

Pain and its Management in Animals

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Abstract

Pain is a perception, an unpleasant experience associated with actual or potential tissue damage. It is usually caused by mechanical, chemical or thermal stimulation of specialised pain receptors (nociceptors) in tissues. In routine veterinary practice, such acute insults causing intense stimulation encountered include tissue trauma, including surgery, burns and fractures. As veterinary practitioners, we are ethically obliged to prevent pain and suffering where possible and alleviate it, should it occur, as it contributes to increased morbidity and mortality. In order to do this, we need to be able to assess pain in animals and manage it appropriately. Pain assessment can be made based on anthropomorphism, behavioural responses of the patient and clinical signs. The behavioural and physiological responses that accompany pain such as vocalization, withdrawal reflex, guarding of the affected area and increased activity of the sympathetic nervous system are measurable. Pain control in animals can be achieved through limitation of nociceptor stimulation, interruption of peripheral transmission, inhibition of nociceptive transmission at the level of the spinal cord, modulation of brain pathways by systemic administration of analgesics or, through 'balanced' or 'multimodal' analgesia by simultaneous use of a number of the above strategies. Although the selection and techniques of administration of individual analgesic drugs vary, local and opioid analgesics, non-steroidal anti-inflammatory drugs, tranquilizers and other combination therapies when used appropriately can control pain and alleviate suffering in animals experiencing pain. This paper looks at pain and its management in *animals*.

Introduction

Pain has been defined by the International Association for the Study of Pain (IASP) as 'an unpleasant sensory or emotional experience associated with actual or potential tissue damage or described in terms of such damage' (Short, 1995; Muir, 1998). It can be present in mild and severe forms (quality) and in acute and chronic forms (temporal). There is no dispute that all mammals have the anatomical and physiological pathways required for the perception of pain and learn to avoid painful stimuli (Morton and Griffiths, 1985).

One of the noblest goals of medicine is the alleviation of pain and suffering. Although knowledge and techniques to control pain exist in both human and veterinary medicine, in many instances, clinicians do not utilize them (Tranquilli and Raffe, 1989; Carroll, 1996). In human medicine, relieving chronic pain and pain associated with surgery and trauma has become an important subspecialty of anaesthesiology and intensive care (Tranquilli and Raffe, 1989).

One of the most important treatment decisions to make as veterinarians is whether to control pain in patients undergoing surgery. Indeed, pain and inflammatory

responses are induced by surgical procedures and anaesthesia related muscle ischaemia. These produce a series of behavioural, neurophysiological, endocrine, metabolic and cellular responses (stress response) which initiate, maintain and amplify the release of pain and inflammatory mediators (Muir, 1998).

Because non-verbal animals are incapable of describing pain, veterinarians are left with the task of evaluating patients for assorted signs of pain. Animals in pain exhibit both physiological and behavioural signs which should be used inclusively to assess pain. The most recognized behavioural manifestation of pain is vocalization, which includes crying, howling, barking, growling, purring or moaning. Other behavioural and clinical indications of pain include changes in posture or facial expression, guarding or protecting a limb, self-mutilation, dilated pupils, salivation, muscle rigidity or weakness, and changes in sleeping and eating patterns.

In the management of pain in animals, consideration ought to be given to the location of the pain, pain mechanisms involved in transmission, the mechanisms of action of the medication chosen, and its potential to block or alleviate the source, or recognition of the painful condition (Short, 1995). To control pain in animals, many techniques are available and these include limitation of nociceptive stimulation, interruption of peripheral transmission, inhibition of nociceptive transmission at the level of the spinal cord, modulation of brain pathways or, through a combination of any of these techniques. All these techniques use the many drugs available for control of pain, by administering them locally or systemically (Quandt and Rawlings, 1996). Medication for control of pain can be chosen from non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, opioids, alpha₂-adrenergic agonists, anaesthetics and other central nervous system (CNS) response altering agents (Short, 1995).

Terms used to define and describe pain

Several terms are used to define and describe pain. Noxious stimulus is a stimulus (mechanical, chemical or thermal) of sufficient intensity to threaten or overtly cause tissue damage. Nociception is the process of pain perception via pain receptors (nociceptors). Hyperalgesia refers to increased response or hypersensitivity to a noxious stimulus, either at the site of injury (primary) or in surrounding undamaged tissues (secondary). Hyperaesthesia refers to increased sensitivity to non-noxious stimuli. Allodynia is pain produced by non-noxious stimuli. Pre-emptive analgesia deals with the prevention or minimization of pain by administering analgesics prior to pain production or prior to introduction of a noxious stimulus as in surgery, if pain already exists. Pre-emptive analgesia is aimed at provision of therapeutic intervention in the advance of pain in order to prevent or minimize the central nervous system response to noxious stimuli (Muir, 1998).

Classification of pain

Pain can be classified into 'physiological' or 'clinical'. Pain is considered to be 'physiological' when it operates to protect the body by warning of contact with tissue damaging stimuli (Woolf and Chong, 1993) and this type of pain is produced by stimulation of nociceptors innervated by high threshold A-delta (Group III) and unmyelinated C (Group IV) fibres. 'Clinical' pain is produced by peripheral tissue injury or damage to the central nervous system (Woolf and Chong, 1993). This clinical pain is categorized as inflammatory or neuropathic. Inflammatory pain can either be visceral or somatic in origin. Visceral pain is poorly localized, cramping or gnawing and may be referred to cutaneous sites far from the site of injury. Somatic pain on the other hand is easily localized, can be aching, stabbing or throbbing and generally is acute. This includes cutaneous or incisional pain after operations. This pain is frequently referred to as superficial, when involving the skin or deep, when involving joints, muscles and the periosteum. Neuropathic pain results from damage to peripheral nerves or the spinal cord and is described as burning, stabbing and intermittent, often unresponsive to treatment. Both inflammatory and neuropathic pain can produce allodynia, hyperalgesia and central nervous system and peripheral sensitization to external stimuli. Idiopathic pain, which is pain that persists in the absence of an identifiable organic substrate is often excessive and accentuated by activation of the sympathetic nervous system due to emotional stress (fear) or excitement (Muir, 1998).

Pain processes and the resultant effects

Pain perception and nociception can be considered to involve four primary physiological processes of transduction, transmission, modulation and perception. Noxious stimuli are transduced into electrical impulses by peripheral pain receptors and subsequently transmitted throughout the sensory nervous system. These electrical impulses are modulated by endogenous systems, which include the serotonergic, cholinergic, noradrenergic and opioid systems in the dorsal horn of the spinal cord and, then transmitted to the brain from where emotional, behavioural and physiological responses are initiated. Mechanical, chemical, or thermal activation of small diameter high-threshold A-delta and C sensory nerve fibres normally produces pain. Several chemical mediators of pain and inflammation are recognized. These include histamine, serotonin, bradykinin, leukotrienes, prostaglandins (PGF₂, PGI₂, PGE₂), interleukins (IL-1, IL-6), neutrophil-chemotactic peptides, nerve growth factor (NGF) and neuropeptides including substance P (Levine *et al.*, 1993; Woolf and Chong, 1993). Their role is in the enhancement of the excitability of sensory nerves and postganglionic sympathetic nerve fibre activity leading to peripheral sensitization, hyperalgesia and allodynia. On the other hand, inflammation increases the sensitivity of peripheral terminals of A-delta and C-fibres which causes some A-beta fibres to express substance P and stimulate the synthesis and release of nerve growth factor (NGF), a peptide which increases the synthesis of substance P and calcitonin gene related peptide (CGRP). This process stimulates the release of histamine and leukotrienes and

is associated with the development of sensory hyperexcitability and hyperalgesia. The consequent result of these inflammatory and tissue chemical responses is the development of diverse but interrelated positive feedback loops, which enhance neural sensitivity and intensify the pain response (Muir, 1998).

After transduction, electrical impulses are transmitted to C-fibre terminals in the dorsal horn where the excitatory neuropeptides (tachykinins), substance P, neurokinin A (NKA), CGRP and the amino acid glutamate are released to activate post-synaptic tachykinin (NK₁, NK₂), CGRP and glutamate (N-methyl-D-aspartate [NMDA]; amino-hydroxy-methyl isoaxalepropionic acid [AMPA]; Kinate [KA]) receptors. Cumulative increases in the number of electrical impulses produced in the dorsal horn cells and large motor neurons of the ventral horn in response to increased C-fibre stimulus frequency eventually results in increase in excitability of the spinal cord neurons and central nervous system leading to central sensitization, hyperalgesia and allodynia (Muir, 1998).

Assessment of pain

Pain can be assessed based on one or a combination of several criteria. The criteria include anthropomorphism, unprovoked behaviour, behavioural responses to external stimuli, and clinical signs. Anthropomorphism (extrapolation from human experience) relies on the fact that if a procedure will cause pain in a human, then it is likely to do so in our patients. From this, the likely severity of untreated pain from a surgical procedure may be predicted on the basis of the extent of damage to the tissues and anatomical site of the proposed surgical injury. Unprovoked behaviour relies on responses to pain that include vocalization; restlessness; attempts to escape; changes in normal sleeping patterns; changes in appetite; changes in temperament including increased anxiety and withdrawal, guarding or protecting the affected area and turning the head towards the painful stimulus; self mutilation including biting, chewing or scratching of the painful area and, lameness including limb disuse, unusual posture (e.g. hunched up) and, slow movement. Behavioural responses to external stimuli include assessing animal responses when interacting with humans and their response to gentle handling of the surgical site or source of pain. The use of clinical signs to judge whether an animal is in pain is only useful for acute pain. The clinical signs that can be used include increased heart rate and blood pressure, peripheral vasoconstriction and pallour of mucous membranes, cardiac arrhythmias, sweating in some species, hyperventilation and reduction in peristalsis (Morton and Griffiths, 1985). Increased plasma catecholamine and cortisol concentration and increased systolic blood pressure have been shown to be very useful in predicting post-operative pain in cats (Morton and Griffiths, 1985; Smith *et al.*, 1996).

Justification for pain therapy

Pain treatment is justified for several reasons.

- (i) Treatment or alleviation of pain reduces patient suffering.
- (ii) Pain increases morbidity, the cost of patient care and occupies time better spent on more productive work.

- (iii) Pain increases patient risk during anaesthesia as more drugs are required to maintain a stable plane of anaesthesia.
- (iv) Pain exaggerates the inflammatory response, which in turn increases the production of pain neurotransmitters (substance P, CGRP) and increases the excitability of sensory neurones.
- (v) Pain produces a catabolic state, suppresses the immune response and promotes inflammation which delays wound healing and predisposes the patient to infection and intensified medical care.

In addition to the above, special consideration should be given to post-operative pain, although it is thought that it does not serve any useful purpose. This is because, post-operative pain causes sympathetic stimulation, increased cardiac output and cardiac work, elevation of blood pressure, increase in catabolic hormones and muscle spasm, all of which contribute to increased morbidity and mortality.

Pain therapy

Strategies for pain control

Pain can be controlled by interventions aimed at different points in the pain transmission pathway. Several or a combination of these interventions can be employed. Limitation of nociceptor stimulation can be achieved by gentle handling of tissues to minimize tissue trauma during surgery. Administration of non-steroidal anti-inflammatory drugs (NSAIDs) that inhibit cyclo-oxygenase pre-operatively ensures reduced production of prostaglandins and other substances that sensitise the nociceptors. Interruption of peripheral neural transmission can be achieved through local infiltration of local anaesthetics, nerve blocks or intravenous regional anaesthesia. Inhibition of nociceptive transmission at the spinal cord can be achieved by systemic, epidural or subarachnoid administration of opioids and alpha₂-adrenergic agonists and epidural or subarachnoid administration of local anaesthetics. Modulation of brain pathways to control pain entails systemic administration of opioids, alpha₂-adrenergic agonists and to a lesser extent some NSAIDs. 'Balanced' or 'multimodal' approach to pain control involves the simultaneous use of the above strategies to maximize pain control with minimal doses of drugs. For example, infiltration of the surgical site with local analgesics can be combined with systemic administration of a NSAID or an opioid. Similarly, epidural administration of a mixture of a local anaesthetic and an opioid together with systemic administration of a NSAID can maximize pain control. Combination therapies have been found to be the most useful and rational.

Specific pain therapies

Among the wide variety of pharmacological and non-pharmacological therapies available for the management of pain in animals are local and regional anaesthesia, use of systemic drugs and, analgesic adjuncts.

Local anaesthetic drugs. These can be used in regional and local anaesthetic techniques including epidural anaesthesia and various specific nerve blocks to block nerve electrical activity and therefore block transmission of pain signals (Quandt and Rawlings, 1996; Muir, 1998).

Examples of useful local anaesthetics are lidocaine, mepivacaine and bupivacaine.

Sedatives. Alpha₂-adrenergic agonists (xylazine, detomidine, romifidine), opioids (butorphanol, morphine) and tranquilizers (acepromazine) modulate central nervous system signal processing thus interfering with nociceptive inputs. The alpha₂-agonists that are widely used in horses for provision of analgesia include xylazine (0.5-1.0 mg/kg, intravenous), detomidine (0.01-0.02 mg/kg, intravenous), medetomidine (0.01-0.02 mg/kg, intravenous), and romifidine (0.04-0.08 mg/kg, intravenous) (Muir, 1998).

General anaesthetics. Dissociative anaesthetics (phencyclidine, ketamine) are non-competitive N-methyl-D-aspartate (NMDA) antagonists producing dose dependent prevention of hyperalgesia and allodynia, in addition to amnesia while injectable anaesthetics (thiopentone, propofol) and inhalation anaesthetics (halothane, isoflurane, sevoflurane) interfere with cortical signal processing. It is generally accepted that adequately anaesthetised patients cannot experience pain as cortical signal processing is depressed. However, the magnitude of nociceptive input may vary considerably for different surgical procedures resulting in a variety of physiological responses especially in heart rate, blood pressure and sympathetic outflow, suggestive of increased nociceptive inputs that may require adjunctive pain therapy (Muir, 1998).

Non-steroidal anti-inflammatory drugs (NSAIDs). The most popularly used NSAIDs are phenylbutazone, ketoprofen, carprofen and flunixin meglumine. Their analgesic effects arises majorly through inhibition of cyclo-oxygenase-1 (COX-1) activity. They are used in various animal species to control pain (Table 1). Other NSAIDs in use include ibuprofen, ibufenac, alclofenac, phenoprofen, naproxen and diclofenac (Short, 1995). Most of them have the known potential for gastrointestinal ulceration and renal toxicity (Quandt and Rawlings, 1996; Muir, 1998).

Corticosteroids. Corticosteroids relief pain through the reduction of inflammatory processes, especially soft tissue damage, stabilization of cell membranes and the reduction of oedema without significant central nervous system activity (Short, 1995). The most commonly used corticosteroids are hydrocortisone, dexamethasone, and methylprednisolone. Most often, the use of steroids in horses is by intra-articular injection although systemic administration is also widely practiced in other species. However, the use of intra-articular injection of corticosteroids can cause reduction in cartilaginous tissue responses because of interference with circulation or tissue perfusion (Short, 1995).

Opioids. Opioids activate opioid receptors producing good to excellent analgesia. Of the commonly used opioids, butorphanol, morphine and fentanyl produce analgesia with minimal or no sedation when administered in low dosages. The most potent opioids (e.g. fentanyl) are less likely to develop tolerance than less potent opioids

(e.g. butorphanol). Their use in various animals to control pain is well documented (Short, 1995; Smith et al., 1996; Muir, 1998). Dosages of the more commonly used opioids for the provision of analgesia in various animal species are shown on Table 2. Opioids or opioid and local anaesthetic mixtures can be injected into the epidural space to provide excellent long-lasting analgesia in various animal species (Quandt and Rawlings, 1996).

Combination therapy.

The combination or sequential administration of analgesics that act by different mechanisms (multimodal therapy) is often advocated in order to maximize analgesic drug effects (Muir, 1998). Examples of these are the administration of two major analgesics - NSAID with an opioid or an opioid with an α_2 -agonist. These frequently produce supra-additive or synergistic analgesic effects with the advantage of reduced individual drug dosages thereby reducing the potential for drug related side effects. Synergism or supra-additivity has been demonstrated when local anaesthetics are combined with opioid or dissociative anaesthetics and when NSAIDs are combined with opioids (Henrik and Dahl, 1993). The combination of morphine with xylazine in horses for example, produces excellent sedation, euphoria and potent analgesia allowing for most medical and minor surgical procedures to be completed without the need for further administration of an injectable or inhalant anaesthetic (Muir *et al.* 1979b).

Administration of adjunctive drugs (tranquilizers) in conjunction with major analgesic drugs may potentiate analgesic effects and produces additional calming effects. Some examples of these include acepromazine and meperidine or acepromazine and xylazine (Muir, 1979a,b). Several of the major opioid and α_2 -agonist analgesics can be antagonised in case of adverse effects on their administration which is a distinct advantage over other groups of drugs. However, it is important to note that reversal or antagonism of adverse effects may antagonise the drug's analgesic activity (Muir, 1998).

Pre-emptive analgesia.

The deliberate administration of analgesic drugs 24-48 hours before extensive soft tissue or orthopaedic surgery in order to pre-empt or minimise the response to pain has a number of advantages in that:

- (i) the number and amount of anaesthetic drugs required to produce and maintain surgical anaesthesia is reduced,
- (ii) it helps to stabilise the maintenance phase of anaesthesia,
- (iii) the total amount of analgesic drugs required to control pain both intra-and post-operatively is reduced, and
- (iv) the overall patient morbidity associated with surgery and anaesthesia is decreased (Muir, 1998).

The most commonly used pre-emptive analgesics in the horse for short term pain therapy are combinations of low dosages of opioids with NSAIDs or α_2 -agonists.

Long term pain therapy.

Continued or long term administration of analgesic drugs for pain therapy where necessary poses special problems for the veterinary surgeon. Long term use of opioids may lead to tolerance in addition to the development of constipation and urine retention (Quandt and Rawlings, 1996). Long term use of α_2 -agonists can predispose to impaction or constipation. Prolonged use of Cox-1 inhibitors has the potential for producing gastrointestinal ulceration or renal toxicity (Short, 1995). Drugs that produce analgesia by two distinctly separate mechanisms are likely to be synergistic. For example, although the xylazine and ketamine combination produces synergistic analgesia, it also produces synergistic respiratory depression. In this case, the dosages of each should be reduced to avoid this potential outcome. It should be noted that the development of side effects is almost always a direct consequence of inadequate consideration of the drug's toxic effects, dose-response characteristics and patient status prior to drug administration (Muir, 1998).

Table 1. Dose rate and route of administration for commonly used NSAIDs as analgesic agents. (The duration of action for each drug is shown below each dose).

DRUG	DOG	CAT	HORSE	PIG	SHEEP/GOAT	CATTLE
Aspirin (mg/kg)	10-20 PO 8-20 hours	Max. 10 PO 48 hhours				
Ketoprofen (mg/kg)	2 IV,IM,SC 24 hours	2 SC 24 hours	2 IV 24 hours			
Carprofen (mg/kg)	4 IV,SC Not IM 24 hours		0.7 IV 24 hours			
Flunixin (mg/kg)	1 IV 24 hours		1.1 IV 24 hours	2.2 deep IM 12 hours		2.2 IV 24 hours
Phenylbutazone (mg/kg)	10 PO 8-12 hours		5 PO 24 hours 3-6 IV 12 hours			

IM = Intramuscular; IV = Intravenous; SC = Subcutaneous; PO = Oral; NR = Not Recommended.

Table 2. Dose rate and route of administration for commonly used opioids as analgesic agents. (The duration of action for each drug is shown below each dose).

DRUG	DOG	CAT	HORSE	PIG	SHEEP/GOAT	CATTLE
Morphine (mg/kg)	0.25-0.5 IM,SC 3-4 hours 0.1 epidural 10-23 hours	0.05-0.1 IM,SC 3-4 hours 0.1 IV 0.1 epidural				
Pethidine (mg/kg)	2-5 IM,SC 1-2 hours	2-5 IM,SC 1-2 hours	2-4 IM 15 minutes	2 IM 4 hours	200mg total IM	2 IM
Fentanyl (μ /kg)	5-10 IV 20 minutes	NR				
Buprenorphine (μ /kg)	10-15 IV,IM,SC 6-8 hours	5-10 IV,IM,SC 6-8 hours		5-10 IM to 10 hours	5 IM to 12 hours	
Butorphanol (mg/kg)	0.05-0.2 IV 0.2-0.5 IM 1-2 hours	0.05-0.2 IV 0.2-0.5 IM 1-2 hours	0.022 IM 2-4 hours			
Codeine (mg/kg)	1-2 PO to 6 hours	NR				
Methadone (mg/kg)	0.25-0.5 IM,SC 4 hours	0.2-0.3 SC 4 hours				

Source: Unnamed, (1996).

IM = Intramuscular; IV = Intravenous; SC = Subcutaneous; PO = Oral; NR = Not Recommended.

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