

Use of Analgesics in Exotic Felids

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Treatment of pain in domestic and non-domestic cats has been a challenge for the clinician. Many cat species are stoic and show few or very subtle external signs of pain. Additionally, the adverse effects of nonsteroidal antiinflammatory drugs (NSAIDs) in domestic cats are well documented and have discouraged many practitioners from trying novel NSAID's in exotic felids.

As in other animals, each cat's response to pain and analgesics will vary, necessitating an individualized treatment plan. As a rule, always treat painful felids to effect, and not by rote reliance on published dosages. It is frequently necessary to try different agents and combinations to find which produces the optimal analgesic effect in exotic felids. In order to minimize adverse effects, it is desirable to work toward treatment with the lowest effective dose when treating chronic pain.

Non-steroidal Antiinflammatory Drugs

NSAIDs are antiinflammatory drugs which act both centrally and peripherally. The primary effects are believed to be caused by their ability to inhibit cyclooxygenase (COX) enzymes in the arachidonic acid metabolism cascade. The COX-1 isoform is regarded as constitutive (continuously expressed) and is responsible for many homeostatic processes, such as maintenance of gastric mucosal integrity, platelet function, and renal autoregulation. Reduced COX-1 activity is thought to be responsible for many of these agents' adverse effects. The COX-2 isoform is generally thought to be induced in response to noxious stimuli and initiates creation of pro-inflammatory prostaglandins. Inhibition of the COX-2 isoforms prevents the production of these prostaglandins and the associated pain. This simplification of COX and NSAID physiology is under constant revision but remains the basis for categorizing NSAID's activities. All drug dosages, unless otherwise indicated, are as listed in Table 1.

Aspirin is the only NSAID for which a safe chronic dosage has been established in cats but it has been largely replaced in practice by newer NSAIDs. Aspirin has antiinflammatory, antiplatelet, and analgesic effects but is not effective for severe pain. Cats lack the ability to bind many compounds to glucuronides and do not metabolize and excrete salicylates well. As a result aspirin must be given at a less frequent dosing interval in cats than in most other mammals. Vomiting and gastric hemorrhage are the two major adverse effects seen with aspirin administration.

Ketoprofen and carprofen are propionic acid derivatives with analgesic and antiinflammatory properties. Ketoprofen is approved for use in cats in Europe and Canada, in both injectable and oral

preparations. Ketoprofen is considered a COX-1 preferential agent and provides good post-operative analgesia in cats but, because of its reduction of platelet activity, is not recommended for administration prior to surgery. Short-term (up to 5 days) treatment has been investigated in domestic cats but longer term therapy has not been studied.

Carprofen is not approved for use in cats in the United States but is approved as a single dose agent in Europe. It is considered a COX-2 preferential agent and it has been studied as a perioperative analgesic for cats. Several authors caution against long-term use of carprofen in cats (Slingsby 2002) and there is an anecdotal report of a leopard dying with intestinal ulcers after 2 weeks of carprofen therapy.

Meloxicam is an enolic acid compound with analgesic, antiinflammatory, and antipyretic activities and is considered a COX-2 preferential NSAID. It is approved for use in cats in Europe and the United States. The injectable form is approved for single dose administration and the oral form is approved for up to 5 days administration. Both the oral and injectable forms have been used for extended periods in domestic and non-domestic felids with few, if any, adverse effects.

Piroxicam is not related structurally to other NSAIDs but is considered a COX-1 preferential agent. It has antiinflammatory and analgesic properties but has been used most frequently in domestic animals, especially dogs, for its antineoplastic effects. In dogs there appears to be a narrow window of therapeutic safety and other NSAIDs are considered safer alternatives for analgesia. Few studies of its use in cats have been published.

Opioids

Opioids produce their effects by binding with specific opiate receptors. Historically, there was a reluctance to use this class of drugs in cats due to reports of them causing dysphoria, mania, or excitement. These effects were most likely dose- and/or route of administration-related responses and opioids are now routinely used for analgesia in domestic cats. Other adverse opioid effects in cats include respiratory depression, loss of the ability to thermoregulate, sedation, nausea, vomiting, and mydriasis. Effects will vary with the agent and dosage but large cats seem more susceptible to these non-analgesic effects, on a comparable dose basis, than do domestic cats. All opioids have the advantage of having their effects terminated by administration of an opioid antagonist, of which naloxone is the safest.

Morphine, oxymorphone, hydromorphone, and meperidine are mu-receptor agonist opiates which have been used in domestic cats for post-operative pain. Morphine is the agent most

commonly associated with causing dysphoria or excitement in cats. All of these drugs are controlled substances (United States, Drug Enforcement Administration Category-II) and their use in many practices has largely been replaced by the less-stringently controlled opioid analgesics, buprenorphine and butorphanol. The latter are not, however, as potent analgesics as are the pure mu-receptor agents.

Fentanyl is a mu-receptor agonist opiate that has gained wide-spread use as a post-surgery analgesic in domestic species due to its formulation in a transdermal delivery system (patch). Transdermal delivery offers the advantage of long duration delivery and effects (72 hours or more), and the ability to stop administration (by patch removal) should the need arise. There is a lag time, 6-8 hours in domestic cats, after patch application before analgesic effects. As a result, additional analgesia is required to bridge the period between patch administration and onset of analgesia. Patches need to remain in good contact with the skin to be effective and this typically requires bandaging, which is difficult to maintain in non-domestic felids. As a result, fentanyl patches can be used only in select non-domestic felids.

Buprenorphine is a partial mu-receptor agonist with potent analgesic properties. It is available in the United States only in the injectable form but this preparation may also be administered to cats transmucosally, via the oral mucous membranes. Onset of analgesia, following oral transmucosal administration, is more rapid than when used intramuscularly and is a potential way to administer this drug following recovery from surgery (Robertson 2005). Buprenorphine has relatively few adverse effects when used at recommended dosages and has the distinct advantage of a long duration of activity (>6 hours).

Butorphanol is a mu-antagonist which produces analgesia via its binding to kappa-receptors. This combination of receptor affinities results in a 'ceiling' effect to its analgesic and adverse effects- a dosage point above which there is no increase of effects. Butorphanol appears to provide analgesia to the viscera but poor body wall or muscular analgesia. In addition, butorphanol is relatively short-acting (< 2 hours) and effective analgesia following major surgery requires frequent redosing. Large cats seem particularly susceptible to butorphanol's sedative effects.

Tramadol, although it is structurally not an opioid, has weak affinity for mu-receptors. Its principle mechanism of analgesic action appears to be by inhibiting reuptake of serotonin and norepinephrine within the spinal cord and, as a result, it appears to modulate pain at the spinal level. It does not affect COX enzymes and may be given safely in combination with NSAID's. It has

few adverse effects, however a dose-dependent respiratory depression has been observed in anesthetized domestic cats. It appears to have a very low risk of dependency but it is recommended that animals which have been on long-term therapy be weaned off treatment slowly. It is not a controlled agent in the United States and is available only in an oral form.

Treatment of Acute Pain

Assessing the alleviation of post-surgical pain has been the primary model for studying treatment of acute pain in domestic cats. While surgery is not a large portion of non-domestic felid practice, elective and emergency procedures are performed and all require post-operative pain management. Additionally, drug regimens developed for peri-operative situations are applicable to episodes of acute pain.

Acute and post-operative pain is usually treated with injectable agents, frequently while the animal is anesthetized. Due to the frequent reluctance of cats to eat when recovering from surgery and the stress induced by repeated injections, those regimens which provide long post-operative duration of activity are desirable. Fortunately, studies of domestic cats suggest that most analgesic drug regimens have relatively similar results following surgery. Opioids generally perform better the first hours after surgery while NSAIDs provide better analgesia after 4 hours post-surgery. This is likely due to NSAIDs slower onset of action when compared to opioids.

Most experts agree that pre-emptive analgesia (analgesics administered before surgery is initiated) provides superior benefits to the same agents administered after noxious stimuli. There is some debate whether NSAIDs truly have a pre-emptive effect on pain. However, whether their benefits are due to pre-emptive effect or the onset of activity effect, the administration of appropriate NSAIDs prior to surgery is supported by most investigators. The possibility of NSAID's affecting renal blood flow mandates that if they are used pre-emptively, diligent effort should be made to maintain blood pressure and renal perfusion during anesthesia.

Many studies have compared analgesics in cats during the immediate (within 20 hours) post-operative period. A comparison of post-operatively administered buprenorphine (0.006 mg/kg im), meperidine (5.0 mg/kg im), and ketoprofen (2mg/kg sc) showed ketoprofen provided the best analgesia during the 18 hours following ovariohysterectomy (Slingsby 1998). Another study comparing buprenorphine (0.01 mg/kg im), oxymorphone (0.05 mg/kg im), and ketoprofen (2 mg/kg im) administered post-onychectomy, with and without subsequent sterilization, found buprenorphine had the lowest cumulative pain scores for 12 hours post-surgery (Dobbins 2002). A comparison of

post-operatively administered NSAIDs (carprofen (4 mg/kg sc), ketoprofen (2 mg/kg sc), and meloxicam (0.2 mg/kg sc)) after ovariohysterectomy showed very little differences between the treatment groups over 18 hours post-surgery (Slingsby 2000).

When NSAIDs have been compared to butorphanol, the NSAID drugs have provided superior analgesia. Pre-operatively administered meloxicam (0.3mg/kg sc) and butorphanol (0.4mg/kg sc) were compared, following onychectomy, and cats treated with meloxicam were less lame and less painful (Carrol 2005). When pre-operatively administered carprofen (4 mg/kg sc) was compared to post-operatively administered butorphanol (0.4mg/kg sc) both provided similar analgesia for cats undergoing ovariohysterectomy but the carprofen group required fewer administrations of 'rescue' analgesics than the butorphanol group (Al-Gizwi 2004).

Buprenorphine (0.015 mg/kg im after surgery, then 0.005 mg/kg im q.8hrs for 3 doses) has been used in a tiger undergoing abdominal surgery (Hart, 2000) and butorphanol (0.1 mg/kg sc) has been used for analgesia following repair of previously-performed onychectomies in tigers (Conrad, 2002). The author has routinely used butorphanol (4.0-5.0 mg (total dose) sc once) in sub-adult and adult lions and tigers following castration with satisfactory short-term effects.

A few drugs have been investigated for use in the days following surgery (Lascelles 2001). Ketoprofen (< 5 days), and meloxicam (approx. 14 days) are the only two NSAIDs typically recommended for short-term post-operative use in domestic cats (Table 1).

Local and regional analgesia are important methods for perioperative pain relief in cats. Epidural morphine (Morphine Sulfate, 15 mg/ml, Abbott Laboratories, N. Chicago, Illinois 60064, USA) can be used in large cats (>100kg) undergoing laparotomies or caudal limb procedures. Typically 10 ml of the solution is delivered in a manner identical to that used in domestic carnivores prior to surgery. The only adverse effect that has been observed was dysphoria seen in one tiger which received greater than 11 ml of morphine epidurally and additional parenteral morphine for pain.

TREATMENT OF CHRONIC PAIN

In contrast to the treatment of post-surgical pain, the treatment of chronic pain in cats has received very little investigation. Osteoarthritis is a condition that affects many geriatric non-domestic cats and is one of the most common reasons for long-term analgesic therapy in exotic felids. Long-term treatment of pain in these patients can improve their ability to move and their overall quality of life.

Aspirin (10 mg/kg po q. 72hrs) has been used successfully to treat osteoarthritis pain in a tiger and lion for months and over a year, respectively. No adverse effects were found in those animals at necropsy.

Meloxicam (0.1-0.2 mg/kg po or sc, 0.1 mg/kg q.24hrs X 5d, then 0.1 mg/kg po q.48-72 hrs.) has been used in a variety of non-domestic felids (Whiteside 2004). Our experience indicates that adequate analgesia may be achieved with lower doses or longer dosing intervals than those cited above (see Table 1) and that non-domestic felids can be maintained on meloxicam for months. Limited experience suggests piroxicam may be similarly effective, while considerably less expensive than meloxicam. Multiple month therapy for treatment of pain has not yet been attempted with piroxicam.

Tramadol has also proved to be a very effective oral analgesic in lions, tigers, and a clouded leopard. It can be used long-term and sedation and ataxia, in animals given higher doses, were the only adverse effects encountered. Because it is not an NSAID, it can be used more confidently in geriatric cats with renal disease or gastro-intestinal problems. It may be used alone or in conjunction with an NSAID, such as meloxicam, in refractory animals.

Etodolac is an indole acetic acid derivative with selective COX-2 inhibition. It has not been recommended for use in domestic cats but it has been used (5 mg/kg po q.48 hrs for 5 doses, then q.72 hrs) to treat osteoarthritis pain in tigers (Ball 2001). There is an anecdotal report of a tiger developing gastric ulcers after etodolac treatment.

Adjunctive therapies such as weight reduction, nutraceuticals, rearrangement of exhibit 'furniture' and other options should also be considered when treating feline osteoarthritis.

Other Agents and General Principles

A variety of other agents have been investigated for their analgesic effects, including some immobilization agents commonly used for non-domestic felids. Ketamine and medetomidine, at subanesthetic dosages, have both been shown to have adjunctive analgesic effects. Additionally, certain tricyclicamine drugs, such as amitriptyline, traditionally used for treatment of behavior disorders in people and animals, are being investigated for treatment of chronic pain (Robertson 2004).

Concluding Remarks

Buprenorphine, carprofen, and meloxicam offer practitioners several good options for pre-emptive treatment of surgical pain in non-domestic felids. Due to its short duration of analgesic

effects, if butorphanol is used for post-surgery analgesia, redosing at approximately 2 hour intervals, or as needed, should be performed. Ketoprofen and meloxicam are good choices for oral treatment of pain in the days following surgery. Meloxicam and tramadol appear to be the best agents at this time for the long-term treatment of chronic pain in non-domestic felids.

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Table 1. Analgesics of potential use in non-domestic felids.

<u>Agent</u>	<u>Perioperative Use</u>	<u>Short-term Use</u>	<u>Long-term Use</u>
Buprenorphine	0.01-0.02 mg/kg sc, may also given im or orally	bid-qid	--
Butorphanol	0.1-0.4 mg/kg sc *4-5 mg sc (total dose for adult tiger)	0.4-1.0 mg/kg po q.4-8hrs	0.09-0.2 po bid
Tramadol	--	1-4 mg/kg po bid	*50-100 mg (total dose per adult lion or tiger) po bid
Aspirin	--	--	10 mg/kg po q.72hrs
Ketoprofen	2 mg/kg sc	1.0 mg/kg po q.24 hrs	--
Carprofen	4 mg/kg iv,im,sc	2.0-2.2 mg/kg im,sc,po bid for 2 days	--
Meloxicam	0.2 - 0.3 mg/kg sc	Day 1: 0.1-0.2 mg/kg po once; Days 2-4: 0.05- 0.1 mg/kg q. 24hrs; Days 5 on: 0.025 mg/kg q.48hrs	
Piroxicam	--	0.3 mg/kg po, for 4 days, then q.48 hrs.	