INNOVATIONS IN ANESTHESIA: WHAT'S NEW?

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Abstract

Acute and chronic pain is underdiagnosed and treated in veterinary medicine. New metrology and assessment tools are helping us "measure" pain and our toolbox of pharmacological and non-pharmacological drugs is growing. As the underlying mechanisms of pain become better understood targeted therapies are being developed. In addition, we are revisiting old drugs such as ketamine and beginning to understand its unique role in acute and chronic pain management. The current opioid shortage in the United States has pushed us to use more local anesthetic techniques in our surgery and trauma patients and the benefits of these are becoming clear. Liposomal based local anesthetics can provide analgesia for up to 72 hours and improves compliance as they are administered during surgery, and fewer rescue analgesics which often cause sedation and inappetence are required. The future of pain management for companion animals looks bright.

Keywords: opioids, local anesthesia, ketamine, acute, chronic, pain

Introduction

Acute and chronic pain afflicts millions of humans and animals and current treatment options do not fully meet the needs of all patients. We now know that poorly managed acute pain can progress to long term or maladaptive pain, so addressing perioperative pain in a multimodal and robust manner is essential. The most common cause of long-term pain in dogs and cats is

osteoarthritis; this disease is not currently curable therefore treatment is aimed at managing the pain associated with it. Although non-steroidal anti-inflammatory agents are widely used, they are not always fully effective or are sometimes associated with adverse side effects. An active ongoing goal of pain research is to better understand the underlying mechanisms of pain and to identify new specific therapeutic targets which should be more effective and have fewer unwanted side effects.[1]

Acute pain

As we are all aware there is a shortage of specific opioids in the USA, including morphine, hydromorphone, and fentanyl, while methadone has become cost prohibitive in most situations. The shortage is a result of several factors including closure of USA based production plants, the destructive hurricanes that hit Florida, Houston and Puerto Rico in 2017 (where many drugs are manufactured) and decreased production mandated by the Drug Enforcement Administration **(**DEA). Due to the issue of diversion and the opioid addiction crisis the DEA cut production of specific opioids by 25% in 2017 and plan on continuing a 20% decrease each year. These shortages have impacted human medicine and have produced a trickle-down effect in veterinary practice. The opioid shortage in veterinary medicine highlights the need for drug companies to seek approval for veterinary approved opioids so we become independent of shortages in the human medical field. In the USA, the only opioids that have veterinary approval are butorphanol and "24-hour buprenorphine" (Simbadol™, Zoetis, United States) which is only approved for cats. In many European countries, methadone and fentanyl have a veterinary label.

Preventing central plasticity

Preventing central plasticity (sensitization or "wind-up") is a major goal of perioperative analgesic protocols. This process occurs at the N-methyl-D-aspartate (NMDA) receptors in the

dorsal horn of the spinal cord. Ketamine has traditionally been considered only as a dissociative anesthetic but its role as an analgesic and anti-hyperalgesic agent has evolved over the years in both human and veterinary medicine.[2] Ketamine is a non-competitive NMDA receptor antagonist. It has been described as a "reset" button for chronic pain, treatment of depression and post-traumatic stress syndrome in humans. It is being used for reducing pain related to trauma, and for procedural sedation in children, with the advantage that it can be given intranasally.[3,4] Its role as a treatment for peripheral and central pain following major limb injuries suffered in combat is well documented and initiatives are underway to optimize how it is used for neuropathic pain management.[5,6] Other areas where ketamine shows promise include ischemic and reperfusion injury and neuroprotection following acute injury to the central nervous system.[7,8] In 2017, the International Anesthesia Research Society published an infographic titled "Villain to Victor: Ketamine in Acute Neurologic Injury", stating that although still investigational, ketamine shows tremendous promise as a neuroprotectant.[9] New guidelines have been released on its use for chronic pain; the reason behind these is to guide clinicians because of the wide variation in dosing regimens and because ketamine is not yet FDA approved for treatment of chronic pain in humans.

Several clinical studies in dogs undergoing surgery have shown beneficial effects of ketamine. In a study of female dogs undergoing ovariohysterectomy (without known analgesics) dogs received a sub-anesthetic dose of ketamine (2.5 mg/kg intramuscularly) pre-operatively or post-operatively (at extubation), or saline.[10] Mechanical nociceptive thresholds were measured, and pain scores recorded before premedication and post-operatively for up to 18 hours after extubation. Dogs in the control (saline) group required more rescue analgesics, showed more wound sensitivity and had higher pain scores throughout the post-operative period than those in

the two ketamine groups. Wagner and colleagues studied the effects of adding low dose ketamine infusion (a control group received saline infusion) to an already established analgesic protocol that included pre-operative morphine and intra- and post-operative fentanyl infusion in dogs undergoing forelimb amputation.[11] The ketamine protocol used was: 0.5 mg/kg IV (bolus) given before surgery followed by 10 $\mu g\ kg^{-1}\ min^{-1}$ during surgery and 2 $\mu g\ kg^{-1}\ min^{-1}$ for 18 hours after surgery. At 12 and 18 hours after surgery the ketamine treated dogs had lower pain scores and on the third post-operative day this group were also significantly more active. Ketamine has anti-proinflammatory actions, which may provide additional benefits. In a clinical study dogs diagnosed with pyometra and undergoing surgery were sequentially allocated to receive a standard anesthetic and analgesic protocol, with or without low-dose ketamine infusion (not blinded).[12] Serum C-reactive protein (CRP) was measured before, 24 and 48 hours after surgery. Low dose ketamine attenuated the post-operative increase of serum CRP.[12]

Local anesthetics

The opioid shortage has pushed us to be more creative with multimodal analgesic therapy including more use of local anesthetic techniques. Whenever possible a local anesthetic should be incorporated into every surgery; they are the only class of drugs that can produce complete analgesia. By blocking transmission from the surgical site to the central nervous system they can decrease central sensitization. The techniques used can be a simple as wound infiltration, intraperitoneal instillation[13] or more advanced such as femoral and sciatic nerve blocks for stifle surgery. Drugs such as lidocaine and bupivacaine have a duration of 1.5 and 4-5 hours respectively; much shorter than the duration of inflammation and pain resulting from surgery. One way to extend the duration of action is to use wound diffusion catheters which are placed in the surgical site at the time of surgery; for example, limb amputations and large soft tissue

resections such as mastectomies. It is important to use bacterial filters and sterile technique every time an injection is made. Two (2) mg/kg of bupivacaine can be infused every 6-8 hours. In cats undergoing major soft tissue surgery the addition of wound catheters to an already robust multimodal plan had benefits including earlier return to eating and discharge from the hospital.[14] A new option for the veterinary profession is to use long acting formulations of bupivacaine which have been approved for use in humans for many years. A liposome formulation of bupivacaine that produces local post-operative analgesia directly at the surgical site has been approved by the FDA for use in dogs (Nocita®, Aratana Therapeutics). In dogs it is currently labelled for cruciate surgery and is administered as a single treatment into the tissue layers during surgical closure and is released over time at the surgical site, providing local post-operative relief for up to 72 hours. This product has recently been approved by the FDA for use in cats as a peripheral nerve block to provide regional post-operative analgesia following onychectomy.[A]

Lidocaine infusions

In dogs, intravenous lidocaine infusions can be used as an anesthetic sparing technique (decreased inhalant anesthetic requirements) and to provide analgesia. However, after stopping the infusion analgesia is only maintained for a short period of time. Recommended doses are a 0.5-1.0 mg/kg IV bolus followed by an infusion of 20-50 $\mu g\ kg^{-1}\ minute^{-1}$. NOTE: lidocaine infusions are not recommended in cats due to the cardiac depression and poor perfusion they cause.[15] Lidocaine infusions show promise for alleviating chronic pain in humans[16] and anecdotal reports indicate it should be evaluated in dogs for this purpose.

Current and future treatment strategies for chronic (maladaptive) pain

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the primary class of drug used for the treatment of pain related to osteoarthritis (OA) in all species including humans. However, it is not surprising that if used alone, they may fail to be fully effective. It is estimated that 20 to 40% of humans that suffer from OA associated pain have a central or maladaptive "drive" to their pain. Only one veterinary study has been published combining a NSAID with a centrally acting drug. The combination of a NSAID with the NMDA receptor antagonist amantadine was beneficial.[17]

Piprants

A new class of drugs called the piprants are being widely studied and one such drug, grapiprant, is available for the treatment of osteoarthritis associated pain in dogs. Grapiprant is a selective antagonist of the EP4 receptor, one of the four prostaglandin E_2 (PGE_2) receptor subtypes. There are likely to be fewer unwanted side-effects with this class of drug because the COX-1 and COX-2 pathways are not affected. Although not yet approved for use in cats, the safety data is encouraging.[18]

Neurokinin-1 antagonists

Maropitant is a NK-1 receptor antagonist that inhibits binding of substance P to NK-1 receptors and is marketed as an antiemetic for dogs and cats. Because substance P is involved in pain pathways maropitant may have some analgesic properties. Preliminary work evaluating its anesthetic sparing effects suggests it may provide visceral analgesia in dogs and cats, but more studies are needed to define its role in pain management.[19]

Monoclonal antibodies

There is a huge growth in the use of monoclonal antibodies to treat numerous diseases in humans and this has spilled over into veterinary medicine. Nerve growth factor (NGF*)* has been

identified as an important mediator of inflammatory and neuropathic pain and is therefore a potential therapeutic target. NGF levels are increased in many naturally occurring acute and chronic pain conditions and in animal models of pain. Inhibiting or sequestering NGF alleviates hyperalgesia in many of these models. Current areas of study for targeting NGF include monoclonal antibodies to NGF or its tyrosine kinase receptor and sequestration of NGF with a soluble receptor protein with high binding affinity. A fully caninised anti-NGF monoclonal antibody (NV-01, Ranevetmab) has been developed for use in dogs with osteoarthritis. In one clinical trial, Canine Brief Pain Inventory scores decreased for up to four weeks following intravenous administration of NV-01.[20] A felinized product (NV-02, Frunevetmab) has also been developed and early reports indicate adequate safety and efficacy for up to 6 weeks after a single subcutaneous injection in cats with naturally-occurring degenerative joint disease.[21] There is an excellent Open Access review on the role of anti-nerve growth factor monoclonal antibodies for the control of pain in dogs and cats.[22]

Cannabinoids

There is great interest in the use of "medical marijuana" by owners and veterinarians alike. All animals except insects have an endocannabinoid system. Hemp oil extracts and medical marijuana are possibilities for our patients but there can be toxicity and quality control issues with current products. There is potential for use in pets with osteoarthritis and cancer pain if the correct receptors are targeted. Hemp oil tends to target the cannabidiol (CBD) and cannabinol (CBN) receptors and not the tetrahydrocannabinol (THC). Currently many needed research studies are hampered by the strict control of the parent product (DEA Schedule 1). However, some clinical trials have been conducted (e.g. in dogs with osteoarthritis) and encouraging results

are being reported.[23] It is imperative that veterinarians follow federal, state and local VMA rules about discussing or recommending cannabinoid products to their clients.

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Resources

- Liposome encapsulated bupivacaine (Nocita®): https://nocita.aratana.com/
- IVAPM Opioid-Sparing Task Force White Paper: https://ivapm.org/professionals/opioid-shortage

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- World Small Animal Veterinary Association Global Pain Council Guidelines for the Recognition, Assessment and Treatment of Pain: www.wsava.org/guidelines/global-pain-council-guidelines
- World Small Animal Veterinary Association Global Pain Council Education “how to” videos: www.wsava.org/Committees/Global-Pain-Council