the perioperative period. NSAIDs inhibit the cyclooxygenase (COX) enzyme of arachidonic acid metabolism, resulting in a number of antiinflammatory, antipyretic, and analgesic effects. COX products of arachidonic acid metabolism include the "classic" prostaglandins (e.g., prostaglandin E2), prostacyclin and thromboxane. Many of these metabolites are important mediators of the peripheral inflammatory response that contributes to peripheral hypersensitization. More recently, it has been recognized that NSAIDs produce much of their analgesic effect

by inhibiting COX activity (more specifically COX-2 activity) centrally [7].

These drugs do not cause sedation, excitement, respiratory depression, or hypotension when used at therapeutic doses. However, care must be taken with their use. It is now apparent that the COX enzyme exists in at least two isoforms, COX-1 and COX-2 (recently, a COX-3 isoform has been identified in the brain) [17]. COX-1 is always present in tissues (i.e., constitutive), including the gastric mucosa, liver, kidneys and platelets. Prostanoid products of COX-1 actively mediate gastric mucosal barrier protection, maintain liver and renal perfusion, particularly in conditions of decreased blood flow, such as hypovolemia and/or hypotension, and normal platelet aggregation. In contrast, COX-2 is primarily an inducible enzyme found predominantly in inflammatory cells, peripheral nerves and the central nervous system, although it is also found constitutively within the central nervous system as well as the kidney, where it plays a role with the COX-1 isoform in physiologic renal functions. There is evidence that COX-1 expression in the spinal cord increases in the post-surgical period [7].

COX-2 activity, both peripherally and centrally, increases following peripheral inflammation. The increase in COX-2 activity peripherally, with a concomitant increase in the production of prostaglandin E2, leads to many of the signs associated with inflammation, including heat, redness, and swelling. In addition, prostaglandin E2 contributes to sensitization of peripheral pain receptors, increasing their duration of firing. Until recently, inhibition of peripheral COX activity was believed to be the primary mechanism of action through which NSAIDs provided analgesia. However, it is now recognized that much of their analgesic effect is due to inhibition of the cyclooxygenase enzyme, more specifically the COX-2 isoform, centrally. Therefore, an opportunity exists for development of effective analgesic agents with selective antiinflammatory effects (i.e., COX-2 inhibition) with minimal gastric side effects or effects on coagulation [18]. However, care must still be taken when using these newer drugs in the perioperative period to ensure adequate renal perfusion, including administered fluids and monitoring blood pressure intraoperatively. In addition, while inhibition of COX-2 activity should not directly cause gastrointestinal ulceration, COX-2 inhibition may influence ulcer healing because of its effects on angiogenesis. Idiosyncratic side effects may also occur.

Side Effects

1. **GI ulceration and hemorrhage**: One of the most serious side effects of non-steroidal use is GI ulceration and hemorrhage. This is usually seen with chronic use, but some agents may cause ulceration with perforation after only a few doses and patients should be watched carefully for signs of GI upset (nausea, vomiting) or melena [19]. The incidence of ulceration is greatly increased in patients receiving NSAIDs in combination with steroids, so this combination should be avoided. COX-2 preferential inhibitors should cause less GI ulceration, although direct effects resulting in GI irritation (vomiting, diarrhea) may still occur. If GI ulceration is present, therapy is discontinued until healing has occurred, even when switching to a COX-2 preferential inhibitor, since COX-2 inhibition can decrease the rate of angiogenesis (new vessel growth required for wound healing).
2. **Nephrotoxicity**: NSAIDs may cause renal ischemia, especially in patients with decreased peripheral perfusion. This is due to inhibition of local prostaglandin production in the kidney. Although prostanoids do not play a major role in the normal healthy kidney, prostaglandins normally cause vasodilation and help maintain renal perfusion in low flow states. Therefore, NSAIDs (whether non-selective or COX-2 preferential) should be avoided in hypotensive or critically ill patients. Sodium and water retention may also occur and these drugs should be avoided in patients with congestive heart failure.
3. **Hepatotoxicity**: Hepatotoxicity caused by NSAIDs is generally considered idiosyncratic. Administration of carprofen has been associated with an idiosyncratic, cytotoxic hepatocellular reaction [20]. Anorexia, vomiting, icterus, and elevated liver enzymes may be seen. Most dogs recover with discontinuation of the drug and supportive care. Liver and kidney enzymes should be monitored prior to and a month after initiation of a NSAID regimen and then yearly; drug administration must be stopped if significant elevations in enzymes occur.
4. **Decreased platelet function**: NSAIDs inhibit platelet function due to inhibition of thromboxane production, a potent platelet aggregator and vasoconstrictor. This is a COX-1- mediated event. Therefore, care should be taken if bleeding is anticipated or a primary concern (i.e., surgery). This is especially important when using aspirin, since this drug causes irreversible inhibition of the cyclooxygenase enzyme by acetylation and new platelets must be produced before clotting function returns to normal. COX-2 preferential drugs should not affect hemostasis intraoperatively if used preoperatively and may be preferred in the perioperative period.

Specific NSAIDs

Aspirin (acetylsalicylic acid): Nonselective COX inhibitor

- May cause GI hemorrhage (buffered preparations available)
- Acetylates and irreversibly inhibits the cyclooxygenase enzyme on the platelet membrane, decreasing platelet aggregation and coagulation until new platelets are formed
- Not approved for use in the dog

Flunixin meglumine (Banamine ®): Nonselective COX inhibitor
- May cause gastrointestinal (GI) ulceration after only a few doses and it is recommended that its use be limited to 3 days with careful monitoring
- Nephrotoxicity has also been reported after prolonged use

Piroxicam: Nonselective COX inhibitor (preferential COX-2 in dogs) [21]
- May cause GI ulceration
- Immunomodulatory as well as anti-inflammatory

Phenylbutazone: Nonselective COX inhibitor
- One of the first NSAIDs used in veterinary medicine
- Causes a number of side effects in dogs (e.g., GI ulceration) - other NSAIDs are preferred

Ketoprofen: Nonselective COX inhibitor
- Nephrotoxicity (see flunixin)
- Injectable or oral tablets
- Increased intraoperative bleeding has been reported when used preoperatively

Carprofen (Rimadyl ®): Preferential COX-2 inhibitor
- Some studies suggest that the decreased incidence in GI side effects may be due to its relative lack of efficacy at the COX enzyme overall, rather than COX-2 selectivity.
- GI ulceration has been reported after its use in dogs
- Both nephrotoxic and hepatotoxic effects have been reported after its use [20].
- Injectable and oral tablet preparations are available

Etodolac (Etogesic®): Marketed as a COX-2 preferential NSAID,
- Some studies suggest that in dogs, this drug may not be COX-2 preferential.
- Although efficacious as an analgesic, anecdotally reported to have a relatively high incidence of GI ulceration.

Deracoxib (Deramaxx®): Targeted COX-2 inhibitor, little activity at COX-1 at clinical doses
- First of the "coxib"-class of NSAIDs approved for use in the dog
- Has proven efficacious in providing analgesia for both postoperative orthopedic procedures and chronic osteoarthritic pain.
- Recent research looking at the effects of coxib-type drugs and COX-2 inhibition in certain models of cancer suggest that these drugs may not only provide pain relief, but may also decrease local tumor invasion and metastasis (possibly related to effects of angiogenesis)

Meloxicam (Metacam®): Preferential COX-2 inhibitor
- Narrow therapeutic margin - GI ulceration and perforation have been reported at twice the label dose
- Available in injectable and oral suspension
- Approved for use in dogs and cats
- Easy to dose appropriately in smaller exotic species

Tepoxalin (Zubrin®): Nonselective COX inhibitor
- Lipoxygenase inhibitor (potential use in asthma patients?)

Firocoxib (Previcox ®): Targeted COX-2 inhibitor
- Coxib class of NSAIDs
- Licensed for use in dogs for osteoarthritis
- Literature describes use in dogs and cats [22,23]
- Available as chewable tablets
- Side effects and precautions similar to those seen with other coxibs

Acetaminophen (Tylenol ®): COX-3 inhibitor
- Can be combined with other COX inhibitors to improve analgesia
- Toxicity and death when used in cats

Naproxen (Aleve ®):
- Naproxen is not recommended for use in dogs. Perforated gastric ulcers have been reported in dogs, even after only one dose.

Other Analgesics

Steroids

Steroids produce analgesia due to an antiinflammatory effect similar to that of the NSAIDs. Steroids block both

cyclooxygenase and lipoxygenase pathways due to inhibition of phospholipase A2. Release of arachidonic acid from the cell membrane via the actions of phospholipase A2 and C is the rate limiting step in arachidonic acid metabolism. Risk of GI ulceration is high, especially when used in combination with a NSAID. Other side effects may occur due to a host of systemic effects and other analgesics are generally preferred.

Alpha - 2 Agonists
Alpha adrenoreceptors are located in several areas within the spinal cord and brain stem concerned with analgesia. Alpha-2 agonists (e.g., xylazine, detomidine, medetomidine) when given systemically, provide analgesia and cause sedation. They also produce pronounced cardiovascular side effects including vasoconstriction-associated hypertension, which is followed by hypotension (primarily with xylazine) secondary to a decrease in norepinephrine release and sympathetic outflow centrally, with pronounced decreases in heart rate and cardiac output. They may cause respiratory depression, emesis, and increased urine production. For these reasons they are not usually a first choice for analgesia although various techniques have been developed recently to optimize the analgesia while minimizing the side effects associated with this family of analgesics [24]. Low doses (0.5 - 3 micrograms/kg/hr) of intravenous medetomidine administered as a CRI have been shown to provide analgesia with minimal cardiovascular effects [25]. Also, alpha-2 agonists given epidurally or intrathecally, can provide analgesia with a decreased incidence of untoward side effects. These drugs have already become popular for epidural use in large animal patients, and are likely to become more popular in small animal patients as well.

Ketamine
Ketamine is an NMDA receptor antagonist and may be useful as an adjunct analgesic to prevent "wind-up" [26]. An adjunct analgesic is one that does not provide adequate analgesia unless used in combination with an opioid or local anesthetic. Ketamine appears to be most effective in patients undergoing surgery that includes extensive tissue trauma (thoracotomy, amputation, superficial wounds). Ketamine, when used as an analgesic adjunct, is given at sub-anesthetic doses (0.1 - 0.5 mg/kg, IV), or given as a CRI (0.1 - 0.6 mg/kg/hr with the higher end of the dose range administered intraoperatively and the lower end administered postoperatively). It may interact with the opioid receptor and prevent the development of opioid tolerance, so it is usually administered in combination with an opioid or local anesthetic.

Gabapentin
Tricycylic antidepressants, antiepileptic agents such as phenytoin, gabapentin (Neurontin ®), pregabalin (Lyrica ®) and other agents have also proven effective for certain types of chronic pain syndromes (e.g., neuropathic pain, diabetic neuropathy) not amenable to more classic analgesic treatment. Gabapentin, developed as an anticonvulsant, was initially recognized for its effectiveness in reducing the hyperalgesia and allodynia associated with neuropathic pain. It has since been shown to be effective in reducing acute pain due to incisional injury and arthritis [27]. It has also been shown to reduce the need for other analgesics when administered concurrently in a multimodal regimen. Therapeutic dosing has not been established for dogs and cats but extrapolation of doses recommended for humans suggests a starting dose of 1.25 - 4 mg/kg, PO to as high as 50mg/kg once daily [28]. This dosing range may change as scientific studies are published since gabapentin has a high therapeutic range (when used as an antiepileptic, it is used at doses between 800 to 1500 mg daily).

Tramadol
Tramadol (Ultram ®) is an unscheduled, synthetic analgesic drug that causes its effect by action at several types of receptor. It inhibits the re-uptake of the neurotransmitters serotonin and norepinephrine [29], but binds weakly to opioid receptors. However the dominant metabolite, M1 (O-desmethyltramadol), has a 20 - 200 fold greater affinity for mu receptors compared to the parent compound. M1 is formed by the action of cytochrome P450 (CYP) 2D6, the same CYP that metabolizes codeine to morphine. Tramadol does not cause clinically significant cardiovascular or respiratory depression, has antitussive properties, and has been reported to have little potential for addiction and abuse. In dogs after ovariohysterectomy, tramadol at a dose of 2mg/kg has been shown to provide comparable analgesia to that achieved by 0.2mg/kg of morphine [30]. Recommended dosing for dogs varies from 8 - 10mg/kg, PO once daily [28], to 5 mg/kg, PO four times a day, or 2.5 mg/kg every 4 hours [31]. Intravenous dosing in dogs and cats is recommended at 2 - 4 mg/kg [28]. Because it is not a controlled drug and is reasonably priced, it is easy to send home with clients for short term treatment of acute pain in dogs and cats. It can also be administered intermittently to dogs and cats with chronic pain when maintenance analgesics such as NSAIDs are inadequate. Long term administration of tramadol for chronic conditions is not currently recommended unless other options have been exhausted.

Amantadine
Amantadine (Symmetrel ®), like ketamine, is a noncompetitive NMDA receptor antagonist that is available in injectable and tablet forms. Its advantage over ketamine is that it has no psychotropic side effects, is not a controlled drug, and can be administered at home with other analgesic drugs in a multimodal regimen to reduce postoperative pain associated with central sensitization. Originally developed as an antiviral drug, it has been shown to be effective in reducing neuropathic pain due to surgery in cancer patients and is synergistic with morphine in some types of pain in laboratory animals [32]. It is effective in the treatment of opioid tolerance and allodynia at a recommended dose of 3 - 5 mg/kg, PO daily for dogs and

cats [28].

New research involving the use of neurotoxins has proven effective for chronic osteoarthritic patients and may become more available in the future.

References

1. Classification of Chronic Pain, 2nd Ed, IASP Task Force on Taxonomy. H. Merskey and N. Bogduk. Seattle: IASP Press, 1994; 209-214.

2. McGuire L, Heffner K, Glaser R, et al. Pain and wound healing in surgical patients. Ann Behav Med 2006; 31:165-172.

3. Muir WW. Pain and stress. In: Gaynor JS, Muir WW, eds. Handbook of Veterinary Pain Management. Philadelphia: Mosby, 2002; 46-59.

4. Raja SN, Meyer RA, Ringkamp M, et al. Peripheral mechanisms of nociception. In: Wall PD, Melzack R, eds. Textbook of Pain. 4th Edition. London: Churchill Livingstone, 1999; 11- 57.

5. Lamont LA, Tranquilli WJ and Grimm KA. Physiology of pain. Vet Clin North Am Small Anim Pract 2000; 30:703-728.

6. Dray A. Inflammatory mediators of pain. Br J Anaesth 1995; 75:125-131.

7. Beiche F, Scheuerer S, Brune K, et al. Up-regulation of cyclooxygenase-2 mRNA in the rat spinal cord following peripheral inflammation. FEBS Lett 1996; 390:165-169.

8. Woolf CJ. Somatic pain - pathogenesis and prevention. Br J Anaesth 1995; 75:169-176.

9. Doubell TP, Mannion RJ, Woolf CJ. The dorsal horn: state dependent sensory processing, plasticity and the generation of pain. In: Wall PD, Melzack R, eds; Textbook of Pain. 4th Edition. London: Churchill Livingstone, 1999; 165-181.

10. Yaksh TL. Pharmacology and mechanisms of opioid analgesic activity. Acta Anaesthesiol Scand 1997;41:94-111.

11. Pascoe PJ. Opioid analgesics. Vet Clin North Am Small Anim Pract 2000; 30:757-772.

12. Stein C. Mechanisms of Disease: The control of pain in peripheral tissues by opioids. N Engl J Med 1995; 332:1685-1680.

13. Waldhoer M, Bartlett SE, Whistler JL. Opioid Receptors. Annu Rev Biochem 2004; 73:953-990.

14. Wetmore LA, Glowaski MM. Epidural analgesia in veterinary critical care. Clin Tech Sm Animal Pract 2000; 15:177-188.

15. Hansen B. Advancements in pain management. In: Proceedings from the Bridge to the Future, 2003, Aug 10-11, Providence RI; 33-38

16. Lemke KA, Dawson SD. Local and regional anesthesia. Vet Clin N Am (Sm Anim Pract) 2000; 30:839-857.

17. Chandrasekharan NV, Dai H, Turepu Roos KL, et al. COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: Cloning, structure, and expression. Proc Natl Acad Sci USA 2002; 99:13926-13931.

18. Mathews KA. Nonsteroidal anti-inflammatory analgesics. Vet Clin N Am (Sm Anim Pract) 2000; 30:783-804.

19. Dowers KL, Rayroux S, Hellyer PW, et al. Effect of sequential NSAID therapy on the upper gastrointestinal tract in dogs. Vet Anaesth Analg 2005; 32(4):16.

20. MacPhail CM, Lappin MR, Meyer DJ, et al. Hepatocellular toxicosis associated with administration of carprofen in 21 dogs. J Am Vet Med Assoc 1998; 212:1895-1901.

21. Streppa HK, Jones CJ, Budsberg SC. Differential biochemical inhibition of specific cyclooxygenases by various non-steroidal anti-inflammatory agents in canine whole blood. Am J Vet Res 2002; 63:91-94.

22. McCann ME, Andersen DR, Zhang D, et al. In vitro effects and in vivo efficacy of a novel cyclooxygenase-2 inhibitor in dogs with experimentally induced synovitis. Am J Vet Res 2004; 65:503-512.

23. McCann ME, Rickes EL, Hora DE, et al. In vitro effects and in vivo efficacy of a novel cyclooxygenase-2 inhibitor in cats with lipopolysaccharide-induced pyrexia. Am J Vet Res 2005; 66:1278-1284.

24. Murrell JC and Hellebrekers LJ. Medetomidine and dexmedetomidine: a review of cardiovascular effects and

antinociceptive properties in the dog. Vet Anaesth Analg 2005; 32:117-127.

25. Pascoe PJ. The cardiovascular effects of dexmedetomidine given by continuous infusion during isoflurane anesthesia in dogs. Vet Anaesth Analg 2006; 33(2):97-103.

26. Schmid RL, Sandler AN, Katz J. Uses and efficacy of low-dose ketamine in the management of acute postoperative pain; a review of current techniques and outcomes. Pain 1999; 82:111-125.

27. Mao J, Chen LL. Gabapentin in pain management. Anesth Analg 2000; 91:680-687.

28. Gaynor JS. Other drugs used to treat pain. In: Gaynor JS, Muir WW, eds. Handbook of Veterinary Pain Management. Philadelphia: Mosby, 2002; 251- 260.

29. Sagata K, Minami K, Yanagihara N, et al. Tramadol inhibits norepinephrine transporter function at desipramine-binding sites in cultured bovine adrenal medullary cells. Anesth Analg 2002; 94:901-906.

30. Mastrocinque S, Fantoni DT. A comparison of postoperative tramadol and morphine for the control of early postoperative pain in canine ovariohysterectomy. Vet Anaesth Analg 2003; 30:220-228.

31. Kukanich B, Papich MG. Pharmacokinetics of tramadol and the metabolite O -desmethyltramadol in dogs. J Vet Pharmacol Therap 2004; 28:239-246.

32. Snijdelaar DG, van Rijn CM, Vinken P, et al. Effects of pre-treatment with amantadine on morphine induced antinociception during second phase formalin responses in rats. Pain 2005; 119:159-167.