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". Surgery produces tissue injury with consequent release of histamine and inflammatory mediators, such as peptides (e.g., bradykinin), lipids (e.g., prostaglandins), neurotransmitters (e.g., serotonin), and neurotrophins (e.g., nerve growth factor). 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. The release of inflammatory mediators activates peripheral nociceptors, which initiate transduction and transmission of the nociceptive information to the central nervous system (CNS) and the process of neurogenic inflammation in which release of neurotransmitters (i.e., substance P and calcitonin gene-related peptide) in the periphery induces vasodilatation and plasma extravasation. An animal’s behavior and interactions can be unique to the type of pain it is experiencing. A patient’s reaction to pain is dependent upon its personality and the degree of pain it is experiencing. Remember that there is no substitute for being familiar with an individual animal in order to recognize how it shows pain. Control of animal pain and the timing, duration (e.g., preemptive analgesia), and fashion in which it is implemented (e.g., multimodal perioperative management) may be important in facilitating short and long-term patient convalescence after surgery.

PREEMPTIVE ANALGESIA

Development of central sensitization and hyperexcitability occurs after surgical incision and results in the amplification of postoperative pain. Preventing the establishment of altered central processing by analgesic treatment may result in short-term (e.g., reduction in postoperative pain and accelerated recovery) and long-term (e.g., reduction in chronic pain) benefits during a patient's convalescence. Experimental studies convincingly confirm the concept of preemptive analgesia in decreasing postinjury pain, and this should be the goal when performing orthopedic surgery on veterinary patients. Definitions of preemptive analgesia include what is administered before surgical incision, what prevents establishment of central sensitization resulting from incisional injury only (i.e., intraoperative period), or what prevents central sensitization resulting from incisional and inflammatory injuries (i.e., intraoperative and postoperative period). The first two definitions are relatively narrow and may contribute to the lack of a detectable effect of preemptive analgesia in clinical trials. Timing of the intervention may not be as clinically important as other aspects of preemptive analgesia (i.e., intensity and duration of the intervention). An intervention administered before surgical incision is not...
necessarily preemptive if it is incomplete or insufficient such that central sensitization is not prevented. Incisional and inflammatory injuries are important in initiating and maintaining central sensitization. Confining the definition of preemptive analgesia to only the intraoperative (incisional) period may not be clinically relevant or appropriate because the inflammatory response may last well into the postoperative period and continue to maintain central sensitization. Other methodologic and study design issues also may complicate the question of whether preemptive analgesia is clinically relevant. A variety of agents and techniques has been used to study preemptive analgesia. Using the broader definition of preemptive analgesia that covers incisional (intraoperative) and inflammatory (postoperative) injuries, the combination of experimental data and positive clinical trials strongly suggests that preemptive analgesia is a clinically relevant phenomenon. Maximal clinical benefit is observed when there is complete blockade of noxious stimuli with extension of this block into the postoperative period. By preventing central sensitization, preemptive analgesia along with intensive multimodal analgesic interventions may reduce acute postoperative pain and chronic pain after surgery. The analgesic benefits of controlling postoperative pain are generally maximized when a multimodal strategy to facilitate the patient's convalescence is implemented. Postoperative pain treatment may not be enough to provide major improvements in some outcomes because it is unlikely that unimodal intervention can be effective in addressing a complex problem such as perioperative outcomes. Principles of a multimodal strategy include control of postoperative pain of the patient to allow early mobilization, early enteral nutrition, education, and attenuation of the perioperative stress response through the use of regional anesthetic techniques and a combination of analgesic agents (i.e., multimodal analgesia). The use of epidural anesthesia and analgesia is an integral part of the multimodal strategy because of the superior analgesia and physiologic benefits conferred by epidural analgesia. A multimodal strategy to control postoperative pathophysiology and facilitate rehabilitation results in accelerated recovery and decreased length of hospitalization. This approach may decrease perioperative morbidity, decrease the length of hospital stay, and improve patient satisfaction without compromising safety.

**ANALGESIC OPTIONS**

Many options are available for the treatment of both intra and postoperative pain, including systemic analgesics either alone or in combination. Opioid analgesics are one of the cornerstone options for the treatment of clinical pain. However, many other agents are now routinely being included in veterinary postoperative analgesic regimens and include: NMDA antagonists (ketamine), alpha-2 agonists, lidocaine and NSAIDs.

**OPIOIDS** These agents generally exert their analgesic effects through μ receptors in the CNS, although there is evidence that opioids may also act at peripheral opioid receptors. A theoretical advantage of opioid analgesics is that there is no analgesic ceiling. Realistically, the analgesic efficacy of opioids is typically limited by the development of tolerance or opioid-related side effects such as nausea, vomiting, sedation, or respiratory depression. Opioids may be administered by subcutaneous, transcutaneous, and transmucosal routes, but the most common routes of postoperative systemic opioid analgesic administration are oral, intravenous, and intramuscular. Opioids also may be administered at specific anatomic sites such as the intrathecal or epidural space. There is wide intersubject and inrasubject variability in the relationships of opioid dose, serum concentration, and analgesic response in the treatment of postoperative pain. Certain routes of administration (e.g., intramuscular) may result in a wider variability in

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serum drug concentrations than other routes (e.g., intravenous). In general, opioids are administered parenterally (intravenously or intramuscularly) for the treatment of moderate to severe postoperative pain, in part because these routes provide a more rapid and reliable onset of analgesic action than the oral route. Parenteral opioid administration may be necessary in patients who are unable to tolerate oral intake postoperatively. The transition from parenteral to oral administration of opioids usually occurs after the patient initiates oral intake and postoperative pain has been stabilized with parenteral opioids. Although oral opioids (typically as part of a combination product that includes an adjuvant such as acetaminophen) are generally prescribed on an "as needed" (PRN) basis postoperatively, there may be a role for sustained-release oral opioids that may provide superior analgesia compared with conventional PRN regimens. Transdermal fentanyl has been used for acute pain management, but transdermal fentanyl cannot be easily titrated. A fentanyl patch can be applied at least 12 hours preoperatively and may provide analgesia for up to 3 days post-operatively. 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. Care should be taken to avoid placing the patch in contact with patient warming devices. If additional opioids are required intraoperatively, fentanyl should be administered and the patient closely monitored to prevent opioid overdose. Almost all opioids are easily reversed with naloxone if adverse effects require treatment (buprenorphine requires significantly higher doses of naloxone and only partial reversal can be achieved). Agonists can be given slowly IV to effect, or IM/SQ. Morphine causes histamine release and should only be given IM, SQ or very slowly IV. Dose should be reduced when administered concurrently with an alpha-2 agonist. Although butorphanol can provide sedation and mild analgesia, it is of short duration and other opioids are much preferred in treating postoperative orthopedic pain. Butorphanol is however useful for reversal of opioid induced side effects at a dose of 0.1 mg/kg IV administered to effect.

**OPIOID DOSAGES:**
- Morphine 0.5 - 1 mg/kg IM
- Oxymorphone 0.05 - 0.2 mg/kg IM
- Hydromorphone 0.05 - 0.2 mg/kg IM
- Fentanyl 0.005 - 0.01 mg/kg IM
- Methadone 0.2 - 0.3 mg/kg IM (may also have NMDA receptor activity)
- Buprenorphine 0.01 - 0.02 mg/kg IM

**KETAMINE** Although ketamine has been used for many years to induce or maintain anesthesia during surgery, it has only recently been shown to be a useful analgesic postoperatively. When administering ketamine at low doses, usually as a constant rate infusion (CRI), it is important to taper off the infusion rate to prevent hypersensitivity that can occur if the infusion is suddenly stopped. Ketamine is most effective when given concurrently with other analgesic drugs, especially opioids. Ketamine, when used as a postoperative 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 beginning with 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. It can provide analgesia by functioning as an antagonist at the NMDA receptor. It potentiates the antinociceptive effects of both opioids and alpha-2 agonists, improving the analgesia achieved from the simultaneous administration of ketamine and
either of these drugs, and is useful for reversing opioid tolerance due to chronic opioid administration. At low doses ketamine has also been shown to have anticonvulsant properties and it is thought to be safe at these doses for relief of pain in seizure prone and head trauma patients.

**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. 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 in the postoperative period.

**LIDOCAINE** Lidocaine administered systemically at antiarrhythmic doses (50 - 80 μg/kg/min) provides systemic analgesia, scavenges free radicals, and increases GI motility. Lidocaine administered to dogs intraoperatively as a CRI at doses of 50 and 200 μg/kg/min has been shown to reduce the minimum alveolar concentration (MAC) of isoflurane required to prevent purposeful movement in response to a noxious stimulus. This effect is dose related and is thought to be due to its analgesic effects although the sedative effects of lidocaine may also reduce MAC. Lidocaine has also been shown to relieve neuropathic pain in humans at a dose of 5 mg/kg/hr and this is also the case in postoperative orthopedic patients (used at a dose initially of 20 μg/kg/min IV, particularly when combined with an opioid.

**NSAID’S** Perioperative administration of NSAIDs, specifically COX-2 inhibitors, reduces inflammation and pain associated with surgery and can be administered orally the night before surgery or by injection just prior to surgery since they do not have clinically significant effects on hemostasis. They should be continued through the postoperative period for 3 - 5 days to reduce the production of inflammatory mediators that play a role in the development of peripheral and central sensitization. Although there is clear indication for the preoperative use of NSAIDs, there are concerns about the effects of these drugs on kidney and liver function in the face of hypotension, which occurs in many patients during general anesthesia. Interestingly, there are several studies assessing the effects of COX-2 selective NSAIDs on the kidneys of healthy and compromised anesthetized patients and none of them demonstrated any adverse effect on renal function. There are no studies assessing the effects on liver function in these same patient populations and until such data indicate otherwise, patients receiving preoperative NSAIDs should have blood pressure monitored, IV fluids administered, and hypotension treated with positive inotropes (dopamine) if volume replacement does not effectively treat hypotension. NSAIDs can be administered post-operatively if not already given prior to surgery.

**NSAID DOSAGES:**
- Carprofen (Rimadyl) 2 - 4 mg/kg SQ
- Deracoxib (Deramaxx) 2 - 4 mg/kg PO

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Etodolac 10 - 15 mg/kg PO SID
Firocoxib (Previcox) 5 mg/kg PO
Ketoprofen 1 - 2 mg/kg SQ, SID
Meloxicam (Metacam) 0.2 mg/kg SQ

**CONCLUSION** Animal pain is a complex problem for many veterinarians to manage as many factors may influence the recognition, objective assessment and analgesics available. However, in my practice of veterinary analgesia, if I am in doubt whatsoever that an animal is in pain; I administer an analgesic and then re-evaluate.

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