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Research Article

Neuropathic Pain in Dogs and Cats: Current Evaluation and Treatment Perspectives: Review

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Abstract: During the past decade, the number of scientific papers on the recognition and multimodal management of pain in small animals increased exponentially. However, the variable of neuropathic pain, or adaptive disorder, has not yet been characterized completely. Its genesis is related to several diseases and injuries of the nervous system that change the neuroanatomical structures that participate in pain processing. Finding novel neurobiological mechanisms and the development of techniques for diagnosis and treatment in Human Medicine, are opening great opportunities for research and the understanding of neuropathic pain in pets.

Keywords: α_2-δ ligands, adjuvant analgesics, neuropathic pain, N-Methyl $_D$-Aspartate receptors

INTRODUCTION

The International Association for the Study of Pain (IASP) defines pain as "a disagreeable sensation caused by actual or potential tissue damage" (Merskey and Bogduk, 1994). It has been clearly demonstrated that pain is one of the main multidimensional emotions that we feel, with a certain similarity to animal species due to the phylogenetic closeness and the presence of neuroanatomical pathways, neurotransmitters and opioid receptors (Merskey and Bogduk, 1994; Edwards *et al*., 2006; Fonda, 2007; Hellyer *et al*., 2007). In consideration of the great difference there is in the expression of pain among diverse sub-populations, the IASP added: "the inability to verbally communicate pain does not exclude the possibility of feeling it and it should be relieved through treatment".

Among the methods that have been traditionally used to evaluate pain intensity in Small Species (SS) clinical practice are the uni-dimensional scales that describe ethological behavior and evaluate the physiological functioning of organs and systems (Mathews, 2000) and those that have been modified and developed for humans like the Analogous Visual Scale (AVS), the simple descriptive scale and the numerical scale (Holton *et al*., 2001; Murrell *et al*., 2008), allowing a multimodal management following palliative and pharmacological therapies (Borer, 2006; Hellyer *et al*., 2007; Cassu *et al*., 2008; Jiménez and Avedaño, 2008). There are thus different classification criteria based on the mechanism that generates pain (nociceptive [somatic, visceral, inflammatory] or neuropathic), the progress (chronic or acute), the ethyology (oncological, non-oncological or inflammatory), the location (superficial, deep, referred) and the intensity (slight, moderate, severe). Recently, it has also been proposed to consider it as an adaptive or non-adaptive type response (Woolf, 2004).

Adaptive or nociceptive pain is a mechanism of protection that makes the organism react to an injury or to tissue inflammation, keeping in mind that the main components of pain in acute (injuries, surgical procedures, etc.) and chronic (osteoarthritis, cauda equina syndrome, etc.) processes are the inflammatory mediators (Campbell and Meyer, 2006). In contrast, non-adaptive or neuropathic pain (NPP) indicates a pathological state of the Central Nervous System (CNS) or Peripheral Nervous System (PNS) that is frequently associated with a primary injury, a disease or a dysfunction (usually of the somatosensitive components) (Woolf, 2004; Horowitz, 2007).

NPP is one of the main factors that significantly decrease the quality of life of millions of people worldwide. Its management has historically been

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problematic in response to its complex physiopathology and the diverse clinical manifestations it generates. Additionally, parameters to facilitate its pathognomonic recognition in Veterinary Medicine have not been established, resulting in frequent inadequate or refractory treatments. It has traditionally been classified as central or peripheral following the anatomical location of the neurologic damage (Guevara *et al*., 2006). Its most representative pathognomonic characteristics are: alodinia, hyperalgesia, hyperpathia, spontaneous pain, etc., however, its location is non-specific and may change during the course of a disease (Campbell and Meyer, 2006).

NPP in pets has been associated with different health problems including: spinal cord and peripheral nerveinjuries (Van *et al*., 2008), neuropathic endocrino pathies (hyperthiroidism and diabetes), immune-mediated diseases (polyarthritis), congenital diseases (syringomyelia) (Rusbridge and Jeffery, 2008), degen erative diseases of the joints (osteoarthritis) (Lascelles *et al*., 2008), neoplasia (Lamagna *et al*., 2006), medical iatrogenia (Anterior cruciate ligament and sciatic nerve damage) (Forterre *et al*., 2007; Ryan *et al*., 2008), cerebrovascular accidents (Wessmann *et al*., 2008), etc.

PHYSIOPATHOLOGY

Advances in brain neurochemistry research have allowed the evaluation of new therapeutic targets in animal models and patients with NPP. As was stated above, it is generated by the disfunction or modification of the somatosensitive pathway (Caviedes and Herranz, 2002). This has been detected in peripheral nerve endings, dorsal root ganglia, posterior horn of the spinal cord and the somatosensorial cortex. It is agreed that one of the main physiopathological mechanisms of NPP is "spinal sensitivity" or the "wind-up" phenomenon (Neira and Ortega, 2004) that is generated by the sustained activity of the A and C δ fibers that modify the processes of algogenic information in the posterior horn of the spinal cord through the *in situ* liberation of excitatory neurotransmitters such as: P substance, A neurokinin, glutamate, etc., favoring activation of N-Methyl $_{D}$-Aspartate (NMDA), AMPA and kainic receptors, the survival genes (with changes in the phenotype), on the regulation of anomalous Na_V and Ca_V channels (Caviedes and Herranz, 2002; Vajdovich, 2008), etc., magnifying the painful signal of the second neuron and generating hyperactivity in those of the dorsal horn (Guevara, 2004; Horga and Horga, 2006) In addition, the response that is orchestrated by the immunological system contributes to magnify the neuroinflammatory process through the *in situ* liberation of pro-inflammatory cytokines such as Interleucin-1 beta (IL-1β), IL-6, Tumoral Necrosis Factor-alpha (TNF-α), etc. (Misha *et al*., 2008), activating the arachidonic acid cascade (leucotrienes, prostaglandins, tromboxanes, cyclooxygenase 1 and 2 enzyme [Cox] etc.), T CD^{4-8+} lymphocytes, microglia cells (resident macrophages of the CNS), astrocytes, etc. (Ji *et al*., 2006; Inoue *et al*., 2007).

In short, the aggravation of the processes unchained in the organism (enzymatic, molecular, cellular, gene expression, etc.) generates alodinia in face of non-painful stimuli due to:

- Afferent neuroanatomical reorganization
- Loss of the inhibition mechanisms of the neurons
- A decrease in serotonin and noradrenaline in the descending inhibitory neurons, etc (Caviedes and Herranz, 2002).

ETHYOLOGY

The inappropriate management of nociceptive pain (chronic and acute) generates neuroanatomo physiological changes that present syndromes of the non-adaptive type (Caviedes and Herranz, 2002). Examples are dogs with chronic pain due to otitis, that potentially develop pathognomonic signs such as hyperalgesia or alodinia (Martin and Martin, 2006), as well as neutered cats that, due to the same reason and at the same time ([adaptive pain/nociceptive mechanisms] [alteration in structures of the nervous system/non-adaptive pain]), present a third painful mixed-type variable (Hellyer *et al*., 2007). Following the same line of thought, since the use of NSAIDs was approved for dogs, they have been prescribed in a general way to control chronic pain in diseases like osteoarthritis (Pollmeier *et al*., 2006; Mansa *et al*., 2007; Shaffran, 2008). However, clinical studies (Lascelles *et al*., 2008) and experimental models have recently demonstrated that AINES *per se* are inadequate at certain stages of a disease (Renberg, 2005; Lascelles, 2007), as the chronic stimulation of the adaptive pathways favours the activation and increase of NMDA receptors, modifying the neuroanatomical structures that play a part in NPP. In addition, peripheral neuropathies (hyperalgesia, alodinia and spontaneous pain) develop in the case of endocrinopathies such as Diabetes Mellitus (DM) and hypothyroidism. In diabetic patients, hyperglycemia is the main risk factor for the appearance of NPP, following alterations in the metabolism of the neurons, mainly:

- An intracellular accumulation of sorbitol
- A decrease in mioinositol and ATPase Na-K activity
- An increase in non-enzymatic glycosylation
- Hypoxia/ischemia
- Neurotropic factors
- An increased response of the immunological system, etc. (Betancourt *et al*., 2006; Russell *et al*., 2006; Scott-Moncrieff, 2007; Betancourt *et al*., 2008)

Another frequent cause of NPP in pets are injuries to the spinal cord or peripheral nerves (injuries, cervicalgies, cauda equina syndrome, syringomegalia, tumors, iatrogenic neuralgias, etc.), as the acute or intermittent compression of the structures of the nervous system generates:

- Changes in nerve endings of the A and C δ myelin fibres
- A local accumulation of neuro-inflammatory mediators
- Rise of afferent neurons in the de-nerved region
- A loss of inhibition mechanisms (normally active)
- Neuroanatomical reorganization
- A decrease in neurotransmitter receptors such as GABA
- A decrease in the activity of the dorsal horn plates, etc.

The pathognomonic components that are usually observed are: spontaneous pain (constant), spontaneous neuralgic pain and those which includes alodinia, hyperpathia and hyperalgesia (located in the painful area) (Malcolm, 1996; Mayhew *et al*., 2002; Webb, 2003; Robertson, 2005; Lamagna *et al*., 2006; Santoscoy, 2006; Lopez and Mejia, 2006; Terre *et al*., 2007; Carvallo *et al*., 2007; Harris and Dhupa, 2008; Andrews *et al*., 2008; Morales, 2008; Rusbridge and Jeffery, 2008; Santoscoy, 2008).

CLINICAL HISTORY

Family members should be asked about the presence of certain pathognomonic characteristics considering the diseases or injuries (chronic or acute) that could generate it.

Localization: NPP may remain unnoticed by pet owners. A representative example was reported in a study of 156 dogs with lumbosacral stenosis, in which 41.7% of the clients observed pain in the affected region of the patients, whereas 66.7% of the patients felt pain during a physical examination (Suwankong *et al*., 2008). Similarly, dogs with hypothyroidism may present pain, during handling, in the gleno-humeral joint, unilateral renunciation (giving up activity) and disfunction of different pairs of cranial nerves (facial, trigeminal and vestibulocochlear) (Vitale and Olby, 2007; Scott-Moncrieff, 2007).

Time of evolution: Dogs with chronic pain from osteoarthritis (frequently at the lumbosacral level) gradually present changes in their activity and physical prowess (renunciation) (Holton *et al*., 2001; Lascelles *et al*., 2008, Seibert and Landsberg, 2008) eating habits (anorexia) (Laflamme, 2005; Delaney, 2006) and behaviour (aggressiveness, lack of interest in their habitat, etc.) (Seibert and Landsberg, 2008). In contrast, it is not common to observe renunciation in cats with osteoarthritis due to their peculiar life style. However, they present less washing and interaction with family members and frequently refuse to jump (Robertson, 2005).

Duration pattern (paroxistic, intermittent, permanent, continuous): Iatrogenic injuries in peripheral nerves (sciatic, anterior crusiate ligament) may be caused by badly applied injections, toxicity of the adjuvant or during surgeries like perineal hernorrhaphy and osteotomies (Andrews *et al*., 2008). Among the signs that patients present are acute pain, vocalizations and renunciation, all in agreement with the degree of neurological damage (Terre *et al*., 2007). Dogs with cauda equina syndrome present lumbosacral pain, renunciation and different degrees of neurological deficit (urinary and fecal incontinence, dysesthesia) related to how chronic the condition is (Mayhew *et al*., 2002; Santoscoy, 2006; Santoscoy, 2008).

Evaluation: The evaluation of NPP in dogs and cats requires a multidisciplinary approach due to the ethyological heterogeneity and the variety of clinical symptoms it generates. General and neurological physical examinations are the optimum tests to identify the pathognomonic signs or diseases that lead to a diagnosis. The signs are classified as positive when the threshold of the receptors decreases (alodinia, hyperal gesia, hyperpathia, dysesthesia, etc.) and as negative when the threshold increases (hypoesthesia, anesthesia). Also, one mechanism may be responsible for different symptoms and symptoms may be generated by other mechanisms (Aguilera *et al*., 2005). This variability may be observed through a positive response to pharma cological treatment (Campbell and Meyer, 2006).

Neurological evaluations must consider the following aspects:

Sensitive nervous system (propioception and perception): Painful areas must be emphasized (clinical background and physical examination) and presence of alodinia, hyperalgesia or segmented patterns by root affection (dermatome of a specific nerve) must be determined through mechanical (pressure, touch, pinching) and thermal (cold, heat) stimuli In addition, a numerical scale may be used to subjectively evaluate pain intensity (where cero means no pain and ten represents the greatest pain). Harris and Dhupa (2008) studied cats with Hansen type I and II intervertebral disk disease and reported that 100% of the experimental sample presented spinal hyperpathia at the lumbosacral level and pain when hyperextension of the tail was applied during the clinical examination. The most relevant neurological signs were: paraparesis, paraplegia, megacolon, vesical atony, absence of anal

reflex, urinary and fecal incontinence, perineal analgesia, etc., similar to those presented by dogs (Mayhew *et al*., 2002; Santoscoy, 2006; Santoscoy, 2008).

Motor nervous system: The segmentary strength (innervation patterns), tone, muscle trophism, abnormal movements, analgesic positions and disfunction in active and passive movements are evaluated. The scale for muscular strength is as follows: (0) no movement, (1) traces of active movement, (2) active movement without the effect of gravity, (3) active movement against gravity, without resistance, (4) active movement capable of overcoming gravity and a degree of resistance and (5) active movement with normal strength. The osteomuscular and deep tendon reflexes are also evaluated with 0 to 3 crosses (+), where (0) is the absence of reflex, (+) is hyporeflexia, (++) is a normal reflex and (+++) is hypereflexia.

Autonomous nervous system: The body temperature and that of the affected regions, the pilomotor reactions to different stimuli, trophic changes (in hair, nails and skin) and other anomalies (neuropathic peripheral edema) are evaluated. Dogs with NPP due to immune-mediated polyarthritis present a variety of clinical signs. Díaz and Santoscoy (2006) reported the following for a patient during therapy (58 days):

- Thoracolumbar hyperalgesia (associated with chronic nociceptive pain refractory to treatment with AINES)
- Joint pain (carpus, tarsus and phalange) that increased after rest or during movement
- Inflammation of joints and soft tissues

PHARMACOLOGICAL TREATMENT

The therapeutic management of people with NPP is based on the pharmacological control of the painful symptoms and the application of non-conventional analgesic measures. The medicines that have proven most effective in controlled clinical studies are considered adjuvant, as their main therapeutic objective is not analgesia (Knotkova and Pappagallo, 2007). This groupincludes: anti-convulsive (pregabalin, gabapentin), tri-cyclicanti-depressive (amitriptilin) and anti-arrhythmia medicines, the first two representing treatment corner stones. It is important to mention that up to the time of writing this study, no strong scientific evidence was found regarding the analgesic efficiency of the AINES and opioids per se (except for tramadol) in the control of NPP (Aguilera *et a*l., 2005; Guevara *et al*., 2006).

Antagonists of the ca_v α_2-δ channels: The gabapentinoids gabapentin (Neurontin®) and pregabalin (Lyrica®) are compounds that are structurally related to an analogous of GABA (they are not active at the GABAergic level) and easily pass through membranes and compartmental barriers. They are indicated as anti-convulsion medicines. However, the physiopathological similarity of neuronal hyper-excitability during convulsive crises and NPP has allowed the evaluation and confirmation of the antiallodynic and antihyperalgesic effect in animal models (DM, spinal cord and peripheral nerve injury, neurotoxicity from vincristin, osteoarthritis, etc.) and controlled clinical studies (Boileau *et al*., 2005; Horga and Horga, 2006; Thrasivoulos *et al*., 2008). The action mechanism takes place at the pre-synaptic level, joining the auxiliary subunit α_2-δ of the Ca_V channels and decreasing the idem flow of excitatory neurotransmitters (glutamate, noradrenaline, P substance) in nerve endings.

They have been considered to be neuromodulators as they act specifically on hyperexcited neurons (Field *et al*., 2006; Knotkova and Pappagallo, 2007). The synergic properties of gabapentin/opioids in the treatment of hyperalgesia have also been established (O-Arciniega *et al*., 2007; Keskinbora *et al*., 2007), as well as the effect of pregabalin in retarding osteoarthritic changes in dog cartilage (Boileau *et al*., 2005). The most adverse effects in people are: drowsiness, fatigue, difficulty to concentrate and edema.

n-methyl $_D$-aspartate antagonists: NMDA receptor antagonistsallow the control of alodinia and hyperpathia. This group includes: dextromethorphan, methadone, memantine, amantadine and ketamine. In Veterinary Medicine, the most used antagonist is ketamine. Its application in continuous perfusion (Jiménez and Avedaño, 2008) minimizes the wind-up phenomenon and it may be combined with morphine and lidocaine (MLK) to treat acute pain (Martin and Martin, 2006; Knotkova and Pappagallo, 2007). New medicines like Amantadine have opened new prospects in the management of NPP in small animals, as they do not generate the secondary effects of ketamine. This was originally developed for antiviral treatments and, after some time, it was found to be useful in controlling the extrapyramidal reactions of diseases like Parkinson´s due to its inhibitory properties in the prolongation of the de-polarization generated by the NMDA receptors. In the clinical practice of small animals, the standard dose that has been used is 3-5 mg/kg SID (Gaynor, 2002). Adverse effects are sporadic, though they can cause agitation or diarrhea. A clinical study of dogs with refractory pain due to osteoarthritis (treated with AINES) showed that adding Amantadine (3-5 mg/kg/24 h [42 days]) to the analgesic program significantly favored improvement of the clinical signs (Lascelles *et al*., 2008).

CONCLUSION

NPP is frequently present in dogs and cats in various ways. Its management requires considering the following:

- Similar injuries in patients of the same species may produce different pain signals (alodinia, hyperalgesia, paresthesia, etc.)
- The ethyology and physiopathology must be identified
- The pharmacological treatment differs from that of other painful variables as it does not respond adequately to traditional analgesics and may persist after the initial cause has disappeared. It is also necessary that the personnel in charge of preparing study programs for Bachellor´s, Postgraduate and Continuous Education courses stress the relevance of clinical, ethological and pharmacological research in order to unify terms and algorithms for clinical practice that will aid in diagnoses and therapeutic management.

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