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Adjunctive Analgesic Medicines, With No License for Veterinary Use, Are Commonly Used for Musculoskeletal Pain Management in Veterinary Small Animal Species. Does the Evidence Support this Practice?

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Abstract

Chronic Musculoskeletal related pain such as Osteoarthritis or Inter Vertebral Disk Disease are originally caused by a localized inflammatory process leading over time to reversible plasticity at the level of the CNS in a process called Central Sensitization. Neuropathic pain is defined as pain resulting from a lesion or disease involving the somatosensory nervous system. In human medicine, NP is often refractory to treatments, reduces quality of life, and impairs sleep and, causes anxiety and depression.

Keywords: Analgesic; Pain; Osteoarthritis; Musculoskeletal

Introduction

Chronic Musculoskeletal (MSK) related pain such as Osteoarthritis (OA) or Inter Vertebral Disk Disease (IVDD) are originally caused by a localized inflammatory process (following a trauma or not) leading over time to reversible plasticity at the level of the CNS in a process called Central Sensitization (CS) [1]. As those diseases progress, somatosensory remodeling including nerve losses and neo-innervation in the cartilage and synovial lining for OA, and the inter vertebral disk for IVDD will lead towards peripheral Neuropathic Pain (NP) [2-4]. In addition, in the case of IVDD, disk herniation may compress Dorsal Root Ganglion (DRG), nerve root or spinal cord, leading also to NP [4]. Neuropathic pain is defined as pain resulting from a lesion or disease involving the somatosensory nervous system [5]. In human medicine, NP is often refractory to treatments, reduces quality of life, and impairs sleep and, causes anxiety and depression. It serves no purpose. Peripheral NP is a complex process characterized by at least 3 main events:

- Afferent nerve trauma leading to: Hypersensitivity and ectopic foci through an increased number of voltage-gated sodium channels (i.e. Nav 1.7, Nav 1.8 and Nav1.9); modulation of voltage-gated Ca channels (α2δ subunits); or even neuronal demyelination; nerve sprouting (Aβ in lamina 2); electric (ephatic) and chemical cross talk through disruption of the glial sheath.
- Central sensitization involving, among others, NMDA receptors, NK1 receptors.
- Reduced activity of the descending inhibitory (serotoninergic, adrenergic and dopaminergic) and the endogenous endorphin systems.

More information about the NP process may be found elsewhere in the literature [6]. As OA or IVDD are mostly inflammatory in origin, the first and most commonly used pharmacological intervention will be based on the Non-Steroidal Anti-Inflammatories (NSAID's). As time passes, through CS and the apparition of (peripheral) NP, those agents won't be as effective anymore and the search for an adjuvant will start.

Some Adjuvants

Amongst those adjuvants, the following ones have been shown to be effective in the management of NP in human: TCA's (amitriptyline), anticonvulsants (gabapentin), NMDA antagonists (amantadine), SNRI (duloxetine) and opioids (tramadol) [7,8].

Tricyclic antidepressants (TCA)

Amitriptyline is the most commonly used TCA in humans for the treatment of NP. Its analgesic

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effect is provided at the level of the spinal dorsal synapses through the inhibition of serotonin and norepinephrine reuptake, the antagonism of voltage-gated sodium channels and the antagonism of NMDA receptors [5]. There are no studies in dogs or in cats looking at the efficacy of amitriptyline for the treatment of NP. There is one report of 3 dogs with NP and the use of amitriptyline for its management [9]. Although 2 dogs got better, the mixed results and the low number of animals does not allow for any meaningful conclusion.

Gabapentin

It is an Amino Butyric Acid (GABA) analogue antiepileptic agent, but has, so far, shown no effect on those GABA receptors. It seems to work on the α2δ subunit inhibiting neurotransmitter release by modulation of presynaptic voltage-gated calcium channels at the spinal and supra-spinal level [5,6]. It may also cause voltage-gated sodium channel blockade [10]. In both dogs and cats, there is a lack of studies looking at the efficacy of gabapentin in treating NP. In the cat, there is a recent study looking at the effect of gabapentin in 6 OA cats compared to 4 non-OA cats. The authors found a difference in night time activity (accelerometer) and paw withdrawal threshold (von Frey Hair) [11]. Some reports on the clinical use of gabapentin exist also in that species. In 2013, Lorenz reported the successful use of gabapentin as the sole analgesic agent in 3 cats suffering from MSK-associated pain (6.5 mg/kg, BID up to 12 months) [12]. More recently, in 2018, cats, suffering from feline hyperesthesia syndrome with self-trauma to the tail, were treated with gabapentin either alone (n=2) or mixed (n=3) and showed remission [13]. In dogs suffering from NP associated with Chiari-like malformation and syringomyelia, gabapentin 11 mg/kg three times daily improves quality of life by comparison with carprofen (NSAID) but did not show any improvement compared to another antiepileptic, topiramate [14]. Although there is little to no evidence in its efficacy in treating NP, its clinical use seems to be common in the dog. While no effect was shown in reports on forelimb amputation or hemilaminectomy, some sparing effect on opioids use were reported in a mastectomy report [15-17]. Pharmacokinetic (PK) studies highlight the fact that a possible cause for the reported lack of efficacy could be related to a low dose and low frequency of administration (10 mg/kg BID *vs.* 10 to 20 mg/kg, TID) [18].

Amantadine

It is a NMDA antagonist. There are, so far, no studies in cats about its efficacy to treat NP. A study in dogs with OA reported some increase in physical activity when administered concomitantly with an anti-inflammatory agent, meloxicam [19].

Tramadol

Tramadol has a dual mechanism of action: Weak μ opioids and inhibition of serotonin and nor epinephrine reuptake. While the parent drug inhibits both serotonin and nor epinephrine reuptake, one of its metabolites (M1) provides most of the μ opioids-like effect. By opposition to cats, dogs produce very little or none of the metabolite M1 [10]. Tramadol is a very commonly used agent in the veterinary clinical setting although very little information exists about its efficacy in regard to NP in both dogs and cats. It success might be related to its low price and lack of administrative burden related to its use. There are 2 studies in dogs with OA. In the first one, tramadol 4 mg/kg 3 times a day was reported to be as good as carprofen 2.2 mg/kg daily using CPBI (owner based chronic pain questionnaire) and accelerometer force plate analysis [20]. In a more recent study, with random allocation to the groups, cross over design (10 day on 7 days off for washout), positive (carprofen) and negative (placebo) control, found no effect from Tramadol 5 mg/kg TID, in dogs with OA using peak vertical force and CPBI [21]. The dog under carprofen did improve. The lack of efficacy from tramadol is not surprising in that species when we look at its pharmacokinetic profile: 1) it has a very short half-life (1.1 h); 2) dogs do not produce M1; 3) tramadol absorption decrease up to 70% with repeated administration (over one week) [22,23]. Only one study looks at the use of tramadol as the sole agent in cats with naturally occurring OA [24]. Fifteen (15) cats with OA went through a randomized cross over placebo design where tramadol (3 mg/kg twice daily) or a placebo was given for 19 days followed by a 3-month washout period and another 19 days of treatment. Night mobility (accelerometer) and nociceptive hypersensitivity (response to mechanical summation) were significantly improved with tramadol. In another placebo-controlled study in OA cats where tramadol in association with meloxicam oral spray was compared with tramadol oral spray alone, no advantage of the combination was shown using accelerometer and peak vertical force analyses. Interestingly, there was an improvement with hypersensitivity [25]. From those last 2 studies in cat, we can speculate that tramadol, alone and in combination with meloxicam, by decreasing hypersensitization, may reduce CS, the basis of early neuroplastic changes in the central nervous system. Therefore, Tramadol might effectively be a very useful drug to treat NP in that species [26,27].

Conclusion

It is currently difficult to make an evidence-based recommendation about which drugs should be used and in what order. There is an urgent need for well-designed studies looking at the use of adjuvants in dogs and cats suffering from NP. Those studies will need to be at least randomized, placebo controlled, and, if possible, with a positive control. One of the challenges researchers will meet is the difficulty associated with the confirmation of the presence of NP and the identification of the underlying disease. In addition to good history and physical examination, objective tests including Quantitative Sensory Testing (QST) will be necessary. Quantitative sensory testing allows for identification of neuropathic component of the disease as well as for the assessment of the response to treatment. The sensory threshold of the QST is expected to be decreased with disease causing NP (hypersensitivity). Electronic von Frey anesthesiometer or pressure algometer have been developed for use in (client owned) dogs and cats. Another important factor will be for the researchers to make sure to use an effective drug dosage associated with an effective frequency of administration derived from PK studies. In clinical terms, the treatment of patient with NP will have to be polymodal involving different disciplines (i.e. physio, acupuncture). Contrarily to what some may think, similarly to human medicine, the pharmacological aspect of the NP treatment will consist more in a "combo" type therapy where the NSAID and an adjuvant (or 2) will be used concomitantly.

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