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REDUCING THE PAIN FACTOR – AN UPDATE ON PERI-OPERATIVE ANALGESIA

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Analgesic techniques have appeared on the program of almost every small animal veterinary conference for the last 10 years, reflecting the importance and evolving nature of the topic.

The use of opioids and NSAIDs has not changed markedly in this time but with greater incite into how these agents function and how nociceptive information is transmitted the use of alternative drugs and fine tuning of dose and route allows for safer and more effective analgesia.

An understanding of the pain pathways is necessary to appreciate why various analgesic techniques are effective in preventing or reducing pain sensation.

Current Understanding of Nociceptive Processing

Processing of nociceptive information is not a hard-wired system in which nociceptors (pain receptors) are stimulated, information transmitted in a uniform manner to the spinal cord via nerve fibres, synapsing with spinal neurons and further transmission to the cerebrum so that “pain” is felt. Nociceptive transmission is in fact quite fluid and many factors influence the duration and potency of the message reaching the brain.

Nociceptors are free nerve endings that have their cell bodies in the dorsal root ganglia. There are mechanical, thermal, and chemical nociceptors found peripherally in the skin, periosteum and joints whereas internal organs have only a small number of nociceptors that transmit aching pain when tissue damage occurs. Sensitivity of these receptors can be variably affected by the presence of surrounding tissue trauma, inflammatory mediators and duration of the nociceptive stimulation.

Nociceptive information is transmitted by A δ and C fibres. A δ fibres are small myelinated neurons that mediate sharp, acute pain that is felt rapidly after actual or potential tissue injury, is easily localised and is termed **fast pain**. **Slow pain** is mediated by slower, unmyelinated C fibres that result in aching or throbbing pain that is poorly localised. Nociceptors do not adapt to continuous stimulation by down-regulating as many other nerves do but in fact appear to up-regulate so that minor stimuli can be perceived as painful (hyperalgesia). The A δ and C fibers terminate within superficial layers of the dorsal horn and second order neurons cross the midline to take the nociceptive information cranially to the thalamus, brainstem and cerebral cortex.

Pain perception is modified by many factors including other incoming information, descending pathways and multiple chemical substrates and neurotransmitters. Surgery and trauma directly stimulate nociceptors and also result in local damage that causes release of inflammatory mediators such

as prostaglandins. These mediators lower the threshold for nociceptor firing, increase spontaneous activity, and increase and prolong firing. This effect is called peripheral sensitisation and results in low intensity stimuli that don't usually cause a painful response to be perceived as pain (allodynia). Central sensitisation results from an increase in spinal neuron receptivity due to long exposure to nociceptive afferent input from the peripheral neurons. N-methyl-D-aspartate (NMDA) receptors in the spinal cord are responsible for central sensitisation. Peripheral and central sensitisation combine to produce "wind-up" that is responsible for a decrease in the pain threshold at the site of injury and in the surrounding uninjured tissue. In addition continued input from peripheral nociceptors may result in the establishment of abnormal synaptic connections which enhance the pain sensation and are not responsive to usual analgesic agents

Pre-emptive Analgesia

It has been theorised that sensitisation and wind-up can be prevented by administering analgesic drugs that inhibit input of nociceptive information. Pre-emptive analgesia is the term given to providing analgesia before the onset of pain perception and it is thought to decrease overall pain sensation and the amount of analgesic agent needed to control pain. It has been demonstrated that this is clearly the case in many laboratory studies but data from human clinical trials provides little conclusive evidence that pre-emptive analgesia reduces post-surgical pain or the need for analgesia. Various studies in small animals have shown both an effect and lack of effect depending upon type of drug, parameters monitored etc. Pre-emptive analgesia makes theoretical sense and ought to work so provided that it doesn't harm the patient in any way then it should be considered routinely. Drugs that have been used as analgesics in these studies include the usual analgesic agents such as opioids, NSAIDs, alpha-2 agonists, and in addition ketamine and dextromethorphan (NMDA antagonists).

Now down to the practical part of this paper

Techniques for providing analgesia

Local anaesthetic techniques

Local anaesthesia fits the category of pre-emptive analgesia perfectly because it is usually administered prior to surgery. The duration of blockade is determined by both the agent used and to a lesser degree by the site of administration. Lignocaine (lidocaine) has a fairly rapid onset (10-15 minutes) and short duration of action (1 to 1½ hours) whereas bupivacaine has a slow onset (20-30 minutes) but longer duration of action (4 to 6 hours). The agents are often combined to provide rapid onset and long duration of effect. In our practice local infiltration is commonly provided during dental extractions and forelimb surgery and epidural techniques for hind limb surgery. Not only is intra- and post-op analgesia provided by local anaesthesia, but the anaesthetic period is frequently stable because the lack of sensation prevents variable CNS stimulation.

NSAIDs and Opioids

These groups of agents are the mainstay of analgesia in small animal patients. Opioids are commonly provided in the peri-operative period because they do not have the potential to induce renal dysfunction as the NSAIDs can and they provide sedation in the pre-operative period. A combination of ACP (0.01-0.04 mg/kg), morphine (0.2-1.0 mg/kg) and atropine (0.03-0.04 mg/kg) given SQ is our primary choice but ACP (0.01-0.02 mg/kg) and methadone (0.2-0.4 mg/kg) given intravenously provides excellent sedation within 5 to 10 minutes and is also frequently used. For post-operative analgesia we have been using higher doses of buprenorphine that are recommended in most texts and now routinely provide 0.03 mg/kg to 0.04 mg/kg SQ to all post-operative patients. The advantage of buprenorphine is that it provides pain relief while not sedating the patient so that they will get up, move, drink and eat as normal while the other longer acting opioids often result in sedation. Constant rate infusions of morphine are commonly recommended for post-operative analgesia and while they do provide excellent pain relief the patients can also become heavily sedated and so must be constantly monitored while they are receiving the drug. In our practice we have seen heavy sedation on low doses (0.1 mg/kg/hr IV) so do not use this form of pain relief unless the patient can be monitored.

There are pros and cons to using the NSAIDs for peri-operative pain relief. They are not controlled in the same manner as the opioids, they can provide excellent analgesia but they can also induce transient or permanent renal dysfunction, most commonly seen in cats. The advent of the new COX-2 selective agents was hailed as the era of the safe NSAIDs as they were not thought to interfere with renal function but this has not been the case and they are shown to be constitutively produced in the kidney and involved in prostaglandin-dependent renal homeostatic processes.

There has been no clear evidence that the pre-emptive use of these agents reduces pain perception or analgesia requirements and they should not be routinely administered in the pre-operative period. Rather than routine administration each case should be considered on the merits of administering a NSAID versus the potential side effects. If given pre- or intra-operatively close monitoring during the anaesthetic period is required to ensure that blood pressure and tissue perfusion are maintained within the 'normal' range and that adequate fluids are provided to support renal perfusion.

Ketamine

Ketamine has been shown to reduce wind-up of pain by blocking the NMDA receptor in the CNS. For intra- and post-operative analgesia it is given as a CRI (constant rate infusion) and at the doses used has minimal cardiovascular or respiratory effects. Given intra-operatively it reduces the requirements for the more depressant inhalational agents and smooths out the anaesthetic period. It can be given in conjunction with any of the opioids. The dosage is 0.1 mg/kg IV as a loading dose followed by 2 µg/kg/min. After

an infusion the dose should be tapered to prevent hypersensitivity that may occur if the infusion is suddenly stopped. Dextromethorphan and amantadine are also NMDA antagonists and are given by the oral route.

Alpha-2 agonists

The alpha-2 agonists are frequently given for sedation while we often disregard their analgesic properties. Low doses of medetomidine at 1-2 ug/kg can provide analgesia with reduced but not absent cardiovascular side effects. It may also be given as a CRI but even at low doses (1.5 µg/kg/hr) in healthy dogs there is a cardiac output and tissue oxygen delivery. Consequently patients must be closely monitored and this technique should be used in patient with cardiovascular compromise.

Lignocaine (lidocaine)

Lignocaine is commonly administered as a CRI for management of arrhythmias but at a similar dose rate (50-80 µg/kg/min) it can also provide dose related systemic analgesia. It has also been shown to have oxygen-derived free radical scavenging ability and can improve GI motility. Administered during surgery it reduces the concentration of inhaled anaesthetic agent needed to maintain anaesthesia. related

Summary

Analgesia should be considered in all surgical patients to smooth the anaesthetic and post-surgical periods. Pre-emptive analgesia should be provided in all patients with the proviso that no harm should come to the patient with the administration of the agent. Finally, consider some of the 'old' local anaesthetic techniques to provide analgesia to your anaesthetised patient and also some of the 'new' CRIs for intra- and post-operative analgesia.