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REVIEW ARTICLE

Pain management in cats—past, present and future. Part 1. The cat is unique

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Summary Cats are popular pets but until recently their perioperative and traumatic pain was seriously underestimated and under treated. There are several causes of this under treatment. First, it may be difficult to detect pain in cats, because they do not demonstrate overt pain-associated behaviour. Secondly, there are relatively few analgesic drugs with market authorisation for cats. Thirdly, cats have an unfortunate reputation for toxicity from analgesic drugs, particularly opioid-induced mania and classical non steroidal anti inflammatory drug toxicity. Fourthly, cats are deficient in some metabolic pathways used to metabolise analgesic drugs in other species; this may lead to genuine toxicity or to lack of effect. Recently, understanding of feline behaviour and physiology has improved, leading to better clinical management of this enigmatic species. Behavioural methods are proving to be the best means of assessing pain, and knowledge of unique feline physiology has enabled rational treatment protocols to be developed specifically for cats.

Introduction

In many countries cats are the most popular pets; there are a reported 69 million cats in the USA (Wise et al., 2002) and 9 million in the UK alone. The majority of these are neutered, so very many cats undergo surgery at least once in their lifetime. In spite of this, they tend to be under treated for pain and remain the ''poor relative'' of the dog (Dohoo and Dohoo, 1996; Joubert, 2001; Lascelles et al., 1999; Watson et al., 1996). For example although veterinary surgeons scored the pain associated with an exploratory laparotomy in dogs and cats equally, 71% of dogs received analgesics for this procedure compared to 56% of cats (Lascelles et al., 1999). Fortunately, in the last few years, the cat has received greater attention and various methods of managing surgical, traumatic and chronic pain have been developed and assessed.

Cat pain is under treated for several reasons, but not because of a lack of compassion by caregivers. Before we can say we have treated pain in cats, we must be able to recognise it and this presents one

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of the greatest challenges in pain management of cats. Pain is difficult to recognise in this species as they do not demonstrate pain overtly; indicators of pain may be subtle and easily missed even by diligent observers (Lamont, 2002; Lascelles and Waterman, 1997). Proper assessment of pain in cats will depend on the development and validation of behaviour based multidimensional pain measurement tools. Such tools exist for dogs (Holton et al., 2001), but similar tools for cats are in their infancy.

Further reasons for under treatment of pain in feline patients are the limited number of analgesics with market authorisation for cats and the fear of side effects. Cats continue to have an undeserved reputation for becoming maniacal and excited when given opioids. This stems largely from historical reports where excessive doses (20—40 times an adequate clinical dose) were given (Fertziger et al., 1974; Watts et al., 1973). With appropriate use, opioids can provide excellent analgesia in cats. The non-steroidal anti-inflammatory drugs (NSAIDs) have also been withheld due to fear of toxicity. NSAIDs should be used with caution in cats because they have a very low capacity for hepatic glucuronidation, which is the major route of metabolism and excretion for this category of drugs. However, there is now considerable experience with NSAIDs in cats, particularly the newer compounds, and with appropriate doses and dosing intervals, NSAIDs can be used safely and effectively in this species.

This paper examines the peculiarities of the feline species and demonstrates how better understanding of their unique physiology and behaviour may be exploited to improve our clinical care of this enigmatic species.

Metabolism

Compared to other mammals, cats have a very low capacity for hepatic glucuronidation of exogenously administered drugs. Recently, a molecular genetic basis for this deficiency has been identified (Court and Greenblatt, 1997a,b, 2000). Domestic cats have fewer hepatic UDP-glucuroninosyltransferase (UGT) isoforms, and novel cloning techniques have identified mutations of UGT and pseudogenes. Cats may lack these metabolic pathways because of their carnivorous diet and lack of exposure to plants containing phytoalexins.

These metabolic differences can lead to toxic side effects if doses and dosing intervals are not adjusted. Alternatively, if the parent compound must be metabolised to an active component via this pathway, the drug may be ineffective. Deficient glucuronidation pathways explain the cat's susceptibility to the toxic side effects of phenolic drugs such as paracetamol (acetaminophen) and long half lives of other drugs such as carprofen and aspirin. Cats produce very small amounts of the active metabolite morphine-6-glucuronide (M-6-G) which contributes to the overall analgesic profile of morphine; this may explain why morphine seems less effective in cats compared to other species (Taylor et al., 2001).

When do cats need analgesics?

In broad terms, cats require analgesics under the same circumstances as any other species, particularly to treat acute traumatic and perioperative pain. The incidence of chronic pain in cats is not well documented but it is associated with many conditions including osteoarthritis, cancer, interstitial cystitis, dental disease and long-standing dermatitis and wounds.

There are obvious benefits to the cat's welfare in providing pain relief (Fig. 1). In addition, severe pain causes marked physiological effects, and there is substantial evidence supporting the benefits of good pain relief at the time of surgery or trauma in humans (Capdevila et al., 1999; Holte and Kehlet, 2002). The stress response and need for tissue repair after surgery or trauma increases the patient's energy requirements, and if this is not met by an increase in caloric intake, severe weight loss with a negative nitrogen balance develops. Although objective outcome data are not yet available for cats, the effect of pain on a cat's attitude, and in particular its willingness to eat, are

Figure 1 Good pain management results in a comfortable cat that will eat, drink and relax even while recovering from severe trauma.

well recognised in clinical practice. Pain relief and positive energy balance are also required for a fully functional immune system, essential for healing in the face of any infection.

There may be added benefits of aggressive pain management during surgery and after trauma, by preventing central sensitisation or ''wind-up'' (see Physiology section below) (Honore et al., 2000). Although controversial, there is good evidence from clinical studies in people and animals that prevention of ''wind-up'', by pre-emptive and aggressive multimodal perioperative pain therapy, leads to better postoperative analgesia (Katz et al., 1992, 1996; Lascelles et al., 1995; Slingsby et al., 1998). Human studies report improved mobility after orthopaedic surgery when intraoperative analgesia is provided and low doses of ketamine appear especially beneficial (Menigaux et al., 2001).

Chronic pain is undoubtedly a clinical problem in cats, but is not well documented (Fig. 2). Compared to dogs very little is known about degenerative joint disease in cats (Hardie, 1997), but radiographic evidence in geriatric cats suggests the incidence may be as high as 90% (Hardie et al., 2002). Because of a pet cat's lifestyle, lameness is not a common owner complaint, but changes in behaviour including decreased grooming, reluctance to jump up on favourite places, and soiling outside the litter box should prompt the veterinarian to look for sources of chronic pain. Many signs are insidious and not obvious to the owner who sees the cat every day. In addition, many owners disregard these changes as inevitable with ageing. Owners may not realise how debilitated their pet was until they see dramatic improvements following treatment. Radiographic lesions in the lumbosacral area have been correlated with neurological disease (Hardie et al., 2002). Recently, modifications of pressure platforms have enabled gait evaluation of cats (Conzemius et al., 2003), which may offer an objective method of assessing lameness and efficacy of treatment in this species.

Figure 2 Osteoarthritis of the hip joints in a cat causes chronic pain and inactivity.

Much of the supportive management recommended for canine osteoarthritis, such as weight loss and controlled exercise, are difficult to implement with cats. The mainstay of drug therapy for osteoarthritis in most species is a NSAID. Once again this poses a challenge in cats due to their susceptibility to NSAID toxicity, especially with long term dosing. Nutritional supplements or nutraceuticals may be beneficial but controlled scientific studies are lacking.

Another chronic pain problem in cats is interstitial cystitis which shares many of the features of this debilitating disease in humans (Westropp and Buffington, 2002). Feline interstitial cystitis waxes and wanes and may be exacerbated by stress (Westropp and Buffington, 2002). The aetiology of this disease is unknown but is associated with increased plasma noradrenaline which may alter nociceptive processing (Buffington and Pacak, 2001). This may explain why the tricyclic antidepressant amitriptyline, which has sympatholytic actions, can be helpful in these patients (Chew et al., 1998).

Recognition of pain in cats

Observation of behaviour is undoubtedly the best means of assessing the degree of pain experienced by a cat (Lascelles and Waterman, 1997). Studies that have tried to correlate objective physiological data such as heart rate, temperature, respiratory rate, plasma cortisol and beta-endorphins (Cambridge et al., 2000; Smith et al., 1999) with pain in cats have been unsuccessful as these are influenced by many factors other than pain. Cats in acute traumatic or postoperative pain are usually depressed, immobile and silent (Fig. 3). They may appear tense and distanced from their environment and do not respond to petting or attention and may often try to hide (Fig. 4). Some cats become manic and aggressive, growl and hiss and roll around their cage. Cats do not like bandages so the observer must differentiate between pain and the dislike of restrictive dressings (Fig. 5). Levy et al. (1999) reported that bandages alone caused a 200% increase in urine cortisol, suggesting that cats find this stressful. One important step in pain evaluation is to manipulate the affected area to confirm the presence, or absence of pain. Cats with

Figure 3 A cat in pain after surgery is hunched, immobile and unresponsive.

abdominal pain adopt a sternal posture, with elbows back, stifles forward and abdominal muscles tensed. Limb pain prevents weight bearing and may cause self-mutilation at the site of pain. One of the many commonly reported problems following onychectomy is excessive licking and chewing of the feet (Patronek, 2001).

Physiology of pain

Effective treatment of pain requires a good understanding of the underlying mechanisms of nociception and pain perception. Noxious stimuli are translated into electrical signals by nociceptive nerve endings responding to thermal, mechanical or chemical stimulation; this process is termed transduction. Signals are then transmitted through the sensory nervous system via the peripheral nerves and the dorsal root ganglia to the dorsal horn of the spinal cord. Sensory input is generally modulated in the spinal cord, and then continues to travel cranially to the brain, finally reaching the cerebral cortex, allowing pain to be perceived. Nociception is simply the process by which the noxious stimulus is transmitted to the CNS by the processes of transduction, transmission and modulation. Pain can only be perceived in a conscious animal with a functional cerebral cortex. During anaesthesia, nociception can still occur, and reflex

Figure 4 A pain-free cat after surgery responds normally to petting.

responses to noxious input such as tachycardia and hypertension may develop during surgery, but the animal is unconscious and therefore cannot experience pain.

Figure 5 Differentiation between dislike of bandages and pain may be difficult. This cat has undergone onychectomy and is clearly in pain, being hunched, immobile and unresponsive. Good pain management is essential after this painful operation which is for the benefit of the owner, not the cat, and is not permitted in many countries.

Much of the modulation of incoming noxious information from sites of tissue damage occurs in the dorsal horn of the spinal cord and this process has considerable impact on the pain that is ultimately perceived. Both endogenous (enkephalins and endorphins) and exogenous drugs (opioids) may modify afferent input in the dorsal horn. Numerous other drugs may be involved in similar processes in the spinal cord, particularly *N*-methyl D-aspartate (NMDA) antagonists including ketamine, and alpha2-adrenoceptor agonists such as medetomidine. Descending adrenergic and serotonergic pathways may also be activated and contribute to modulation in the dorsal horn.

Noxious stimuli produce physical changes in the spinal cord, and the degree of these changes is correlated with the size, duration and intensity of the stimulus. Limited input, leading to ''physiological pain'' does not cause long-term effects and is essential for survival. Physiological pain allows detection and reflex withdrawal from potentially damaging insults such as heat. This type of pain hurts, but it is fleeting and sensation quickly returns to normal. If the input is more intense and prolonged as a result of significant tissue damage, ''clinical'', or ''pathological'' pain ensues, predominantly a result of inflammation. Clinical pain is the result of a sensitised central nociceptive system. Peripheral sensitisation also occurs, as the products of inflammation decrease the threshold of the nociceptors at the site of injury. An example of the clinical effects of sensitisation are the phenomena of hyperalgesia, where formerly mild stimuli now feel more intense, and allodynia, where a stimulus that normally would not cause pain now does. Other effects are a result of ''rewiring'' of the complex interneurone system in the dorsal horn, which leads to secondary hyperalgesia and increased sensitivity at distant sites in the body. This process of sensitisation of the nervous system is termed ''wind-up'', and its prevention is an important goal of clinical pain management. Blocking or modulating incoming nociceptive signals is the premise of preemptive analgesia. This subject has been much debated and many clinical human studies fail to show benefits of preemptive analgesia (Moiniche et al., 2002). However, with greater attention to the details of dose, type of drug and timing, many studies, including those in rats, dogs and cats, do show the benefits of preemptive strategies (Lascelles et al., 1995, 1998; Slingsby et al., 1998).

General anaesthesia by its very nature, provides analgesia because the cat is unconscious. However, unless the anaesthetic protocol includes drugs that are themselves analgesics (would cause analgesia in the conscious animal), hypersensitisation from ''wind-up'' will still develop, and postoperative pain will be severe when the cat regains consciousness; the neurones will still be sensitised even though the surgical stimulus has stopped. Following surgery, there is also the continued noxious input from the inflammation that develops at the surgical site. Hence, postoperative analgesia will be markedly improved if analgesics are used as part of the anaesthetic protocol. A number of reports demonstrate dramatically how acepromazine-thiopentone-halothane results in more postoperative pain than medetomidine or xylazine-ketamine (Robertson et al., 1995; Slingsby et al., 1998). Preoperative opioids or NSAIDs also provide better postoperative analgesia (Lascelles et al., 1995).

An additional benefit of giving analgesics preoperatively is that opioids, local anaesthetics, and alpha-2 agonists reduce the required dose of anaesthetic used for induction and maintenance, leading to safer anaesthesia, less cardiopulmonary depression and faster recovery. In particular, systemic opioids have an anaesthetic sparing effect. Minimum alveolar concentration (MAC) reduction is commonly used to evaluate this effect. However, compared to the dog less MAC reduction is achieved with most opioids in cats and it does not appear to be dose related (Ilkiw et al., 2002). For example, the isoflurane MAC reduction achieved with the same dose of morphine in dogs and cats was approximately 50% and 28% respectively (Ilkiw et al., 2002). Up to a 69% reduction in MAC has been reported with alfentanil in dogs, but only 35% has been achieved in cats (Ilkiw et al., 1997; Troncy et al., 2002). Epidural opioids also decrease anaesthetic requirements (Golder et al., 1998) and can be used as a component of balanced anaesthesia.

Complementary therapies

Complementary or alternative veterinary medicine covers a wide range of practices such as acupuncture, homeopathy, herbal and manual or manipulative therapies. In recent years, the popularity of a more ''holistic'' approach to medicine for both humans and pets has increased. Historically the legitimacy of acupuncture has been questioned, due to a lack of well controlled scientific and clinical trials, but the tide has turned, and in 1997 the office of alternative medicine based at the National Institutes of Health in the USA issued a statement declaring that there was sufficient evidence of the value of acupuncture to expand its use into conventional medicine and encourage further

studies. Acupuncture is now a respected component of treatment in human pain clinics and there are many veterinarians pursuing formal training in this discipline; the International Veterinary Acupuncture Society (IVAS) has certified over 1300 veterinarians. Acupuncture is an ancient Chinese discipline that can be used for many ailments and includes pain relief. It involves placing needles at specific points on the body and the cause of the resultant analgesia is complex but involves the release of endogenous opioids. A detailed discussion of acupuncture is outside the scope of this paper but there are several excellent reviews (Janssens et al., 1988; Mittleman and Gaynor, 2000; Pascoe, 2000). Most cats tolerate needle placement surprisingly well and acupuncture should be considered a viable choice for analgesic therapy especially for chronic conditions where there are few pharmacological choices in this species.

Oral nutritional supplements (nutraceuticals) have been advocated for treatment of chronic pain from osteoarthritis in cats as in dogs, although in both species the benefits are still somewhat controversial. (Hardie, 1997) suggests that Cosequin (Nutramex Laboratories, Baltimore, MD, USA) may have some benefits in the treatment of osteoarthritic pain in cats. Some practitioners consider that nutraceuticals may be the first choice of treatment in cats with osteoarthritis. Glucosamine hydrochloride, chondroitin sulphate and manganese ascorbate have all been used in feline practice, but their safety and efficacy in this species have not yet been the subject of controlled clinical trials.

Nursing techniques

It is also important to remember that general care of the cat makes a considerable impact on the degree of pain experienced. Pain is an emotional state, and an animal that is cold, wet, frightened, hungry, thirsty or unable to empty its bladder will suffer more from its painful condition than one that is warm, comfortable, well fed and happy. Immobilisation of an injured body part can contribute to analgesia; however, cats do not always tolerate bandages well, particularly on hind limbs, and immobilisation must be used judiciously. It is also important to remember that not all cats have a history of interaction with dogs and exposing cats to the smell and noise of dogs may be stressful. Ideally, hospitals should have separate areas for nursing dogs and cats. If this is not feasible, then cats should be provided with a box or covered bed so they can hide and feel safe (Fig. 6). Often the presence of a familiar toy or blanket is reassuring.

Figure 6 Pain management is improved if the cat is relaxed and happy. The cat should be given a place to hide to give security when hospitalised in a strange environment.

Research in cats

Cats have been, and continue to be used extensively in neurophysiological research including visual, spinal cord injury, and laryngeal and cough reflex studies, but in this setting they are used as a model for humans. Until recently there have been remarkably few analgesic studies conducted primarily for the benefit of cats themselves. Any research that depends on behavioural changes as the endpoint is difficult in cats because they are mysterious and fickle creatures, and the very

Figure 7 The feline thermal threshold testing system developed by Dixon et al. (2002) allows humane study of analgesics in cats, without restraint.

experiments designed to assess analgesia may alter their behaviour. With the growing popularity of cats and increase in animal welfare awareness over recent years, both clinical and laboratory investigations have been conducted, and these have improved our knowledge of pain behaviour and analgesic pharmacology in cats. Clinical studies in the UK (Slingsby et al., 1998, 2001; Slingsby and Waterman-Pearson, 1998, 2000, 2002), a range of studies from the USA (Carroll et al., 1998; Gellasch et al., 2002; Glerum et al., 2001; Smith et al., 1999), and investigations in a research setting using the feline thermal threshold testing system (Dixon et al., 2002) have contributed considerably to this area of study in the last decade (Fig. 7). Recently the thermal threshold system has been developed to allow study of NSAIDs in addition to opioids (Taylor et al., 2003).

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