PAIN MANAGEMENT VIA SYSTEMIC APPROACH BEYOND OPIOIDS

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Pain is defined as “an unpleasant sensory and emotional experience in response to an inflict in the tissue”. Pain management in cats and dogs at perioperative and postoperative periods presents a significant challenge to clinicians. The obvious lack of communication dictates the therapy to depend on the animal’s behaviour to assess the degree of pain. The ability to relate such signs with pain management will be crucial to the success of pain control. In addition, sound knowledge in physiology of pain and pharmacology of pain control substances will be critical for successful therapeutic outcome in animals.

Several pharmacological classes are available as analgesics, but most effective ones belong to opioids. However, mild to moderate pain can be successfully managed with non-opioid analgesics. Practical use of opioids is often limited by inconvenience in prescription because of strict government regulations as scheduled substance. Many practitioners would be concerned about potential abuse by the owners and hospital staff exposed to these medications. Other analgesics free of such concern include NSAIDs, corticosteroids, NMDA antagonists, alpha 2 agonists, and sodium channel blockers (local and systemic). Although pharmacological therapy is increasingly accompanied by physical therapies including massage and ultrasound, acupuncture and chiropractics, transcutaneous electrical nervous stimulation (TENS), laser irradiation, and magnetic therapy, current presentation will focus on pharmacological management.

Pharmacologic choices
A variety of drugs have been advocated to treat pain in dogs and cats. Available routes of drug administration of analgesics at perioperative periods are IV, IM, transdermal, oral, subcutaneous, and rectal routes, but IV, IM and SQ routes are most favored at perioperative periods because of quick onset and control of pharmacological effect both in time and efficacy.

For synergism, it is not uncommon to co-administer analgesics of different classes such as opioids, NSAIDs, alpha 2 agonists, and NMDA antagonists. It is also not uncommon to combine a specific analgesic
drug with an anxiolytic or sedative which enhances analgesic properties, suggesting pain a complex phenomenon which can be controlled by even through behaviour modification.

**Non steroidal anti inflammatory drugs (NSAIDs)**

Modern potent NSAIDs such as carprofen, meloxicam and ketoprofen can be regularly prescribed at post operative period for provision of analgesia. It is probable that they do not provide any surgical analgesia (carprofen does not reduce the MAC of halothane in dogs by an appreciable scale). When compared with opioids for post operative analgesia, the NSAIDs have the advantage of not decreasing consciousness or causing respiratory depression. Their anti inflammatory action speeds healing and decreases pain. They are toxic, and tend to be cumulative. There are major species differences in elimination times and toxicity, and data and doses cannot be transposed between species. Carprofen has been widely used as analgesic in the dogs, and appears very effective at doses of 4mg/kg IV or SQ given at premedication or induction. Other useful perioperative NSAID analgesics include meloxicam, ketoprofen, firocoxib, etodolac, and tepoxalin, and much of the toxicity is claimed to have been lessened due to their selective COX (particularly COX2) or LOX inhibitory action. Many NSAIDs including carprofen may be given by the oral route, making them useful for the later stages of postoperative analgesia.

**Alpha 2 adrenoceptor agonists**

It provides some effective analgesia, particularly effective in visceral pain in comparison to somatic pain. Most commonly used alpha 2 agonists in small animals are medetomidine, dexmedetomidine and xylazine. When used during anesthesia it reduces the dose of other anesthetics required. However, as analgesia is accompanied by sedation, in addition to all the other side effects particularly with profound bradycardia, their use for post operative analgesia is not common. Alpha 2 agonist and opioid combination shows marked synergism, and it is possible to obtain all degrees of sedation and, in some cases, anesthesia with such combinations. No pre prepared combinations exist. They can provide effective analgesia with minimal side effects when used by the epidural route, and this is discussed more in detail in other presentation in this series. If antagonists such as atipamezole or tolazoline have been used, analgesia is reversed alongside sedation and other adverse side effects.

**Other non-opioid, non-NSAID analgesics**

**Tramadol**

Tramadol has gained more acceptance in veterinary use in recent years in treating post-operative or chronic pain. It may act on mu opioid agonist and as monoamine reuptake inhibitor. This may offer advantage in animals where NSAID is contraindicated. However, it may induce stomach ache, agitation, salivation, excitement, constipation, meiosis, and bradycardia. In severe overdose, it may induce a seizure.

Tramadol comes in tablets, capsules, or ampules but in some countries (US) injectable form isn’t available yet. It has a bitter taste and therefore usually mixed with syrups to increase acceptance by the animal. Recommended dose ranges between 4-8 mg/kg every 6-8 hours in dogs and 1-2 mg/kg every 12 hours in cats. Tramadol can be co-administered for synergism with gabapentin, NSAID, opioid, and amantadine, but must not
be used with tricyclic antidepressant, selective serotonin reuptake inhibitor, or monoamine oxidase inhibitor.

Gabapentin

Mechanism of action for gabapentin’s analgesic effect is not well understood, although a few studies indicate a possible involvement of GABA and alpha 2 receptors. Gabapentin has been successfully utilized in humans as adjunctive analgesic for treating neuropathic pain when opioids and other analgesic classes may not provide adequate pain relief. However, in veterinary application, it has been more commonly utilized as anticonvulsant rather than for pain relief. Nevertheless, this agent appears to offer a unique place in veterinary patients as has been in humans, particularly in animals suffering from neuropathic pain or in orthopaedic procedures. The most common side effect with gabapentin is expected to be mild sedation and ataxia in veterinary use.

Gabapentin is typically administered as oral supplement in dogs with onset of effect in one to two hours. The recommended dose rate is 10 mg/kg twice daily in treating pain, but much higher dose at shorter interval is required for treating seizure. Although the drug dose and frequency is not well established in cats for analgesic use, a lower dose is suggested.

Amantadine

Amantadine was originally developed as antiviral agent to treat influenza infection, but in subsequent years it was discovered to be effective in relieving Parkinsonian symptom and neuropathic pain, possibly mediated by dopaminergic agonism and NMDA receptor antagonism, respectively. The recommended dose is 3-4 mg/kg twice daily in dogs as analgesic. Observed side effects in humans include hallucination, seizure, hyperactivity, dizziness, arrhythmia, diarrhoea and flatulence. Indication for amantadine include treating pain in animals suffering from cancer, osteoarthritis, hyperalgesia, allodynia, and other types of neuropathic pain.

Tricyclic antidepressants (amitriptyline, clomipramine)

TCAs are mainly used for treating depression. They act primarily as serotonin-norepinephrine reuptake inhibitors (SNRIs), which results in an elevation of the extracellular concentrations of serotonin or norepinephrine, and increased availability of these neurotransmitters responsible for mood elevation. Additionally, they may also interact with NMDA receptor and transmembraneous sodium channel which may account for analgesic effect. Amitriptyline is the most commonly prescribed TCA both in humans and animals to treat neuropathic pain. Many side effects may be related to the antimuscarinic properties of the TCAs including dry mouth, mydriasis, constipation, drowsiness, agitation, sweating, muscle twitches, tachycardia, and rarely, irregular heart rhythms. TCAs must not be co-administered with tramadol due to potential serotonergic storm. The recommended dose ranges from 1-6 mg/kg twice daily in dogs for behavior modification or cataplexy, but not many data are available currently for analgesic use.
Physical therapy including Acupuncture and TENS

More practitioners are willing to incorporate acupuncture or other physical therapy including transcutaneous electrical nerve stimulation (TENS), laser and magnetic therapy in treating acute or chronic pain in veterinary patients in recent years.

Mechanism of acupuncture in relieving pain is not fully understood, but the gate control theory proposed by Melzack and Wall seemed to offer a partial explanation as to why acupuncture or TENS are effective. Briefly, in gate control theory, both thin (sensory) and large diameter (motor) nerve fibers carry information from the periphery into the dorsal horn of the spinal cord where signal transmission synapses at different speed. They postulated that these differences account for rubbing of a hammer smacked hand in order to relieve pain sensation, and analgesia achieved by acupuncture or TENS primarily through stimulation of large diameter fiber transmission.

TENS and acupuncture are also similarly proposed to provide pain relief by stimulating endogenous pain suppression system (eg release of endogenous opioid peptides). Although many advocate strongly for its efficacy, and recognize its unique place in pain management, it is not widely accepted yet.

Summary

What determines which agents or methods should be used for pain control would depend on the type of procedures, severity of pain and economic consideration for each individual circumstance. Our understanding of pain in its manifestation, mechanisms, assessment, and alleviation in animals is still improving. It is imperative to ensure continuous effort in establishing information on safe and appropriate use of different classes of analgesics in animals. However, it must be remembered that no pharmacological intervention can supersede tender loving care which animals deserve most during their suffering.

Further suggested readings