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Assessment and management of acute pain in cats

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Abstract: Cats are popular pets, but until recently, their peri-operative and traumatic pain had been seriously underestimated and under-treated. The lack of treatment stems from difficulty in recognizing pain, lack of licensed analgesic drugs, fear of toxic side effects, and lack of information specific to cats. Fortunately, in the last decade, many advances have been made in feline analgesia. It is now obvious that because of the cat's unique metabolism, species-specific studies are essential. Opioids are the mainstay of any analgesic protocol for acute pain and can be used with few side effects. Other drugs that can be utilized include the α_2-agonists, local anesthetics, and non-steroidal anti-inflammatory drugs. Pain assessment in cats is challenging and developing, and validating pain scoring systems remains an important goal. The information in this article will help the critical care and emergency clinician formulate a safe and effective analgesic plan for feline patients.

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Introduction

Based on several market surveys (http://www.avma.org/membshp/marketstats/sourcebook.asp, http://www.appma.org/membership/survey.asp, http://www.aahanet.org/index.html) and publications by professional organizations,[1] the number of pet owning households has increased by over 10% in the past 15 years. Of note is that cats recently overtook dogs as the most popular pet with current numbers estimated at between 70 and 77.7 million in the United States alone. Concurrent with this has been a long awaited increase in the publication of studies relevant to assessment and alleviation of pain in this species which has previously lagged behind the information available for dogs. However, feline practitioners are still faced with several challenges including the cat's unique metabolism of many drugs and the lack of licensed analgesic drugs. In the field of emergency medicine, the veterinarian will deal primarily with acute pain that may be related to trauma, non-elective surgical procedures, or medical diseases. Acute pain has a wide variety of causes and sources (soft tissue, orthopedic, ocular, somatic, visceral), variable intensity (from minor lacerations to multiple fractures, acute peritonitis, or pancreatitis), and expected duration (days to weeks), which may all require a different approach to treatment.

The aim of this paper is to review current knowledge of acute pain assessment in cats, and the most useful drugs and techniques for its alleviation.

What Is Pain and How Do We Measure It?

Pain is a complex, multidimensional experience involving both sensory and affective components. All mammals possess the neuroanatomic and neuropharmacologic components necessary for transduction, transmission, and perception of noxious stimuli (nociception). A recent consensus statement indicated that animals are capable of emotions and, therefore, do experience pain, although it is unclear whether all species, including humans, feel pain with the same qualities and intensities.[2]

Cats are under-treated for pain.[3–6] When veterinarians were asked their opinion on an exploratory laparotomy in dogs and cats, they considered this procedure equally painful in both species, yet only 56% of cats received analgesics compared with 71% of dogs.[5] To overcome this bias, we must understand why cats come in second in the pain stakes. The reason for undertreating feline pain is not lack of compassion by caregivers. The most often cited reasons for withholding analgesics from cats are difficulty in recognizing and assessing pain, the limited number of analgesics with market authorization, lack of published information, and the fear of adverse side effects.[5]

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If we want to say we have treated pain, we must first recognize it and measure it in some way. In 2003, the American Animal Hospital Association introduced pain management standards that must be met for accreditation and a mandate is that pain must be assessed in all patients regardless of the presenting problem. This is one of the biggest challenges feline practitioners face. We must know first if they do indeed hurt and, if so, how much. To assess pain in animals, we must observe them carefully and know what behaviors indicate pain; by definition, this is subjective and, compared with humans and young children who can communicate, there is more room for error. Put simply, in humans, pain is what the patient says it is and in animals it is what we decide it is.

Currently, there is no gold standard for assessing pain in animals. The issue in animals is complex because we must consider differences in species-specific responses to pain, but even within a species there is considerable variation. Few veterinarians would disagree that the different temperaments of individual cats complicates the picture. Investigators looking for objective measure of pain have failed to find a good correlation between physiologic variables (respiratory rate, heart rate, blood pressure) or plasma cortisol levels and pain scores in cats because these are influenced by many factors other than pain.[7–9] Changes in wound sensitivity have correlated well with visual analog pain scores in cats[10] suggesting that palpation, which is a simple clinically applicable technique, is a valuable tool and should be incorporated into an overall assessment protocol.

In an emergency clinic, a pain scoring system must be simple and quick to perform, but be valid, reliable, and sensitive. Observation of behavior is undoubtedly the best means of assessing the degree of pain experienced by a cat[11]; however, in the emergency setting, the veterinarian may have had no prior contact with the cat and will require the owner's input on what is normal for that particular patient. More information can be gathered if you first observe the cat from a distance, then assess its response to a person's approach, and finally interact with it by stroking it and palpating the wound or area you suspect is painful.[7] Use of a dynamic interactive visual analog scale (DIVAS) by one individual unaware of treatments detected both differences between 2 analgesics and between treated and untreated cats.[12] Acute pain related to trauma may result in a depressed, immobile, and silent cat that is tense, distanced from its environment and that tries to hide and does not respond to stroking or attention. Alternatively, cats can be manic and aggressive, growling, hissing, and rolling around their cage; these are difficult patients to assess and treat and are discussed later.

Cats with abdominal pain adopt a hunched sternal posture, with their head hung lower than their body, elbows drawn back, stifles forward and abdominal muscles tensed. Cats may lick, chew, and self-mutilate an injured area and this is documented following onychectomy.[13] If part of the treatment involves bandaging or taping, the observer must differentiate between pain and the dislike of restrictive dressings. Levy et al.[14] reported that bandages alone caused a 200% increase in urine cortisol, suggesting that cats find this stressful. Cats that are comfortable can perform normal functions including stretching, back arching, climbing into a litter box, grooming and adopting normal postures such as laying curled up in lateral recumbency.

Regardless of the scoring system adopted, it should become part of the routine assessment – temperature, pulse, respiration, and pain score ('TPRP'). Analgesic intervention should restore normal behavior and lower the pain score.

Why Treat Pain?

Treating pain has obvious welfare benefits but also many other less obvious dividends pertinent to traumatized or critically ill cats. These include better cardiovascular stability, decreased metabolic and hormonal responses, and less catabolism and immunosuppression.[15] Surgical or accidental trauma results in primary (at the site of injury) and secondary (at sites distant to the injury) nociceptive sensitization that can lead to prolonged and intensified pain.[16,17] The benefits of pre-emptive analgesia in limiting central sensitization and 'wind-up' has been a controversial topic in human medicine but can be demonstrated.[18] In animals, there is good evidence that this is a worthwhile strategy[19,20] and data in cats are encouraging.[21] In emergency practice, the patient is often not seen until already in pain, but early intervention is still beneficial – the longer it takes before initiating an analgesic plan, the harder it becomes to achieve relief.

Drug Strategies for Alleviating Acute Pain

There are several factors to consider when choosing an analgesic drug for feline patients, including the unique metabolism of cats, availability of species-specific data including both the pharmacokinetic and pharmacodynamic profile of the drug, and also ease of administration (Table 1).

Hepatic metabolism

Cats have a reputation for adverse drug reactions; some of these are warranted and others are not. Cats have a low capacity for hepatic glucuronidation of exogenou-

Table 1: Drugs that can be used in cats for the treatment of acute pain. See text for further details

Drug	Dose (mg/kg)	Route	Comments
Opioids			
Butorphanol	0.1–0.4	IV, IM	Short acting (less than 90 minutes) Increasing the dose does not provide more intense or longer periods of analgesia
Buprenorphine	0.01–0.02	IV, IM, transmucosal	
Fentanyl	0.005–0.01 25 μg/hour patch	IV transdermal	May take up to 12 hours to reach effective plasma concentration. Uptake affected by body temperature
Hydromorphone	0.05–0.1	IV, IM	SQ route associated with vomiting Doses of 0.1 mg/kg and higher can produce hyperthermia
Meperidine	5–10	IM	Must not be given IV
Morphine	0.2–0.5	IV, IM	May be less effective in cats compared to other species due to lack of active metabolites
Oxymorphone	0.05–0.01	IV, IM	
NSAIDs			Do not use in hypotensive or hypovolemic patients
Carprofen	1–4	SQ	Not licensed for cats in USA Should not be repeated
Ketoprofen	1–2	SQ	Not licensed for cats in USA Can be repeated with care (1–5 days at 1 mg/kg)
*Meloxicam	0.2 or 0.1	SQ, IV, PO	One dose. Dose dependent on degree of pain (e.g., orthopedic versus soft tissue).
	0.1		Repeat once daily for 3 days
	0.025 (0.1 mg/cat) lean weight		Alternate day or twice weekly.
Local anesthetics			
Lidocaine	2–4	Local anesthetic blocks	Duration of action 1–2 hours Constant rate infusions not recommended in cats due to cardiovascular depression
Bupivacaine	2	Local anesthetic blocks	Duration of action 4–5 hours
α_2-*agonists*			Use with great care in cats with cardiovascular disease
Medetomidine	0.005–0.02 0.01	IV, IM, SQ epidural	Low doses combined with an opioid offer good sedation and analgesia
Other			
Ketamine	2	IV	No published data in cats on the efficacy of low dose constant rate infusions

*Only licensed NSAID for cats in the USA (injectable, one dose at 0.3 mg/kg SQ). The author and editor do not advise using this 0.3 mg/kg dose as further dosing is frequently required. Based on experience the 0.2 or 0.1 mg/kg (still effective dosages) followed daily with reduced dosages permits management of pain for an extended period of time. The oral formulation is off-label, however, this has been used in cats with careful attention to dose delivered.
IM, intramuscular; IV, intravenous; PO, per oral; NSAID, non-steroidal anti-inflammatory drug; SQ, subcutaneous.

sly administered drugs which has a molecular genetic basis.[22–24] Domestic cats have fewer hepatic UDP-glucuroninosyltransferase (UGT) isoforms, and mutations of UGT and pseudogenes have been identified by cloning techniques. Exposure to plants that contain phytoalexins stimulate development of these pathways but cats have historically been obligate carnivores and this may, in part, explain the differences between species. These metabolic differences can lead to toxic side effects if doses and dosing intervals are not adjusted. In contrast, if the parent compound must be metabolized to an active component via this pathway, the drug may be less effective. Deficient glucuronidation pathways explain the cat's susceptibility to the adverse side effects of phenolic drugs such as acetaminophen (paracetamol) and long half lives of other drugs such as carprofen[25,26] and salicylates.[26,27] 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 with other species.[28]

Drugs

The analgesic drugs that are most useful to the critical care and emergency clinician are the opioids, α_2-agonists, and local anesthetics. The NMDA receptor antagonist, ketamine, has been used extensively in cats for chemical restraint but may also have analgesic actions. With care, the non-steroidal anti-inflammatory drugs (NSAIDs) may also have a place for acute pain management.

Opioids

Opioids comprise the backbone of pain management in the critical care or emergency patient because of their efficacy, good safety margin and versatility. The lethal dose of individual opioids is not well documented in the cat, but in the rat, the median lethal dose of morphine is 64 mg/kg and for buprenorphine it is 234 mg,[29] which is 32 and over 4000 times the recommended analgesic dose, respectively. The safety of opioids is also enhanced by their reversibility with drugs such as naloxone or naltrexone. Butorphanol, buprenorphine, fentanyl, meperidine (pethidine), morphine, hydromorphone, and oxymorphone have all been used clinically in cats.[11,30] Butorphanol is classified as an agonist-antagonist (having a ceiling effect), buprenorphine as a partial agonist, and the others are opioid agonists. The opioid agonists have a linear dose–response and can be titrated to effect. Buprenorphine behaves like an opioid agonist and the so-called 'bell-shaped' curve is not seen at clinical doses. It is a misconception that cats are at a high risk of excitement or 'morphine mania' following opioid administration. Such reports were based on early literature when excessive doses (20 mg/kg of morphine) were administered.[31,32] Recent studies show that with appropriate dosing the behavioral effects usually include euphoria, with purring, rolling, and kneading with the front paws.[33–36] One exception is butorphanol which has been associated with dysphoric behavior.[37] An elevated body temperature is a concern in a sick or injured cat as the cause may be infection, administration of certain drugs or overzealous warming and the cause must be identified so that the correct treatment can be started. The practitioner should also be aware of opioid-related hyperthermia in cats. At doses of morphine >1 mg/kg, cats may become hyperthermic[38] and meperidine at 3 times clinically recommended doses resulted in temperatures as high as 41.7 °C (107 °F).[39] This phenomenon appears to be dose related, but even at commonly used clinical doses, some opioids may result in elevated body temperature. In a retrospective clinical study (Niedfeldt and Robertson, unpublished data), there was a strong association between the use of hydromorphone (at 0.05–1.0 mg/kg intramuscular [IM] or intravenous [IV]) and hyperthermia. Some of these cats had received only 1 dose, and others 2 or more. Rectal temperatures over 40 °C (104 °F) were recorded in 75% of the cats that received hydromorphone and a peak temperature of 42.5 °C (108.5 °F) occurred in 1 cat. Temperatures over 40.5 °C (105 °F) are cause for concern and may respond to external cooling such as fans and application of cool water to the fur.

However, higher temperatures are potentially life-threatening and in the study by Niedfeldt (2004, unpublished), 2 cats were open-mouth breathing and panting with body temperatures over 41.5 °C (107 °F). These cats responded quickly to naloxone but this opioid antagonist also reverses the analgesic effects of hydromorphone. The high incidence of hyperthermia at clinical doses has greatly reduced the use of hydromorphone in the author's clinical practice.

Cats treated with a transdermal fentanyl (TDF) patch had higher rectal temperatures than those given butorphanol.[40]

Opioids cause marked mydriasis in cats; this may cause them to bump into objects and they may not see a handler approaching. For these reasons, approach slowly while talking to the cat so it is not startled. Also, keep them out of bright light while their pupils are dilated.

Nausea, vomiting, and salivation can be seen after morphine and hydromorphone injection but is uncommon after buprenorphine, meperidine, or butorphanol.[33,34,41] The incidence of nausea and vomiting is also related to the route of administration; subcutaneous (SQ) hydromorphone results in a higher incidence of vomiting than the IV or IM route.[41] When administered to painful cats or in combination with acepromazine, the incidence of opioid-induced vomiting is considerably less.

Specific opioids

Butorphanol is a μ antagonist, which produces analgesia through its κ agonist activity. It is commonly used in cats in North America, and is generally given at doses from 0.1 to 0.4 mg/kg.[3] More recently, its analgesic properties have been called into question in both dogs and cats.[42] Butorphanol exhibits a 'ceiling' effect after which increasing the dose does not produce any further analgesia.[37,43] Butorphanol appears to be an effective visceral, but poor somatic analgesic.[43] Both clinical studies and experimental investigations indicate that butorphanol is short acting (<90 minutes)[34,43] and requires frequent dosing to be effective. Butorphanol is a poor analgesic choice in the face of both somatic and visceral pain, but would be a reasonable choice for acute visceral pain such as that associated with acute cystitis or enteritis.

Meperidine is only given by the IM or SQ route because of reports of excitement after IV dosing. In clinical studies (3.3–10 mg/kg IM), it appears to have a fast onset but short duration of action[12,44] and research studies suggest that at a dose of 5 mg/kg its duration of action is less that 1 hour.[33]

Morphine has been widely used in cats and doses of 0.1–0.2 mg/kg are effective in clinical cases and do not cause excitement.[11] Both clinically[11] and in research models[34] onset of action is slow. Morphine appears less effective in cats compared with dogs and this may be

related to their limited production of the active morphine metabolites morphine-6-glucuronide[45] which may contribute significantly to morphine's overall analgesic effect in humans.[46]

Oxymorphone has been a popular analgesic for many years in the USA.[35,47,48] Using a visceral pain model, Briggs et al.[48] reported that a combination of oxymorphone and butorphanol produced a greater degree of analgesia than either drug used alone and that this could be further enhanced by adding acepromazine. Clinically, oxymorphone does not appear to be associated with hyperthermia and is effective for many different types of pain with duration of effect of 2–4 hours.

Hydromorphone has become popular in veterinary medicine and has, to a great extent, replaced oxymorphone because it is less expensive.[49] Doses of 0.05–0.2 mg/kg of hydromorphone are generally recommended.[49] The relationship between dose and thermal antinociception (a measure of analgesia) of IV hydromorphone administration has been studied in cats. At doses of 0.025 and 0.05 mg/kg there was a small increase in thermal antinociception of short duration [Robertson, unpublished observations]. An IV dose of 0.1 mg/kg produced a substantial increase in thermal antinociception for up to 7 hours.[50] Route of administration has a significant effect on quality and duration of analgesia and side effects. When the analgesic and side effects of 0.1 mg/kg given by the IV, IM, or SQ route were compared, the IV route produced the greatest intensity and duration of antinociceptive effect with the least incidence of vomiting and salivation.[41]

In contrast to the study by Briggs et al.[48] a combination of hydromorphone (0.1 mg/kg IM) and butorphanol (0.4 mg/kg IM) did not have additive effects on thermal antinociception, but rather produced a longer lasting (up to 9 hours) but less intense effect than hydromorphone alone.[51]

Buprenorphine is the most popular opioid used in small animals practice in the UK[5] and is also widely used in the rest of Europe, Australia, and South Africa.[4,6] In research cats, it has been studied after IM,[34] IV, and oral transmucosal (OTM)[52] administration. IM doses of 0.01 mg/kg resulted in a slow onset (2 hours) of analgesia with a variable duration ranging from 4 to 12 hours.[34] Systemic uptake of buprenorphine after OTM dosing is almost 100% complete[53] in cats. The pH of the cat's mouth is between 8 and 9, which would enhance absorption, and this may explain the effectiveness of this route in cats compared with other species with a neutral oral pH.[53] There was no difference in onset of analgesia (within 30 minutes), time to peak effect (90 minutes) or duration of action (6 hours) when 0.02 mg/kg was administered by the IV or OTM route in research cats.[52]

In clinical studies, buprenorphine produced better analgesia than morphine in cats undergoing a variety of soft tissue and orthopedic procedures,[54] was superior to oxymorphone for sterilization (with or without onychectomy)[35] and provided longer pain relief than meperidine (pethidine) following ovariohysterectomy.[55] Buprenorphine rarely causes vomiting or dysphoria and has not been associated with hyperthermia (Niedfeldt and Robertson, unpublished data).

There is very little information in the veterinary literature about the effect of organ dysfunction on the metabolism of opioids. In humans with severe renal impairment, the metabolism of buprenorphine following single dosing or infusions was little affected and although metabolite concentrations increased these are unlikely to have significant pharmacological actions.[56] The effect of buprenorphine on gastrointestinal activity is discussed later.

Fentanyl is a potent, short acting pure μ agonist which is commonly used as a constant rate infusion (CRI).[30] In a cat specific study, 10 μg/kg IV provided rapid onset (peak action <5 minutes) of significant analgesia that lasted 110 minutes, with no excitement, salivation or vomiting.[36] In that study, plasma fentanyl concentrations and analgesia were closely correlated and it was concluded that at a plasma value of >1.07 ng/mL fentanyl provides analgesia, which is similar to that reported for dogs[57] and humans.[58] This data should be the basis of formulating more rational CRI and target controlled infusion protocols for cats.

Transdermal delivery systems

In the critical care setting, there has been great interest in transdermal delivery of drugs because they may offer a 'hands off' approach to pain management and could provide a constant delivery of drug thereby avoiding peaks and troughs seen with intermittent bolus administration.

A transdermal (matrix patch) delivery system for buprenorphine is now available for use in humans (Transtec).[a] In cats, there is systemic uptake after application of a 35 μg/h patch but plasma concentrations were very variable and over a 4-day period, no effective analgesia was demonstrated.[59,60]

The transdermal fentanyl (TDF) patch has been used for acute perioperative pain in cats.[40,61,62] Plasma fentanyl concentrations are variable after patch placement in cats[40,61] and in one study,[63] 2 out of 6 cats never achieved plasma fentanyl concentrations above 1 ng/mL. Factors affecting plasma levels include the size of the patch compared with the weight of the cat, skin permeability, and body temperature. In critical care patients, hypothermia, hypovolemia, and decreased skin perfusion will decrease absorption. Mean serum levels in normo-

thermic (38 °C) cats were 1.83 ± 0.63 ng/mL compared with 0.59 ± 0.30 ng/mL in hypothermic (35 °C) animals.[64] In cats weighing <4 kg, placement of a 25 μg/h patch with full exposure of the adhesive layer resulted in a steady state plasma concentration of 1.78 ± 0.92 ng/mL compared with 1.14 ± 0.86 ng/mL when only one-half of the adhesive was exposed.[65] In general, cats achieve steady state plasma concentration within 6–12 hours after patch placement[66] and this persists for up to 18–20 hours[64] after removal. During the uptake phase, other opioids must be administered to provide analgesia and all, except butorphanol, could be used. TDF patches have proved useful in a clinical setting.[40,61,62]

The use of various drugs compounded in transdermal creams has become popular in veterinary medicine despite the lack of scientific studies.[67] Fentanyl compounded in pluronic lecithin organogel failed to be absorbed through the skin of the inner pinna or dorsum of the shaved neck of cats even after a dose of 30 μg/kg, therefore, these formulations cannot be recommended.[36]

Although not classified as an opioid, tramadol has weak binding affinity at μ-receptors and is thought to activate monoaminergic spinal inhibition of pain. In dogs, this drug shows promise for acute pain.[68] A dose of 1–2 mg/kg IV has been suggested for cats, but there are as yet no published reports of controlled clinical studies.

The morphology and sequencing of feline opioid receptors has not been extensively studied[69] but marked inter-cat variation in analgesic response to butorphanol has been reported[37] suggesting that cats also express genetic variability. This highlights the importance of careful assessment of pain in cats as one analgesic at a set dose is unlikely to be equally effective in all patients even with the same injury.

α_2-adrenoceptor agonists

Medetomidine is not licensed for use in cats in the USA but is in several other countries. Medetomidine provides dose-related sedation, muscle relaxation, and analgesia in cats[70] and can be excellent in an emergency setting as it provides reliable sedation and will allow the clinician to perform a clinical examination, take radiographs and perform minor procedures such as bandaging and jugular catheter placement. However, the main concern with its use in a critical care setting is its cardiovascular effects.

Although doses of between 40 and 150 μg/kg have been recommended, clinical experience shows that 20 μg/kg IM provides reliable sedation and analgesia for up to 1 hour. However, even this lower dose causes a significant decrease in cardiac output, stroke volume, and heart rate[71] Bradycardia and decreased stroke volume contribute to the decrease in cardiac output which is substantial, dropping from a mean of 1.3 to 0.49 L/min 15 minutes after treatment; this is accompanied by a 3-fold increase in systemic vascular resistance.[71] At 10 μg/kg IM, medetomidine caused a drop in ejection fraction from a mean of 55 to 43% and a 25% decrease in peak ventricular filling rate.[72] Some authors have cautioned against the use of medetomidine in cats with cardiac disease,[72] whereas others have suggested it may be beneficial in cats with left ventricular hypertrophy and outflow obstruction.[73]

In human medicine, there is great interest in the use of α_2-agonists where low doses of dexmedetomidine have provided excellent sedation, reduced opioid requirements and maintained respiratory and cardiovascular stability in intensive care settings.[74] Dexmedetomidine usage has been reported in cats, and combined with ketamine or butorphanol, minimal cardiovascular effects were reported[75] but because of expense, this drug is not widely used clinically.

The future success of medetomidine in veterinary clinical practice lies with the use of so-called 'microdoses' in the range of 1–5 μg/kg (IV or IM)[76] or as a CRI (1–2 μg/kg/hour) with or without opioids but critical evaluation of the cardiovascular effects of these protocols have not been undertaken in cats.

The actions of medetomidine can be reversed with atipamezole[76] and certainly the ability to antagonize potentially dangerous cardiovascular complications or inadvertent overdose is an advantage. However, in dogs, rapid reversal with IV atipamezole may induce hypotension,[77] therefore, unless it is a life-threatening situation, the IM route should be used or the dose can be given by slow (over 2–3 minutes) IV titration until the desired effect is achieved. This latter technique can be used to maintain mild sedation and analgesia. If medetomidine is used the patient's temperature should be monitored as hypothermia can occur.[76] Xylazine results in hypoinsulinemia and hyperglycemia and although the endocrine effects of medetomidine in the cat are not well documented it should be avoided in diabetic patients. Medetomidine induces vomiting in a high percentage of cats[78] so should not be used when an increase in intraocular or intracranial pressure must be avoided. A further side effect of the α_2-agonists is profound diuresis.

Medetomidine is best reserved for use in previously healthy cats that require sedation following acute trauma, for example a fracture where blood loss is not an issue. Medetomidine should not be given to cats with cardiovascular disease, pre-existing hypovolemia, or head trauma.

Local anesthetics

Local anesthetics can be used for regional blockade (epidural analgesia), to block specific nerves (intercos-

tal, limbs), and infiltrated into wounds or fractures (surgical or traumatic).[30,79] The value of these techniques is underestimated in trauma and surgery patients where they can provide complete analgesia with minimal side effects and whenever possible the clinician should use local anesthetics. Lamont[30] offers a good review of techniques including brachial plexus block. A particularly useful technique is to implant a 'soaker' catheter into a wound (for example, large laceration, degloving injury, post-amputation wound) to provide a method for maintaining continuous analgesia. Lidocaine (2–4 mg/kg) can be repeated every 2–3 hours or as needed based on wound palpation. Bupivacaine is longer acting and 2 mg/kg would be expected to last 4–5 hours. Both these drugs can be diluted with sterile saline to provide a suitable volume. Some authors recommend a combination of lidocaine plus bupivacaine to achieve a fast onset and longer duration of action; in this case the total dose of local anesthetic should not exceed 2 mg/kg.

Topical anesthetic creams can be applied to shaved skin to provide analgesia for venipuncture, large-bore catheter placement, bone marrow aspiration or a variety of other critical care procedures. The 2 commercially available agents are an over-the-counter liposome-encapsulated formulation of lidocaine (ELA-Max®, LMX™)[b] and a prescription only mixture of lidocaine and prilocaine (EMLA® cream).[c] Transdermal absorption did occur after application of 15 mg/kg of ELA-Max®, but plasma concentrations remained significantly below toxic values.[80] There was no systemic uptake of the components of EMLA® cream and its use subjectively eliminated the usual signs of discomfort seen with jugular catheter placement.[81]

In dogs, systemic lidocaine infusion has shown beneficial effects as an analgesic in surgery patients[82] and as an anesthetic sparing technique with no adverse cardiovascular effects.[83,84] In cats, increasing plasma concentrations of lidocaine caused a dose-dependant decrease in isoflurane requirements.[85] Despite a significant reduction in the dose of inhalant agent, lidocaine produced more cardiovascular depression than an equipotent dose of isoflurane alone and was associated with an increase in blood lactate concentration[86] and, for these reasons, cannot be recommended in cats. This study emphasizes once again the importance of species-specific studies.

Epidural drugs

Opioids, α_2-agonists, local anesthetics, or combinations of these drugs can be administered via the epidural route in cats.

Opioids exert their major analgesic effect in the dorsal horn of the spinal cord and intrathecal or epidural administration provides long lasting analgesia with fewer systemic side effects. Morphine (0.1 mg/kg), fentanyl (4 μg/kg), meperidine (pethidine), and methadone have been used successfully via the epidural route in cats[87–92] with morphine being the most clinically useful in terms of analgesia achieved, duration of action and lack of side effects. In 1 study, 2 out of 23 cats that received epidural morphine had urinary retention.[92] Lidocaine or bupivacaine are often co-administered with an opioid to enhance analgesia.[30]

Epidural administration of medetomidine (10 μg/kg) was found it to be superior to fentanyl (4 μg/kg)[90] and systemic effects were mild and short lived.[89]

Epidural techniques may be an option for cats with tail, abdominal, pelvic or hind-limb pain, or that require surgery at these sites. Opioids alone can provide good thoracic analgesia with minimal systemic effects. Epidural injection is technically more challenging in cats because of their small size and because the spinal cord ends more caudally; entering the subarachnoid space is more likely. If this occurs, half of the epidural dose may still be administered.[30]

Ketamine

Ketamine is a non-competitive antagonist of the *N*-methyl-D-aspartate receptor that has been implicated in central sensitization. In human medicine, ketamine is being re-examined for its analgesic potential.[93] In dogs, sub-anesthetic doses of ketamine (2.5 mg/kg) given preoperatively provided better postoperative analgesia than the same dose given at the end of surgery[94] and low dose ketamine infusion in dogs after major surgery is opioid sparing.[20]

Ketamine is widely used in cats as a dissociative anesthetic agent, but there is little information on its role as an analgesic. One study demonstrated a weak visceral analgesic effect[95] and anesthetic protocols that incorporate ketamine provide better postoperative analgesia than those without.[21]

Low dose ketamine (2 mg/kg IV) produced excellent sedation in cats with an initial increase in thermal antinociception but after sedation had worn off there was a delayed onset of significant hyperalgesia or allodynia when even handling and stroking the cats prompted aversive behavior.[96,97] It should be noted that in these studies cats did not undergo any painful procedures. Ketamine can only inhibit NMDA receptors if they have been opened by a noxious stimulus[98] and this may explain the difference between the use of ketamine to sedate pain-free cats compared with those in pain or undergoing surgery. The benefits of using low doses or infusions of ketamine in cats to alleviate pain warrants further study.

Cerebellar dysfunction following general anesthesia is reported to be linked to the use of ketamine in Persian cross cats[99] but anecdotally happens in other breeds and mixed breeds. The cause is unknown, but can range from mild to severe and is usually permanent.

NSAIDs

The use of this group of analgesics in cats has recently been reviewed.[100] They can provide up to 24 hours of analgesia, and are not subject to the legal regulations of opioids. Although several are licensed for use in cats in other countries, only one (injectable meloxicam) is in this class are currently labeled for feline use in the United States.

These drugs act to inhibit cyclo-oxygenase (COX) enzymes and because there is considerable species variation in COX expression, the efficacy and safety of a drug in one species cannot be assumed in another. It was believed that COX-1 was responsible for normal homeostatic functions such as maintenance of gastric mucosal integrity, platelet function, and renal autoregulation, while COX-2 was associated with inflammation. The development of COX-2 selective NSAIDs was hailed as a breakthrough in preventing toxicity from these drugs, but continued reports of problems associated with their use suggest that the simple COX-1/COX-2 concept is flawed and much more complex than previously believed. It is now known that in some species constitutive COX-2 is produced in the kidney and central nervous system and is required for normal function.

As a group, NSAIDs have a lower safety margin than opioids or α_2-agonists and are not reversible. There is potential for NSAID toxicity in cats since their limited ability to glucuronidate exogenous drugs results in prolonged duration of effect with the potential for drug accumulation. The mean half-life of carprofen in cats is approximately 20 hours, twice that of the dog, but can vary from as short as 9 hours up to 49 hours.[25,26] The use of carprofen, meloxicam and ketoprofen is well documented in cats.[12,44,55,101,102]

As in other species, the contraindications to NSAID use are gastrointestinal ulceration or bleeding, platelet dysfunction, renal dysfunction, and concurrent corticosteroid use. Renal autoregulation is prostaglandin dependant in the face of hypotension and NSAIDs must not be given in the face of volume depletion (vomiting, diarrhea, hemorrhage, or other fluid losses) or in situations such as sepsis where low blood pressure is likely or has been confirmed. Cats appear to be particularly susceptible to the adverse renal effects of NSAIDs.

In some situations, for example, the stable normovolemic trauma patient, these drugs can be valuable for alleviating acute pain. Carprofen has a long history in the United Kingdom where the injectable formulation (4 mg/kg) is licensed for a single treatment. However, clinically there seems little benefit of the 4 mg/kg dose over 2 mg/kg,[12] and the lower dose is recommended. There have been reports of gastrointestinal toxicity generally associated with concurrent disease and prolonged administration of the oral formulation.[103] Problems with repeated dosing are likely a result of individual variation in pharmacokinetics.

Meloxicam is a COX-2 selective NSAID that is available as an injectable and oral formulation. In the USA, only the injectable formulation (0.3 mg/kg) is approved for cats and for one dose only. Its use at lower doses (0.1–0.2 mg/kg) appears to be effective and may be preferred over the approved dose. The honey flavored oral liquid marketed for dogs is widely used (off label) in cats because it is palatable and has been used for longer periods.

Ketoprofen is available as an injectable formulation but oral preparations are commonly compounded. The pharmacokinetics and clinical efficacy of ketoprofen are well documented.[55,101,104] and it has been used for up to 5 days to treat cats with musculoskeletal pain[105] Because it is a potent COX-1 inhibitor, it may interfere with platelet function.

There seems to be little difference in the efficacy of the NSAIDs described above for the treatment of acute surgical pain.[101,102] Comparison of injectable NSAIDs given subcutaneously at extubation following ovariohysterectomy (carprofen 4 mg/kg, ketoprofen 2 mg/kg, and meloxicam 0.2 mg/kg), resulted in 9 out of 10 cats in each group having desirable overall clinical assessment scores for 18 hours. Despite the cats' apparent comfort, none of the NSAIDs prevented postoperative wound tenderness.[101] If used as part of an analgesic plan, the choice of agent will depend on personal preference, and intended duration of use.

Effects of analgesics on gastrointestinal function

The effects of pain itself and the analgesics and sedatives used in the critical care setting on bowel function must be considered. Pain can cause bowel stasis, abdominal distension, discomfort, and vomiting adding to the overall misery of the patient. Analgesic intervention often results in a dramatic improvement but if therapy is continued for days or weeks the effects on gastrointestinal function should be monitored.

IM acepromazine (0.1 mg/kg) combined with buprenorphine (0.01 mg/kg) or medetomidine (50 μg/kg) alone provided good restraint and did not alter orocaecal transit time in cats, whereas ketamine (5 mg/kg) and midazolam (0.1 mg/kg) did decrease gastrointestinal motility.[106] The use of TDF patches has not sparked comments about constipation and transdermal bupre-

norphine patches did not affect food intake or frequency of bowel movements.[60] However, systemic treatment with buprenorphine can cause inappetence in some cats after 2–3 days, which often resolves when the dose is reduced (author's own observations), or if there are no contraindications, NSAID therapy can begin and opioid doses decreased or stopped.

In humans, immobility contributes to constipation and this no doubt also applies to animals; although it may be difficult to encourage a cat to exercise, it should be given room to move around and the chance to interact with humans and toys while hospitalized.

Opioid antagonists that work only at peripheral sites and do not antagonize centrally mediated analgesia show great promise in humans[107] for treating ileus but have not been used widely in veterinary medicine.

Special Situations

Management of fractious patients

Fractious cats are a challenge in the emergency setting because the clinician is unable to examine the patient and may have no history or access to previous blood work. It is often unclear if the cat is painful or not. However, physical restraint is often ineffective and can lead to further stress and even worsening of wounds or fractures if the cat continues to resist and becomes explosive. Clinicians often resort to placing these cats in an anesthetic chamber and administering inhalant agent. Great care should be taken as endogenous catecholamines combined with a high concentration of inhalant agent can be a lethal combination. Isoflurane and sevoflurane do not sensitize the heart to catecholamines as much as halothane and these newer agents may reduce the incidence of complications.

Alternative techniques include oral (transmucosal) drug administration. If the cat is injured and, therefore, painful, OTM buprenorphine (0.02–0.03 mg/kg) may be sufficient to sedate the cat. Oral xylazine, detomidine, or medetomidine combined with ketamine can provide useful sedation[108,109] as can ketamine alone.[109]

Head trauma

In several situations such as high-rise syndrome or hit-by-car scenarios, cats have multiple injuries and require analgesic intervention and or anesthesia, but may also have head trauma. In these situations, opioids are the first drug of choice as respiratory depression (which would include hypercapnia and cerebral vasodilation) is unusual at clinical doses. Medetomidine causes unpredictable vomiting and increased intracranial pressure (ICP) and should be avoided.

The use of ketamine in the face of head trauma is controversial but it appears that ketamine may in fact be neuroprotective.[110] In a space-occupying model of brain edema in cats, ketamine (2 mg/kg IV) decreased ICP and improved cerebral perfusion pressure and in a cytotoxic model ketamine had no effect on ICP.[111]

In summary, there is now considerable feline-specific analgesic data available and this can be incorporated into clinical practice. Opioids should be the first choice of drug, with buprenorphine a top choice because of its efficacy and lack of side effects. Local anesthetic techniques are under-utilized and time spent learning specific blocks will be time well spent. With care, the α_2-agonists and NSAIDs can also be used. Ketamine may have a role to play in overall pain management but still requires further study in cats.

Footnotes

[a] Transtec; Napp Pharmaceuticals, Cambridge, UK.
[b] ELA-Max® or L.M.X™; Ferndale Laboratories, Ferndale, MI.
[c] EMLA® Cream; AstraZeneca LP, Wilmington, DE.

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