Pain and Inflammation – An overview from an equine perspective

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The concept of pain in animals and the management thereof have received quite a lot of attention in the press and literature recently. In a holistic approach to patient management, we as veterinarians need to consider welfare and the best possible treatment options available for our patients. Pain can reduce animal well-being substantially and prolong the time needed for recovery from underlying conditions.[1]

Definition Of Pain

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage[2]; or a feeling of distress, suffering, or agony caused by stimulation of specialized nerve endings.[3] It can range from mild localized discomfort to agony.

Pain forms part of the four cardinal signs of inflammation as described by Celsus: Heat (*calor*), redness (*rubor*), swelling *(tumor*) and pain (dolor). Virchow added disturbed function (*functio laesa*) to the list in the 19th century. All of these form part of the body's own attempt at self repair in response to injury or irritation. Inflammation is amongst other things, classified as the first stage of second intention healing.[4]

Pain will cause the animal to rest and guard itself, so it can repair. It is therefore nature's way of slowing down the animal and limiting its activity.[5, 6] Pain therefore holds certain benefits for animals, but it can also adversely affect the animal. A horse in pain might become anorexic, its body going into a catabolic state where muscle mass is broken down. Analgesic intervention should be considered in any animal reacting to pain in a way that is detrimental to the healing process or to the health of the animal or when the inflammatory process itself actually causes further injury.[7]
Analgesic or anti-inflammatory agents will interfere with the normal physiological process of the body to heal it self. By removing the sensation of pain, we are taking away the body's mechanism to guard injured parts. We might also return some function to an area or body part, which might necessitate additional stabilization. Certain analgesics can mask clinical signs of the underlying cause of the pain and this can interfere with making an accurate diagnosis. But we as veterinarians have a moral obligation to prevent the suffering of animals.

Types Of Pain

Dr. Kenneth Joubert in his article on pain control in small animals[8] discusses four types of pain:

- **VISCERAL PAIN**

This pain is described as a dull, deep constant, aching pain that is poorly defined. It is transmitted from abdominal and thoracic nociceptors and it responds very well to narcotic and non-narcotic drugs but it may result in referred pain.

INFLAMMATORY AND SOMATIC PAIN

This pain is well localized, constant and aching. Somatic pain results from nociceptors in joints, muscles and periosteum and is commonly the result of bone metastases, tissue damage and

musculoskeletal and integument pain. Inflammatory pain is the result of the activation of inflammatory cascade and chemoreceptors.

- **NEURITIC PAIN**

Inflammation of the nerves and nerve roots, results in constant dull aching pain. This type of pain can present as part of a paraneoplastic syndrome or the result of direct damage to the nerve endings. Sporadic periods of burning "shock-like" pain are felt.

- **NEUROPATHIC PAIN**

These pains result from direct damage to segments of the nervous system normally involved in pain transmission. Metabolic, immunological and direct physical effects may be inciting causes. This type of pain is very difficult to control. It is usually a burning, stabbing and paroxysmal sensation.[8]

Measuring Pain

So can we measure this pain in our equine patients? To illustrate the complexity of this problem, a human article, published in 1968, described pain as whatever the experiencing person says it is, existing whenever he says it does.[9]

Studies in lambs have revealed that during painful conditions, such as castration, plasma cortisol concentration increases significantly with respect to that of control animals.[5]

Other clinical parameters like heart rates have been used in the equine patient to measure pain. Visual analog scores and numeric rating scales considered the following:

- Head position
- Ear position

- Location in stall
- Spontaneous locomotion
- Response to open door
- Response to approach
- Lifting feet
- Response to grain

But we have to question consistency between single versus multiple observers. There was a lack of consensus among equine veterinarians in the USA on ranking pain after castration in an epidemiological survey. [10]

Dr. Sue McDonnel, a Certified Applied Animal Behaviourist and head of the Equine Behaviour Lab of the Veterinary School of the University of Pennsylvania described the absence of normal behaviour as the most striking sign of pain in animals. Thus, any abnormal posture, movement, expression, attitude or behaviour is a potential sign of pain. This includes obvious signs such as lameness or vital signs outside the normal range. But abnormalities might be more subtle, such as isolation from herd mates, changes in attitude, altered performance ability, loss of libido in breeding stallions, or increased vocalization. The owner or handler of a specific horse in question could therefore serve as your best guide to detect abnormalities in behavior.[6]

Managing Pain

We can manage pain at four different levels in the pain transmission pathway. Using agents with activity on different sites of this pathway could lead to better control of an animal's pain.

- CORTICOSTEROIDS:

The anti-inflammatory activity of the corticosteroids is mediated through prevention of prostaglandin release, by binding to the cytosolic receptors, traveling to the nucleus and increasing the production of protein Lipocortin A. This will in turn inhibit the enzyme Phospholipase A_2 which will decrease the release of Arachidonic acid as precursor of inflammatory mediators. Corticosteroids will provide a broader anti-inflammatory effect than NSAIDs because the mechanism of action occurs closer to the origin along the biochemical pathway as compared to traditional NSAID's.[13]

Clinical and experimental evidence suggests that glucocorticoids may be effective in the treatment of neuropathic pain, but their mechanism of action is unknown (may be due to a reduced expression of TNF_{α}) [14].

Bernd Driessen (2007) gives a good description of the other pharmacological analgesics available on the market.

• NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)
The current belief is that NSAIDs act on the Cyclo-oxygenase enzymes. Prostaglandins formed from constitutive COX-1 regulate the production of cytoprotective gastric mucous and control renal blood flow among other functions. COX-1 is therefore responsible for producing prostaglandins that regulate normal bodily functions such as protection of the gastrointestinal tract from injury.[16] Inhibition of COX-1 is thought to underlie the adverse effects associated with long term use of NSAIDs, such as gastrointestinal ulceration and haemorrhage, coagulopathy, and nephropathy. Prostaglandins formed by inducible COX-2, are generated by immune and tissue cells in the presence of inflammation. COX-2 is typically not present in most tissues, including the gut and joints, unless there is inflammation.[16] Inhibition of COX-2 is thought to be primarily responsible for the anti-inflammatory actions of these agents.[15] Most of the NSAIDs used in equine practice, with a few exceptions are non-selective. In the horse, meloxicam and carprofen have the most favourable selectivity profiles when compared to flunixin and phenylbutazone, with meloxicam more COX-2 selective than carprofen.[17]

• OPIOIDS
It is known that a single injection of opioid dose, known to produce significant analgesia, or antinociception, produce pronounced excitatory CNS effects.[15,18] These drugs are commonly administered in combination with potent sedatives like phenothiazines (neurolept analgesic protocol) or α_2-agonists to control central excitation. Repeated or continuous use of opioids in horses can give rise to an increased risk of ileus due to depression of intestinal motility. [15]

• ALPHA-2 ADRENOCEPTOR AGONISTS
These drugs are used for sedation or premedication to surgery with short duration of analgesia. Activation of α2-receptors in the dorsal horn of the spinal cord is part of the explanation for this group's potent analgesic effects. This will inhibit transmission of nociceptive signals from the peripheral nociceptive nerve fibers to the secondary ascending pathways that convey the information to supraspinal sites, thereby imitating the influence of descending adrenergic inhibitory pathways.[15]

• LOCAL ANAESTHETICS
Lidocaine administered systemically has regained popularity in equine veterinary practice as an anaesthetic-sparing, analgesic, prokinetic, and anti-inflammatory drug in the perioperative period. It may be useful in treating chronic neuropathic pain as it may suppress hyperalgesia. Driessen (2007) found intravenous lidocaine often useful, especially for the treatment of gastrointestinal pain, even though responses to treatment were variable.[15]

Local or regional anaesthesia with procedures like line blocks, perineural blocks and epidurals are common practice and provide good short term analgesia.

• NMDA-ANTAGONISTS
Ketamine is thought to inhibit the actions of glutamate, the major excitatory amino acid neurotransmitter in the mammalian brain. NMDA receptors are also involved in induction of central sensitization and long-term potentiation, promoting development of chronic pain.[15]

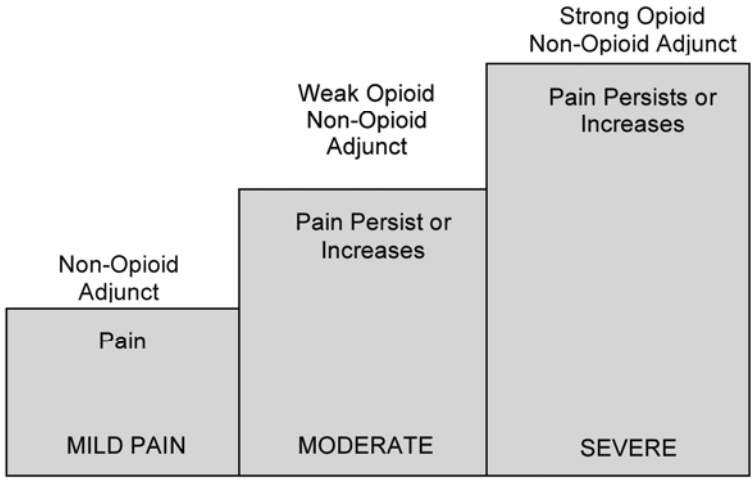
Discussion

Public awareness of pain control in animals is growing. With SAVC no longer condoning procedures like caudectomy and ear cropping in dogs, welfare in animals is getting even more important. We as veterinarians do not only need to treat pain because it is our moral obligation to do so, but also because science shows us that pain can be detrimental to the health of the animal.

The International Veterinary Academy of Pain Management classified pain in horses as follows: [11]

Irritating or mild pain	Mild to moderate pain	Moderate to severe pain	Severe pain
• Intravenous (IV) catheterization • Full bladder, needing to urinate or defecate • Minor cuts or scrapes • Fly bites or "strike" • Improper shoeing	• Endoscopy with biopsy • Arterial catheterization (A-line) • Muscle biopsies • Castration • Hernia repair • Joint strain • Osteochondrosis dissecans (OCD • Bowed tendon • Arthroscopy procedures (chip fractures)	• Small areas of burns or ulcerations • Corneal ulcers • Cellulitis • Joint infections • Arthroscopy procedures(severe ligament injury) • Stabilization of fractures (any part of leg or foot) • Surgeries of the abdomen (colic)	• Large areas of burns or ulcerations • Infections within the abdomen (peritonitis) • Surgeries of the neck, including disc surgery • Laminitis • Founder • Rhabdomyolysis

Dr. Kenneth Joubert classified pain and approach to analgesia as follows: [8]



Pain ladder with suggested analgesia.

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Transduction (inhibit peripheral sensitization of nociceptors)	Inhibit transmission (inhibit impulse conduction)	Modulation of Spinal Pathway (inhibit central sensitization)	Inhibit perception
• Local anaesthetics • Opioids • NSAIDs • Corticosteroids	• Local anaesthetics • α_2-agonists	• Local anaesthetics • Opioids • α_2-agonists • Tricyclic antidepressants • Cholinesterase inhibitors • NMDA antagonists • NSAID's	• Anaesthetics • Opioids • α_2-agonists • Benzodiazepines • Phenothiazines

Different Pharmacological sites of action for analgesia.[12]

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