CHAPTER

6

Analgesia

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OUTLINE

Recognition and management of feline pain are increasingly prominent in veterinary medicine. Given the 63.3 million veterinary visits made annually by an estimated 82.4 million cats owned in the United States,[22,121] there is ample opportunity to include the assessment of pain as a routine component of a feline examination. Published surveys of analgesic use in cats over a 10-year span show a marked increase in the number of cats that now receive perioperative analgesics.[34,55,65,66] Continuing professional education and review articles contribute to this phenomenon.[55,65] Owners are also seeking and demanding appropriate pain management for their cats, both for surgical procedures and for chronic conditions such as degenerative joint disease.

However, there is room for improvement. Some cats continue to be denied analgesics for procedures such as castration, and very few cats receive analgesic agents in the postoperative period despite the fact that many procedures are likely to result in pain lasting several days.[55] The perception by veterinarians that owners will not pay for analgesia is often given as a reason for the undertreatment of pain in cats. This assumption was not supported in a survey of owners in Finland, where 77% of respondents agreed that the cost of treating pain was not a concern.[55,149] Between 78% and 98% of owners also agreed that treating their animal's pain was somewhat to very important to them.[149] The purpose of this chapter is to review the current state of knowledge on the recognition and treatment of acute pain in cats.

PAIN RECOGNITION AND ASSESSMENT

"Before we can treat something we first have to recognize it."
Sheilah Robertson

The American Animal Hospital Association (AAHA) and the American Association of Feline Practitioners (AAFP) have published guidelines for incorporating pain management into veterinary practice.[54] The first and pivotal step in the algorithm is assessing whether the animal is in pain. However, up to 42% of veterinarians consider their knowledge of pain assessment for both dogs and cats to be inadequate.[59,163]

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory or emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[140] The emotional or affective aspects of pain are important but difficult to measure in nonverbal species. Assessment of pain in animals is based primarily on ethological quantification of behavior, but the wide range of feline "personalities" and variety of normal behaviors make this a challenge. Very subtle changes in behavior may indicate pain, and these can be easily overlooked by both owners and professional caregivers. Because the pain experience is unique to each individual, behaviors vary among cats, making standardization of assessment difficult. Behaviors related to fear and stress may be difficult to differentiate from those associated with pain. For

example, one cat may be immobile and crouched in the back of a cage even when no painful procedure has been performed, whereas another cat displaying the same behavior may be in pain. For this reason understanding the individual patient's normal behavior is imperative. Owners can provide valuable insight into their cats "normal" behavior and should be consulted.

A structured assessment tool is necessary both as a baseline and to monitor response to therapy. The components of such a tool must be user friendly, accurate, reliable, and time-efficient. Objective data, such as heart rate and respiratory rate, are easy to collect; however, there is poor correlation between this type of information and observed behaviors in animals after surgery.[24] Blood pressure is a good objective indicator of pain in cats after ovariohysterectomy in a controlled environment, but in a clinical setting this tool is less reliable.[131,132] The use of multiple indicators to assess feline discomfort is beneficial for compiling an overall picture. Compared to dogs, there is currently no robustly tested or validated composite acute pain scale for cats[57,92]; however, such pain scales are currently being developed. Preliminary data suggest that cats in pain show consistent changes in psychomotor behavior (e.g., comfort, activity, mental status), "miscellaneous behaviors," and protective behaviors (e.g., response to surgical wound, abdominal or flank palpation) and that there is a correlation between pain and vocalization.[13] Specific postures are also associated with abdominal pain.[158]

Although visual analog scales and numeric rating scales are technically easier to use compared with a composite pain scale, they are unidimensional, and interobserver variation is large; in one study variability was 36%.[58] When a behavioral pain indicator is used, assigning a descriptor as well as a score assists in reproducibility and consistency of scoring.[92] For example, under the heading "posture," descriptors such as *relaxed, hunched,* and *rigid* could be added. The details of these descriptors and the weighting of scores are not fully worked out. Useful information in the hospital environment falls into several main categories, which are listed in Box 6-1.

A cat in pain shows little interest in interacting with caretakers, does not seek attention, has little interest in its surroundings, is more reclusive, has minimal interest in food, and may not groom itself normally (this may be exhibited either as lack of grooming or as excessive grooming, especially of the painful site). Cats in pain may urinate or defecate outside the litter box because it is too painful to move to or into it. The posture for a cat experiencing pain after abdominal surgery has been described as "half tucked up" or "crouching."[158]

Figure 6-1 shows an example of a pain-scoring system based on posture. Figure 6-2 shows clinical examples that correspond to various places along the scale.

BOX 6-1

Useful Information in the Hospital Environment for Assessing Pain

Behaviors and their deviation from normal
- Interaction with caretakers
- Interest in food
- Interest in grooming
- Interest in the environment
- Normal litter box usage

Posture
Location in the hospital cage
Response and severity of response to palpation

Facial expression has been used to assess pain in newborn infants[118] and may also be useful in cats. Cats in pain often hold their heads low with their eyes half or fully shut and in a slanted position (see Figure 6-2).

Response to palpation of a surgical or traumatic wound yields useful information. The response to palpation may be mild or may elicit a defensive behavior from the cat (e.g., hissing, growling, attempting to scratch or bite). If pain has been well managed, it is possible to apply firm pressure over a wound and the surrounding area without the patient resenting it. In some cases the cat is defensive before any contact is made because it anticipates pain when handled. Although this may be a normal reaction for some cats (reflecting fear rather than pain), it usually indicates pain that is poorly managed. In feral cats whose behavior makes interactions unlikely, the clinician is ethically obligated to treat with the assumption that an injury or surgery is painful and medicate appropriately. Even without palpation, the improvement in their observed behaviors can be obvious after intervention. No animal should be required to "earn" its analgesia.

The timing of assessments is also important. An assessment of the cat *before* a painful event such as surgery or another invasive procedure is often critical to assessing the cat appropriately after that event has occurred. The clinician is looking for changes in behavior, and the goal of treatment is to restore normal behaviors. Frequent observations after painful events are important because the choice of drug, dose, and dosing interval needed to keep each patient comfortable will vary. This decision must be balanced with the need of the animal to sleep and rest. Implementing a practical system of assessing the animal every 2 hours except when the animal is sleeping comfortably is a suitable compromise.

A review of the relevant literature on the treatment of feline pain yields varying methods of assessment. In

Observation	Score	Patient Criteria
Comfort	0	Asleep or calm
	1	Awake; interested in surroundings
	2	Mild agitation; obtunded and uninterested in surroundings
	3	Moderate agitation; restless and uncomfortable
	4	Extremely agitated; thrashing
Movement	0	Normal amount of movement
	1	Frequent position changes or reluctance to move
	2	Thrashing
Appearance	0	Normal
	1	Mild changes; eyelids partially closed; ears flattened or carried abnormally
	2	Moderate changes: eyes sunken or glazed; unthrifty appearance
	3	Severe changes: eyes pale; enlarged pupils; "grimacing" or other abnormal facial expressions; guarding; hunched-up position; legs in abnormal position; grunting before expiration; teeth grinding
Behavior (unprovoked)	0	Normal
	1	Minor changes
	2	Moderately abnormal: less mobile and less alert than normal; unaware of surroundings, very restless
	3	Markedly abnormal: very restless; vocalizing; self-mutilation; grunting; facing the back of cage
Interactive behavior	0	Normal
	1	Pulls away when surgical site is touched; looks at wound; mobile
	2	Vocalizing when wound is touched; somewhat restless; reluctant to move but will if coaxed
	3	Violent reaction to stimuli; vocalizing when wound is not touched; snapping; growling or hissing when approached; extremely restless; will not move when coaxed
Vocalization	0	Quiet
	1	Crying; responds to calm voice and stroking
	2	Intermittent crying or whimpering; no response to calm voice and stroking
	3	Continuous noise that is unusual for this animal
Heart rate	0	0% to 15% above presurgical value
	1	16% to 29% above presurgical value
	2	30% to 45% above presurgical value
	3	>45% above presurgical value
Respiration rate	0	0% to 15% above presurgical value
	1	16% to 29% above presurgical value
	2	30% to 45% above presurgical value
	3	>45% above presurgical value
Total score	(0 to 24)	

IT IS NOT THE INTENT OF THIS FORM TO REQUIRE THAT ANIMALS PROVE THEY ARE IN PAIN BEFORE THERAPY IS INITIATED. Instead, this form is intended to aid in the evaluation of dogs and cats that may be in pain following surgery or trauma. The exact score that will indicate that treatment for pain is appropriate will vary from individual to individual. Animals that are expected to be in moderate to severe pain, based on the surgical procedure performed, should be treated BEFORE assessment indicates severe pain. Many animals will receive analgesics before pain is detected based on this scoring system. Regardless of score, if there is evidence that the animal is in pain, a test dose of analgesic should be administered and changes in behavior noted.

FIGURE 6-1 Example of a pain scoring system based on posture and behavior. Following surgery or trauma the goal is to maintain a score of <1.0. See Figure 6-2 for examples of scoring. *(From Hellyer PW, Gaynor JS: How I treat: acute postsurgical pain in dogs and cats,* Comp Contin Educ *20:140-153, 1998.)*

FIGURE 6-2 **A,** This cat falls in the range of 0.5 to 1.0. **B,** This cat displays the posture and facial expression often observed in cats with untreated acute pain. The cat's head is held low, with its eyes almost completely shut and in a slanted position, and it is hunched or "tucked up." This cat would receive a score of 2.5-3.0. **C,** This cat received a score of 2.5. **D,** This cat is painful and received a score of 3.5 before treatment.

addition to the clinically applicable techniques previously described, several nociceptive threshold testing devices have been successfully adapted for use in cats. These are often used in a laboratory setting to screen putative analgesics for onset, intensity, and duration of antinociceptive actions before clinical testing is performed. In addition, different routes of administration can be compared. Thermal, mechanical, electrical, and visceral stimulation models have all been used in cats.[10,31,32,35]

As with all nonverbal species, cats depend on their owners to seek care and treatment for their ailments, including pain. Differences are present not just among individual cats but also among caretakers. Owners range from novices with a first pet to experienced owners who may care for multiple cats at any one time. This variability in exposure and experience can influence the owner's understanding of a cat's need for analgesia. For example, when owners who currently owned a cat were compared with owners who had no cat ownership experience, members of the former group were more likely to agree with a statement suggesting a similar pain experience between animals and humans,[149] and this may lead to a higher value being placed on appropriate analgesia. In one survey of pet owners, 50% were concerned about postoperative pain,[153,154] so it seems logical that these same owners would be receptive to learning about recognizing and alleviating pain.

The goals of pain management are to minimize pain, not necessarily eliminate it. Only local anesthetics can completely abolish pain, and these are not applicable to all surgical procedures or types of trauma. The aims of the veterinarian are to make feline patients comfortable so that they can perform normal daily activities and to prevent any marked changes in their normal behavior or personality.

ROUTES AND METHODS OF DRUG ADMINISTRATION

Analgesic drugs are given by many different routes, including parenteral (intravenous, intramuscular, subcutaneous), transdermal, topical, oral, transmucosal, and epidural. Careful thought regarding choice of route, both for ease of administration and efficacy, is necessary. For example, the same dose of hydromorphone has very different antinociceptive and side effects depending on whether it is given intravenously, intramuscularly, or subcutaneously.[113]

Because some cats are difficult to medicate, compliance with a recommended treatment is often poor. Therefore the route of administration, number of drugs, and dosing schedules should be carefully evaluated for feasibility in each patient.

When individual drugs are administered by a variety of routes, they will be discussed under that specific drug section. Points pertinent to certain routes of administration deserve specific discussion.

Parenteral Administration (Intravenous, Intramuscular, Subcutaneous)

Parenteral administration of analgesic drugs is straightforward and commonly done in most veterinary settings. If there is a catheter in a cat who needs analgesics, it is logical to make use of the intravenous route. Additionally, familiarity with specific analgesics will help elucidate which parenteral route is appropriate.

Sustained-Release Formulations

Long-acting formulations of drugs are advantageous in some cats. A sustained-release formulation of buprenorphine that is injected subcutaneously has been evaluated in cats.[18]

Constant-Rate Infusions

Opioids, ketamine, and alpha$_2$-adrenergic agonists have all been administered to cats as constant-rate intravenous infusions (CRIs). The goal of a CRI is to achieve a steady-state concentration of the drug and avoid the peaks and troughs of intermittent treatment, thereby resulting in more consistent patient comfort. Selecting the loading and infusion rates to achieve a steady-state concentration requires species-specific pharmacokinetic data as well as plasma concentration–effect data that are not currently available for all analgesic drugs used in cats. However, pharmacokinetic and pharmacodynamic data are available for some opioids, such as fentanyl and remifentanil. Box 6-2 shows the steps for calculating a CRI.

Transdermal Administration

It is easy to understand why a "hands-off" approach for delivering drugs to cats is attractive to caregivers insofar as it precludes the need for intramuscular or intravenous injections and may provide constant and long-term pain relief. Several drugs are available in the form of a transdermal patch, including lidocaine, and the opioids fentanyl and buprenorphine, all of which have been used in cats with varying success.[71,82,96]

Transdermal gels containing a wide variety of drugs have been touted by compounding pharmacies as effective in cats, and the simplicity of this technique is very attractive. Unfortunately, there is little scientific evidence to support that this method of administration results in effective uptake (see Chapter 4). Fentanyl formulated in a pluronic lecithin gel and applied to the shaved skin of the neck or to the pinnae of cats' ears could not be detected in plasma,[112] and this method is not recommended by these authors.

Topical Administration

Cream and gel preparations of local anesthetics are available and have been used in cats; they are helpful for placement of intravenous catheters.[38,41,157]

Oral Administration

Administering a drug by way of the oral route results in absorption from the gastrointestinal tract. In cats the most common analgesic drugs given by this route are the nonsteroidal antiinflammatory drugs (NSAIDs). Tramadol and gabapentin have good oral bioavailability,[105,122] whereas first-pass metabolism of opioids limits their efficacy when given by this route. Palatability is a high priority with oral medications. The oral formulation of meloxicam, an NSAID, is highly palatable to cats,[23,52,79] whereas tramadol is not (in the authors' experience).

Oral Transmucosal Administration

Oral transmucosal, sometimes referred to as *buccal*, administration involves depositing the drug (usually liquid) onto the oral mucosa, where it is absorbed into the bloodstream, thereby avoiding first-pass metabolism. In cats the easiest approach is to deposit the drug in the cheek pouch or under the tongue. A variety of drugs can be administered this way in uncooperative

BOX 6-2
Constant-Rate Infusion Setup

Step 1: Preliminary Information

- Patient's weight in kilograms (kg)
- Analgesic drug and drug concentration
- Method of delivery (syringe pump or fluid bag)

Step 2: Determine Dosage and Time Period for Analgesic Drug

- Is the dose in milligrams (mg) or micrograms (µg)?
- Convert appropriately to desired concentration unit (mg or µg).
- Is there a range of dosages? If so, start out low with the possibility of increasing dose.
- Is the time administration rate per minute or per hour?
- Convert appropriately to desired time unit.

Step 3: Programming a Syringe Pump for Delivery

- Consult the manual about pump programming.
- Calculate the milliliters for delivery in 1 hour.
- Confirm that the pump is set to deliver above volume/h, or
- Recheck syringe pump in 15 minutes to ensure only 25% of the 1-hour volume has been administered, or
- Have appropriately trained staff double-check each other.

Step 4: Using Maintenance Fluids for Delivery

- Determine total volume of fluids per kilogram per hour for administration (mL/kg/h).
- Determine the rate of administration of the constant-rate infusion in milligrams per kilogram per hour (mg/kg/h).
- Determine the total volume for infusion in mL.
- Divide the number of mg/kg/h by the mL/kg/h, with the end result in mg/mL.
- Multiple this number (mg/mL) by the total volume for infusion, resulting in the mg needed to add to the fluids.
- Divide this mg by the drug concentration in mg/mL.
- Add this volume of drug to the predetermined volume of fluids.
- Administer the fluid containing the drug at the rate selected.

Example of using maintenance fluids for delivery in a 5-kg cat receiving 3 µg/kg/h of 50 µg/mL fentanyl*

- Cat will get 2 mL/kg/h of maintenance fluids.
- The drug will be administered at a rate of 0.003 mg/kg/h (= to 3 µg/kg/h).
- We will put 6 h of fluids in a buretrol (60 mL).
- (0.003 mg/kg/h)/(2 mL/kg/h) = 0.0015 mg/h.
- (0.0015 mg/h)/(0.05 mg/mL) = 0.03 mL.
- Add 0.03 mL of fentanyl to 60 mL of selected fluid.
- Administer at 2 mL/kg/h (10 mL/h).

*Bear in mind increasing fluids will increase analgesic drug delivery, so desired changes in fluid administration and drug administration will occur concurrently. The advantage of a syringe pump is the analgesic drug administration is independent of fluid rate and varying the drug delivery has minimal consequences on fluid administration.

patients, such as dexmedetomidine.[128] Buprenorphine, an opioid that is discussed in detail later, has almost 100% bioavailability after oral transmucosal administration.[109,111] Compared with other species that have a neutral oral pH, the more alkaline mouth of the cat may enhance absorption of this drug. Butorphanol has also been administered by the oral transmucosal route in cats, but it is not effective at maintaining the plasma concentrations that are achieved after intravenous dosing.[161]

Epidural

Administration of drugs into the epidural space can provide long-lasting analgesic benefit to the animal, with few systemic effects. The rate of complications for epidurals is low, although urinary retention was noted in 2 of 23 (8%) cats in one study.[148] However, with appropriate nursing care (e.g., observing for urination, expressing the bladder after the procedure, placing a urinary catheter), this complication can be minimized. The spinal cord ends at L7-S1 in the cat, so careful needle placement and observation for the presence of cerebrospinal fluid is necessary to avoid administration of drugs into the subarachnoid space. If the subarachnoid space is entered, the drug volume is halved.[73] Epidural catheters are available for use and have been used successfully in dogs[139] but are not widely used in cats. The epidural space is approached after the cat has been anesthetized. This space is easily palpable with the cat in sternal recumbency, with the hindlimbs pulled forward. The animal is appropriately clipped and prepped; a sterile approach is vital to avoid bacterial contamination of the epidural space. Infected skin is an absolute contraindication to an epidural. The wings of the ilium are palpated bilaterally with the thumb and third finger while wearing sterile gloves, while the index finger palpates the lumbosacral space. Once the space is palpated, it is approached with a 1.5-inch 22-gauge spinal needle at a 45- to 90-degree angle to the skin, targeting midline of the animal and the

center of the epidural space. Often, practice is necessary for proficient placement of a spinal needle. Blood in the spinal needle necessitates aborting the procedure.

ANALGESIC DRUGS

The classic and most commonly used analgesic drugs include the opioids, NSAIDs, and local anesthetics. Historically, information on drug therapy in one species has been extrapolated to the cat without consideration of the ways in which the cat's unique metabolism may alter both the pharmacokinetic profile and pharmacodynamic effect of the drug. Drug metabolism is discussed in Chapter 4, and this information should be kept in mind before using a drug in a cat for any reason, including pain management.

Opioids

Opioids are the cornerstone for the treatment of acute pain in many species, including the cat. The reasons for its popularity include efficacy, high margin of safety,[9] and reversibility. Fortunately, there has been significant progress in dispelling the myth that opioid use in cats results in excitement, making their use inappropriate. So-called morphine mania was documented in the early literature, when doses as high as 20 mg/kg of morphine were used.[138] It is now recognized that when clinically relevant doses of opioids are given, cats frequently display some euphoric responses, such as purring, rubbing, and kneading with the forepaws, and are easy to handle.[109,112] Opioid administration is appropriate for trauma patients, cats undergoing surgery or invasive diagnostic procedures, and those with painful medical conditions (e.g., pancreatitis, cystitis).

Opioids are more effective when given before a painful procedure than after one because of their ability to decrease the development of central sensitization in response to surgical stimulation.[82] This preemptive effect has been demonstrated in many species, including the dog[77] and rat,[83] and there is no reason to believe that it does not also occur in the cat. Therefore opioids should be incorporated whenever possible into premedication protocols for elective surgery. This does not mean that postoperative administration is unnecessary; continued assessment for comfort is essential after surgery and administration of analgesic drugs. Opioids or other analgesic agents may be necessary for several days, depending on the severity of the surgical procedure.

Because of their abuse potential in humans, opioids for veterinary use are subject to strict regulations with regard to prescribing, storage, and dispensing. These rules and regulations differ among countries, and it is important that the clinician be aware of current relevant local statutes.

Side Effects of Opioids

Elevated body temperatures have been reported in cats given opioids between 1 and 5 hours after recovery from anesthesia.[97,102] Hydromorphone at clinically recommended doses (0.05 to 0.1 mg/kg subcutaneously, intramuscularly, or intravenously) was associated with an increase in rectal temperature above 40° C (104° F) in 75% of cats in one study,[97] and in one cat a rectal temperature of 42.5° C (108.5° F) was recorded. In another study most cats undergoing elective surgery that received hydromorphone, diazepam, and ketamine followed by isoflurane had postanesthetic temperatures that exceeded those recorded before anesthesia, with a peak rectal temperature of 41.6° C (107.0° F) reported in one cat.[102] In a clinical setting, one study[102] found that the lower a cat's temperature was during anesthesia and surgery, the more severe the "rebound" hyperthermia.

In a laboratory study, hydromorphone at 0.1 mg/kg (administered intravenously) was associated with a significant increase in body temperature, whereas doses of 0.025 and 0.05 mg/kg were not. However, the lower doses were found to have minimal antinociceptive effects compared with the 0.1 mg/kg dose.[159] Transdermal fentanyl patches resulted in higher rectal temperatures compared with butorphanol for cats undergoing onychectomy, although no temperature exceeded 40° C (104° F).[40] Alfentanil infusions during anesthesia were also associated with increased rectal temperatures in cats.[61]

Recent laboratory studies in cats with implanted thermistors that did not undergo surgery showed that intramuscular administration of the opioids hydromorphone (0.05 to 0.2 mg/kg), morphine (0.5 mg/kg), buprenorphine (0.02 mg/kg), and butorphanol (0.2 mg/kg) alone or in combination with ketamine or isoflurane caused a mild to moderate increase in body temperature (≤40.1° C, 104.2° F), which lasted several hours but was self-limiting.[103]

After the end of anesthesia, body temperature is usually measured until the cat becomes normothermic, but as noted previously, it is prudent to monitor beyond that point and for 5 hours or longer after the end of anesthesia. Using warm air or circulating water blankets can prevent intraoperative hypothermia, which may in turn limit severe "rebound" hyperthermia. If profound hyperthermia develops, treatment includes active cooling or administration of naloxone (0.01 mg/kg intramuscularly, subcutaneously) or both.[103]

Some opioids, including morphine and hydromorphone, may cause retching, vomiting, and nausea characterized by salivation,[110,113] especially when used alone and in pain-free cats (e.g., as a premedicant for an elective procedure). Vomiting and profuse salivation are common after subcutaneous administration of hydromorphone and appears distressing to the cats.[113] Vomiting and retching are best prevented in cats with increased

intraocular pressure, penetrating corneal foreign bodies, and elevated intracranial pressure. In many cases of foreign body ingestion (e.g., needles or linear objects), vomiting and retching can cause penetration of the gastrointestinal tract.

In dogs the administration of acepromazine reduces opioid-related vomiting[151] and is potentially effective in cats. Clinically, vomiting occurs less commonly when opioids are combined with acepromazine than when they are used alone in cats. Maropitant, a neurokinin-1 antagonist, is highly effective against the emetic effects of xylazine in cats,[56] but there are no reports of its use in conjunction with opioids. If vomiting is contraindicated in a feline patient but an opioid is required to provide pain relief, appropriate choices would include buprenorphine or methadone (intramuscular or intravenous) or fentanyl as a CRI.

In the cat opioids induce marked mydriasis. Cats with dilated pupils often appear more agitated, perhaps as a result of reduced visual acuity, which causes them to bump into objects and become startled when approached. Dimming the lights and speaking softly to the cat as it is approached helps reduce these behaviors.

In humans decreased intestinal motility is a common, unpleasant, and problematic side effect of opioid administration.[120] In the authors' experience, it is uncommon to see constipation in cats being treated for acute pain or when opioids are only used for a few days.

Potential Drug Interactions

With the increasing use of psychoactive drugs (selective serotonin reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors and serotonin agonists; see Chapter 14) in veterinary medicine as part of a treatment regimen for behavior problems, there is a growing concern for the possibility of adverse drug interactions.[9,90] Serotonin toxicity—which can range from mild signs such as salivation and diarrhea to severe signs such as myoclonus and hyperthermia resulting in death—can occur when two drugs that increase serotonin levels are co-administered. Meperidine (pethidine), fentanyl, remifentanil, pentazocine, and tramadol impair the reuptake of serotonin. Although not well documented in the veterinary literature, the addition of these analgesic agents to an established psychoactive drug protocol in humans has triggered serotonin toxicity.[85] Before an analgesic plan is drawn up for a cat, it is essential to establish a list of all current medications. This includes any supplements or herbs the owner is administering; St. John's wort *(Hypericum perforatum)*, for instance, alters serotonin reuptake.

Specific Opioid Drugs

Current nomenclature of opioid receptors is based on molecular cloning. The three types of receptors—OP_1, OP_2, and OP_3—were formerly known as delta (δ), kappa (κ), and mu (μ), respectively.[123] Opioid drugs are traditionally classified by their actions on these receptors into agonists, partial agonists, agonist-antagonists, and antagonists. Suggested doses of commonly used drugs are given in Table 6-1.

Butorphanol (Torbutrol, Torbugesic) is one of the few analgesic drugs to have market authorization for use specifically in the cat in some countries, including the United States and United Kingdom. It is an agonist at the OP_2 receptor, an antagonist at the OP_3 receptor, and exhibits a ceiling effect. This is clinically relevant, insofar as increasing doses do not produce further analgesia.[81] In one research model using a somatic thermal stimulus, the duration of action was approximately 90 minutes, regardless of dose,[81] whereas a similar study showed large intercat variability, with antinociception lasting up to 8 hours in some cats.[63] The response to butorphanol may vary depending on the source of pain. Visceral antinociception was demonstrated with 0.1 mg/kg of

TABLE 6-1 Suggested Dose Ranges and Route of Administration for Analgesic Drugs Commonly Used to Treat Acute Pain*

Drug	Dose (Range)	Route of Administration
OPIOIDS		
Butorphanol	0.1-0.2 mg/kg	IV, IM
Buprenorphine	0.02-0.03 mg/kg	IV, IM, OTM
Fentanyl	2-10 μg/kg (bolus) 5-50 μg/kg/hour intraoperatively 2-10 μg/kg/hour postoperatively or in trauma patients	IV IV IV
Hydromorphone	0.05-0.1 mg/kg	IV, IM
Oxymorphone	0.05-0.1 mg/kg	IV, IM
Meperidine (pethidine)	5 mg/kg	IM—not to be given IV
Methadone	0.2-0.5 mg/kg	IV, IM
Morphine	0.2-0.5 mg/kg	IV (slow administration advised to prevent histamine release), IM
NSAIDs	***DOSES SUGGESTED FOR SINGLE USE***	
Carprofen	2-4 mg/kg	SC, IV
Ketoprofen	2 mg/kg	SC, IM
Meloxicam	0.1-0.3 mg/kg	SC

SC, Subcutaneous; *IM,* intramuscular; *OTM,* oral transmucosal; *NSAIDs,* nonsteroidal antiinflammatory drugs.
*For information on repeated dosing and dosing intervals, please see details in the text.

butorphanol, whereas somatic antinociception was unaffected in the same cats.[117]

A large multicenter study comparing the clinical usefulness of butorphanol with that of buprenorphine in more than 150 cats undergoing primarily, but not solely, ovariohysterectomy or castration found that buprenorphine resulted in lower pain scores for a greater duration than did butorphanol.[143] Current data suggest that butorphanol is a sensible choice for acute, visceral pain (e.g., cystitis), but in light of its relatively short duration of action and ceiling effect, it is a poor choice for somatic or visceral pain that is more than transient in nature, such as would occur with invasive surgery.[108]

Nalbuphine (Nubain), like butorphanol, is an opioid agonist–antagonist. Little has been published regarding the use of nalbuphine in cats. One study demonstrated visceral analgesia, with intravenous doses of 0.75, 1.5, and 3 mg/kg producing similar effects that lasted between 156 and 200 minutes.[117] None of these doses resulted in somatic analgesia.

Pentazocine (Talwin), another agonist–antagonist, only provided visceral analgesia when 3 mg/kg (intravenous) was administered.[117] No somatic antinociception was noted with this dose, and undesirable side effects such as ataxia and apprehension were described, which suggests that this drug has little utility in cats.

Buprenorphine (Buprenex) is a partial OP_3 agonist and has been widely studied in cats in both laboratory and clinical settings. It has market authorization for use in cats in some countries. Laboratory studies report varying times to onset of effect and duration of action, which appear partly related to dose and route of administration. For example, when antinociception is evaluated using a thermal threshold model, a dose of 0.01 mg/kg (intramuscular) required up to 2 hours for onset of action, and the duration of effect varied from 4 to 12 hours.[110] In the same model a dose of 0.02 mg/kg (intramuscular) resulted in a quicker onset of antinociception, which was significant at 35 minutes and lasted approximately 5 hours.[63] Intravenous administration of buprenorphine across a range of doses from 0.01 mg/kg to 0.04 mg/kg showed that onset of thermal antinociception time is short (15 minutes), with little difference in intensity or duration of effect. A different test of somatic analgesia (mechanical threshold) did show a dose-related effect; 0.01 mg/kg was ineffective, 0.02 mg/kg was effective but short acting, and 0.04 mg/kg had the longest duration of action.[135] These authors commented that another reason for the variability among studies was significant intercat variability, a reminder that pain and the efficacy of drugs used to relieve it are unique to each individual and that individual assessment is the key to success in each patient.

Similar to the reported effects of subcutaneous hydromorphone, this route also seems less effective when a single dose of buprenorphine is used.[43,134] In a laboratory setting, there was no difference in onset or duration of action (30 minutes and 6 hours, respectively) between oral transmucosal and intravenous administration of buprenorphine at 0.02 mg/kg. In a clinical trial intravenous and intramuscular administration of buprenorphine were more effective than the oral transmucosal route.[43] However, this could be a result of the low oral transmucosal dose used (0.01 mg/kg). Additional information gained from these studies is the time of peak effect, which consistently occurs between 60 and 90 minutes after administration. Pain is often most intense in the immediate postoperative period. Therefore the timing of preoperative (preemptive) buprenorphine administration should be planned to meet these needs.

In several clinical studies, the analgesia produced by buprenorphine (usually given intramuscularly) in cats undergoing a variety of invasive procedures was greater in magnitude and longer lasting than that produced by several other opioids, including butorphanol, levomethadone, morphine, oxymorphone, and pethidine.[33,91,129,133,143] However, it should be noted that equianalgesic doses of opioids were not necessarily used, and the methods of pain assessment were not standardized.

A sustained-release preparation of buprenorphine, available from ZooPharm (Fort Collins, Colo.), for subcutaneous administration has been evaluated in cats undergoing ovariohysterectomy. A single sustained-release dose of 120 µg/kg was as effective as 20 µg/kg buprenorphine by the oral transmucosal route given every 12 hours until 60 hours after the operation.[18] The sustained-release formulation is convenient to use, and in feral cats, which are often difficult to handle after procedures, this formulation is a viable option for providing postoperative analgesia of suitable duration.

Buprenorphine is available for use in humans as a matrix patch. In cats the plasma concentrations were quite variable after application of a 35 µg/h patch, and no analgesia was evident during a 4-day period in one study.[96] Until further studies are performed with different sizes of patches and perhaps using a loading dose of buprenorphine, this method of administration cannot be recommended.

The following conclusions can be drawn from the extensive published data on buprenorphine in cats: Doses for clinical use should be 0.02 mg/kg or greater; intravenous, intramuscular, and oral transmucosal routes of administration are effective, but the subcutaneous route is not; and individual variation is well documented.

OP_3 Opioid Agonists

Fentanyl is a potent opioid used in cats as an intravenous bolus, a CRI, and a transdermal patch (Duragesic).

Intravenous fentanyl (10 µg/kg IV) reaches peak effect in less than 5 minutes and provides significant antinociception for almost 2 hours with minimal to no

adverse effects.[112] The pharmacokinetic profile of fentanyl makes it a suitable agent for use as a CRI. The plasma levels and therefore the degree of analgesia can be rapidly altered, and fentanyl is frequently used in this manner to provide analgesia in trauma cases both during and after surgery. A research model suggests that the effective plasma concentration in cats is 1 ng/mL.[112] The infusion rate required to maintain this plasma concentration has not been verified, and it is likely that requirements will vary depending on the individual and the severity of injury or extent of surgery. These authors have used infusion rates from 0.08 to 0.8 µg/kg per minute (5 to 50 µg/kg per hour) during surgery and from 0.03 to 0.16 µg/kg per minute (2 to 10 µg/kg per hour) postoperatively or in trauma patients.

After application of a transdermal patch, the plasma concentration of fentanyl is highly variable and undetectable in some cats. Many factors may account for this variability, including body weight (which dictates the dose/kg from a standard-size patch), subcutaneous fat, body temperature, and location and method of patch placement. Serum levels of fentanyl are higher in normothermic (38° C) than in hypothermic cats (35° C).[101] Cats weighing less than 4 kg have higher plasma concentrations when the full adhesive layer of a 25 µg/h patch is exposed, as opposed to half.[27] A steady state can be achieved within 6 to 12 hours and maintained for up to 72 hours after patch placement in some cats.[84] The cat's skin may act as a drug depot because, unlike in dogs, the serum concentrations can take as long as 20 hours to decline after the patch is removed.[84] Clinical reports suggest that the transdermal fentanyl patch has clinical utility in cats undergoing onychectomy and ovariohysterectomy,[37,40,47] but clinicians should be aware that just because the patch has been applied does not mean it is providing adequate analgesia in every case.

There is a case report of a dog that became extremely sedate after it punctured and presumably ingested or licked the contents of a transdermal fentanyl patch applied to its flank,[119] and it is highly plausible that this could also occur in a cat. The clinician should consider all consequences carefully before sending a cat home with a patch; this has caused some serious liability issues in human medicine, including diversion, abuse, and accidental ingestion by a child.[146,147]

Remifentanil (Ultiva) is rapidly metabolized and does not accumulate. It is used as an infusion in several species, including humans, because of the ability to change plasma concentrations very quickly. Currently, remifentanil is predominantly used to provide analgesia during anesthesia at rates of 1 to 2 µg/kg per minute (60 to 120 µg/kg per hour), which would cause dysphoric and sometimes frantic behavior in conscious cats.[14] However, if infusion rates are kept below 1 µg/kg per minute (<60 µg/kg per hour), these adverse effects can be avoided and antinociception can still be demonstrated,[14] making it suitable for postoperative use.

Hydromorphone is widely used in veterinary medicine because of its low cost.[5] Hydromorphone and oxymorphone (at 0.05 mg/kg) provide clinically equivalent analgesia in cats undergoing a variety of surgical procedures.[5] In a research model an intravenous dose of 0.05 mg/kg provided moderate antinociception for 80 minutes, whereas 0.1 mg/kg (administered intravenously) provided profound effects for 200 minutes in one study and for up to 7 hours in another.[159,160] Two independent studies noted that vomiting and nausea are a side effect of hydromorphone use.[5,113] The concerns related to hydromorphone-related hyperthermia were discussed previously.

Oxymorphone (Numorphan) is in wide clinical usage, but there is little published information regarding this drug in cats. In a small number of cats, oxymorphone at 0.05 mg/kg (administered intravenously) appeared as effective clinically as hydromorphone at the same dose.[5] In another study oxymorphone was not as effective an analgesic as buprenorphine for cats undergoing onychectomy with or without castration.[33] The published information suggests few adverse effects from oxymorphone, but evidence-based data supporting its use are largely lacking.

Meperidine (Demerol), also known as pethidine, can cause excitement when administered intravenously; therefore only subcutaneous or intramuscular administration is recommended. Both clinical and laboratory studies suggest that it is short acting,[83,88] and clinicians should expect it to be effective for only 1 to 2 hours. Because meperidine can result in sedation, it can be used for this purpose when a traditional sedative or tranquillizer is contraindicated, such as in a hemodynamically unstable patient.

Use of methadone is increasingly popular in veterinary medicine. No pharmacokinetic data are currently available for use in the cat. In addition to its opioid actions, methadone has other desirable properties, including action at the *N*-methyl *D*-aspartate (NDMA) receptor,[50] which is involved in the development of central sensitization. Methadone is available as an isomer (levomethadone) and a racemic mixture. The racemic mixture, at the relatively low dose of 0.2 mg/kg subcutaneously, increased thermal thresholds between 1 and 3 hours but had little effect on mechanical thresholds.[134] In a clinical setting, both racemic methadone (0.6 mg/kg intramuscularly) and levomethadone (0.3 mg/kg intramuscularly) given before ovariectomy provide effective postoperative analgesia, as assessed by palpation and behavior, with no adverse effects.[114] However, compared with buprenorphine or carprofen, levomethadone (0.3 mg/kg subcutaneously every 8 hours for 5 days) was not as effective for orthopedic surgery and was associated with excitement in some cats.[91] It is likely

that better results may have been achieved with a shorter dosing interval; it is unlikely that the duration of action would be 8 hours at that dose.

Morphine has a long history of use in humans and animals and is often considered the gold standard for opioids. Because of the limited ability of cats to glucuronidate drugs, morphine may have less overall efficacy than in other species, insofar as glucuronidation is necessary for the production of morphine-6-glucuronide (M-6-G), a potent and active metabolite. This metabolite was not detected after intramuscular administration of morphine in cats and was detected in only three of six cats receiving intravenous morphine.[144] Because of the belief that morphine caused excitement in cats, lower doses (0.1 to 0.2 mg/kg) have historically been recommended and may have led to the impression that morphine is not an effective analgesic in cats. Owing to the lack of M-6-G production, it is possible that higher doses of the parent compound are necessary to produce analgesia in the cat equivalent to that in species able to produce this metabolite. Intramuscular doses of 0.5 mg/kg are used with success and minimal side effects[103] (in the authors' experience).

Intravenous morphine has been associated with histamine release in dogs in a dose-related manner, although no similar study has been performed in cats.[51] If morphine is used intravenously, slow administration is advised.

Combinations of Opioids

Co-administration of opioids has been proposed as a means of achieving the positive benefits of different drugs. Although mixing of opioids has been reported, the results are variable, ranging from a decrease in intensity of antinociception but prolongation of effect[80] to no measurable effect[63] to improved outcome.[10] Because of this unpredictability, simultaneous administration of different opioids is not recommended. On the basis of reports that ultralow doses of opioid antagonists enhanced the analgesic actions of opioids in rodents and humans,[72] a similar study was performed in cats. Combining low-dose naloxone with buprenorphine failed to show any benefits over buprenorphine alone,[126] which suggests that direct extrapolation of data among species is unwise without careful evaluation in the target species.

Epidural Administration of Opioids

When evaluated in a thermal threshold model, both buprenorphine (12.5 µg/kg) and morphine (0.1 mg/kg) provided analgesia by way of the epidural route, but morphine provided analgesia of greater intensity and longer duration (16 hours as opposed to 10 hours).[107] Meperidine, methadone, and fentanyl have all been evaluated after epidural injection.[35,64] These drugs are more lipophilic than morphine, resulting in systemic diffusion and actions that mimic those of the drug when given by the intravenous or intramuscular route. In contrast, hydrophilic drugs, such as morphine, do not readily diffuse, remaining in the epidural space and providing a long duration of action and minimal systemic effects.[74] Epidural morphine does not produce motor dysfunction and is an excellent choice of technique for perianal surgery and hindlimb surgery, including amputation.

Tramadol

Although not classified as a true opioid, tramadol (Ultram) is included here because much of its analgesia results from its opioid receptor site. Tramadol exerts its action at multiple sites, including opioid, serotonin, and adrenergic receptors.[60] It is available in injectable and oral formulations and is not currently a controlled drug. It has good oral bioavailability in cats, and its active metabolite O-desmethyl-tramadol was found after both systemic and oral administration. The half-life of tramadol is longer in cats than dogs, so dosing intervals can be extended.[105] In a research model, a subcutaneous dose of 1 mg/kg did not increase thermal threshold.[136] However, 4 mg/kg administered subcutaneously clinically improved postoperative comfort in cats undergoing ovariohysterectomy compared with the NSAID tolfenamic acid alone.[20] Similarly, the combination of the NSAID vedaprofen and tramadol at 2 mg/kg improved postoperative analgesia more than either drug given alone.[11,20] In a study done by the same group, no adverse effects with regard to platelet aggregation, vomiting, gastrointestinal function, or biochemical values were found.[12] Tramadol produced mild euphoria,[11] but this was not deemed an undesirable attribute of the drug.

NONSTEROIDAL ANTIINFLAMMATORY DRUGS

NSAIDs are widely used to combat acute pain because the basis of surgical and traumatic pain is inflammation. NSAIDs are convenient because they are not strictly regulated and most provide up to 24 hours of analgesia. However, unlike opioids and alpha$_2$-adrenergic agonists, NSAIDs are not reversible and have the potential to alter clotting function, renal perfusion, and gastrointestinal integrity.

Side Effects of Nonsteroidal Antiinflammatory Drugs

Cyclooxygenase (COX) enzymes are traditionally thought to exist in two major isoforms, COX-1 and

COX-2, but COX-3 and other subclasses are also reported. Initially, COX-1 was considered the constitutive "housekeeping" enzyme responsible for multiple essential physiologic functions, and COX-2 was considered an inducible enzyme that resulted from inflammation. Preferential blockade of the COX-2 enzyme was thought to increase the safety of NSAIDs. It is now understood that the COX enzymes are multifaceted, there is overlap in their functions, and it is unlikely that COX-2 can be inhibited without some impact on the COX-1 enzymes. COX-2 is also constitutive and required for normal function in many tissues—for example, in the kidney of dogs, rats, monkeys, and humans.[69,70,152]

NSAIDs have been used less in cats than other species because of their well-documented toxic side effects. A recent review outlines the challenges of using NSAIDs in cats but also concludes that with proper precautions these drugs can be part of successful acute pain management in this species.[75] Many NSAIDs are heavily dependent on glucuronidation for metabolism, and for this reason some NSAIDs have long half-lives in cats. Although aspirin is the classic example of one such drug, carprofen also has a relatively long half-life in the cat compared with the dog.[99,142] Conversely, NSAIDs that are oxidized (e.g., meloxicam) may have a shorter half-life.[75]

NSAIDs should not be used concurrently with corticosteroids or in cats with gastrointestinal compromise. Meloxicam does not the alter glomerular filtration rate in healthy, euvolemic conscious cats,[48] but in the face of hypotension, renal autoregulation is dependent on prostaglandins, and therefore decreased volume status, as may be seen after acute trauma, is considered a contraindication for NSAID use. Hypotension (a mean arterial blood pressure <60 mmHg or systolic blood pressure <90 mm Hg) is documented in between 10% and 33% of cats under anesthesia.[39,49] For this reason many experts recommend that NSAIDs not be administered before anesthesia and instead be reserved for use in the immediate postoperative period.

NSAIDs can alter hemostasis as a result of their effect on platelets and vascular endothelium. There is no evidence that the newer NSAIDs with market authorization for use in cats have a significant effect on surgical bleeding.[75]

When compared with one another, ketoprofen, carprofen, meloxicam, and tolfenamic acid were equally effective in cats undergoing routine soft tissue surgery,[130] and therefore the clinician may select one on the basis of personal preference, ease of administration (oral versus injection), and market authorization for each drug in different countries.

When a single dose of each drug was given in a clinical setting, carprofen provided better postoperative analgesia than meperidine, butorphanol, buprenorphine, and levomethadone[3,76,91]; this is likely due to the difference in duration of action of the two classes of drugs.

Specific Nonsteroidal Antiinflammatory Drugs

Although aspirin (acetylsalicylic acid) is readily available over the counter, its side effects (e.g., gastrointestinal ulceration, platelet inactivation, and decreased protective renal prostaglandins[15,100]) in combination with a half-life of up to 45 days[29] make aspirin an unsuitable perioperative analgesic.

Only the most widely used NSAIDs are discussed here; for complete information on these and other less commonly used agents, the reader is referred to the review by Lascelles and colleagues.[75] The individual NSAIDs discussed in this chapter have market authorization for use in cats in some but not all countries, and their labeled indication may also vary. Therefore it is strongly recommended that clinicians verify this data in each region before use.

Carprofen (Rimadyl) is a COX-1–sparing NSAID, although this selectivity appears to decrease as dosage increases in in vitro models.[46] Because the half-life in the cat is variable among individuals and ranges anywhere from 9 to 49 hours,[99] repeat dosing is not advised. In countries where it has market authorization for use in cats, it is for one-time use only. In cats that underwent ovariohysterectomy, doses ranging from 1 mg/kg to 4 mg/kg were more effective than meperidine (pethidine) from 2 to 20 hours after surgery.[77] An intravenous or subcutaneous dose of 1 to 2 mg/kg is most commonly recommended.[75]

Ketoprofen (Anafen) is not a selective COX inhibitor and has the potential to produce similar adverse effects as described for aspirin. However, obvious effects on hemostasis are not reported.[75] It is effective in alleviating the pain associated with soft tissue surgery and injury.[79,130] In cats with musculoskeletal pain, it was administered at 1 mg/kg orally for 5 days with beneficial effects.[79]

Meloxicam (Metacam) is a COX-1–sparing NSAID, and decreasing the dosage of the drug may decrease the incidence of COX-1-inhibition–mediated effects.[75] Meloxicam (0.3 mg/kg subcutaneously, given once only) is the only NSAID approved for postoperative control of pain related to soft tissue and orthopedic surgery in cats in the United States. On the basis of multiple behavioral assessments, cats receiving meloxicam appeared more comfortable after onychectomy compared with those receiving butorphanol.[17] Meloxicam was as effective as ketoprofen in alleviating pain in cats with musculoskeletal disease, but an advantage of meloxicam is its palatability.[79] Recent work indicates no measurable effect on glomerular filtration when meloxicam is administered once at 0.2 mg/kg followed by 0.1 mg/kg once daily PO for 4 additional days.[48] Although it is an off-label use, this dosing schedule is widely used to provide 5 days of postoperative analgesia in healthy cats that are normovolemic.

Robenacoxib (Onsior), a COX-1–sparing NSAID,[45] is the most recent NSAID and first coxib class NSAID approved for use in cats. It is available in both injectable and tablet formulations and is marketed for the alleviation of acute pain and inflammation associated with musculoskeletal disorders and soft tissue surgery. The injection is approved for preoperative use, and the tablets for up to 6 days in some countries. At a dose of 2 mg/kg, it was effective at reducing pain and swelling in an inflammatory paw model.[44] There are no published reports of its use in clinical patients at this time.

Tolfenamic acid has limited pharmacokinetic information available, and its status as a COX-1–sparing agent is controversial.[67] Although not licensed in the United States, tolfenamic acid is licensed and popular in many other countries.[75] At 4 mg/kg, it appears to be as effective as meloxicam (0.3 mg/kg subcutaneously) in the cat for control of postoperative pain.[6]

Local Anesthetic Agents

Local anesthetics are versatile agents that have multiple applications in the treatment of acute pain. Unlike the drugs discussed previously, local anesthetics can provide *complete* analgesia by blocking nociceptive transmission. Sadly, these techniques are underutilized, perhaps because cats are under general anesthesia for most surgical procedures and the potential benefits of adding a local anesthetic technique are overlooked. Although general anesthesia provides unconsciousness and immobility, transmission of noxious stimuli still occurs and reaches the spinal cord and brain of the anesthetized patient, where long-lasting effects such as central sensitization and secondary hyperalgesia can develop. Local anesthetics block nociception and transmission of painful stimuli, reducing these deleterious consequences.

Although a multitude of local anesthetics are available, lidocaine and bupivacaine are most frequently used in veterinary medicine. These local anesthetics differ from each other in their speed of onset, as well as potency and duration of action, but both undergo hepatic metabolism. Lidocaine is traditionally thought to have a rapid onset, whereas bupivacaine has a slower onset. Bupivacaine is more potent than lidocaine, and its duration of action is longer.[124] Often, these two local anesthetics are combined to reap the most desirable qualities of each (rapid onset and prolonged action); however, the efficacy of this approach has not been tested. When incorporating local anesthetics into the analgesic plan, the clinician must consider toxicity and calculate a safe dose based on mg/kg for each individual cat. For example, using 4 mg/kg of lidocaine for a 5-kg cat translates to no more than 1 mL of 2% lidocaine total for that animal. If the calculated dose provides insufficient volume for the intended block, the drug can be diluted. Toxic effects of local anesthetics include neurologic signs such as seizures and cardiovascular changes that can be mild or result in complete cardiovascular collapse. Doses reported to cause neurologic signs in cats are 11.7 ± 4.6 mg/kg for lidocaine and 3.8 ± 1 mg/kg for bupivacaine. Cardiotoxic doses of lidocaine and bupivacaine are 47.3 ± 8.6 mg/kg and 18.4 ± 4.9 mg/kg, respectively.[19]

Lidocaine administered by CRI is widely used in dogs to decrease the requirements for inhalant agents and provide intraoperative and postoperative analgesia, but this is not recommended in cats. Serious adverse effects, including cardiovascular depression and increased plasma lactate values, were reported in anesthetized cats with a wide variety of infusion rates,[104] which emphasizes the need to critically evaluate techniques that are successful in other species before applying them to the cat.

Topical application of local anesthetic creams to desensitize the skin can ease catheter placement and venipuncture, as well as aid in a variety of other minimally invasive procedures, such as skin biopsy. Two products are readily available: lidocaine in a liposome-encapsulated formulation (ELA-Max; Ferndale Laboratories, Ferndale, Michigan) and a eutectic mixture of lidocaine and prilocaine (EMLA cream; AstraZeneca LP, Willington, Delaware, and as a generic formulation). There is little systemic absorption after application of the liposome formulation, and no uptake of the components of the eutectic mixture.[38,41] The success rate of jugular catheterization increased by over 20% (from 38% to 60%) when the eutectic mixture was used as part of the catheterization process in one study.[157] The proposed skin site is clipped in advance and cleaned in a routine fashion. The cream is applied and covered with an occlusive dressing, which could be a small square cut from a plastic bag or surgery or examination glove, then covered by a light wrap for approximately 20 minutes. When it is time to place the catheter, the dressing is removed and a final cleansing of the skin performed.

Another method for delivery of local anesthesia is the lidocaine patch (Lidoderm 5%; Endo Pharmaceuticals, Chadds Ford, Pennsylvania). This patch produces high concentrations of lidocaine at the site of application with minimal systemic absorption and appeared effective for the 72-hour duration of assessment.[71] The patch can be cut to any desired size or shape without fear of altered drug delivery, making it a good option for wound management.

Other useful techniques that are worth learning include brachial plexus blocks, dental blocks, distal paw blocks, intercostal nerve blocks, and wound infusion ("soaker") catheters. These techniques are inexpensive, relatively easy to perform, and associated with minimal complications if done correctly.

Local Anesthetic Blocks

Cats are rarely tolerant of a local block performed while awake, and complications can arise if an animal moves at the wrong moment; therefore, heavy sedation or general anesthesia is recommended prior to performing local blocks. Some clinically useful blocks are described below.

Brachial Plexus Block

The aim of this procedure is to block the ventral branches of cervical nerves 6, 7, and 8 and thoracic nerve 1; this technique has been demonstrated to reduce intraoperative inhalant requirement, as well as early postoperative pain in the cat.[93] This is a useful technique for procedures that are located below the elbow joint. A block can be performed in three ways: with ultrasound guidance, with use of a nerve stimulator, or based on anatomic landmarks with no visualization. Ultrasound-guided nerve blocks are a relatively novel technique in animals. Instruction for this technique in dogs is available.[16] Use of peripheral nerve stimulation has been described in the rabbit as well as the dog but not yet in the cat.[8,162] This technique does increase the success rate when used in children[116] and has great potential in cats. Because the appropriate equipment for these two techniques is not yet widely available in general practice, the technique described here is based on anatomic landmarks (Figure 6-3).[73] The point of the shoulder (scapulohumeral joint), first rib, and cervical vertebrae are the anatomic landmarks that will assist with correctly performing this block. Once the hair coat has been clipped and the insertion site prepared using sterile technique, the patient's head and neck are placed in a neutral position (i.e., with minimal flexion or extension). The cervical transverse processes form a line that typically traverses the proximal brachial plexus at the first rib.[73] The first rib is followed dorsal as far as possible, and a 1.5-inch, 22-gauge sterile needle is inserted and advanced toward and caudal to this rib, below the scapula. A syringe containing lidocaine (4 mg/kg) or bupivacaine (2 mg/kg) is attached to the needle. It is critical to pull back on the plunger of the syringe after it is attached to the needle and before drug administration; complications of this block can include injection into the axillary vein or artery, as well as needle placement into the thoracic cavity. If blood or air is aspirated, the procedure is best aborted. If nothing is aspirated, approximately one quarter of the total volume is deposited at this location and the needle is withdrawn a short distance (0.5 cm). After aspirating again, more local anesthetic can be deposited. This continues until the needle is withdrawn from the skin.

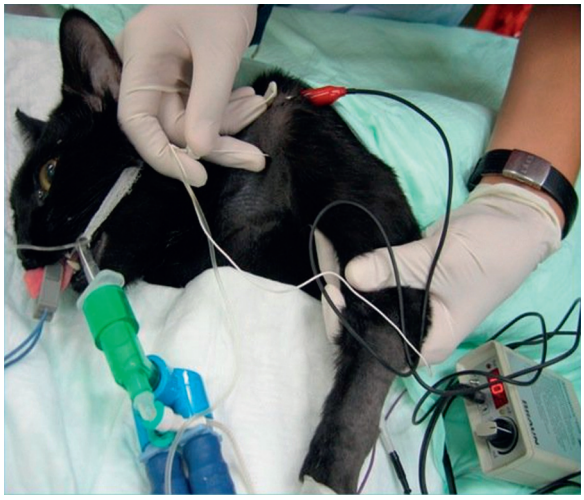

FIGURE 6-3 A cat receiving a brachial plexus block. *(Image courtesy Heidi Reicht and Martina Mosing.)*

Dental Blocks[73]

Dental blocks are often used to help manage pain associated with surgery of the jaw and face and dental procedures, targeting (as appropriate) the mental, inferior alveolar (mandibular), and infraorbital nerves. The mental nerve foramen can be palpated rostrally between the canine and the first premolar tooth, on the buccal side of the mandible. The inferior alveolar nerve is blocked intraorally, from either an external or internal approach, at the caudal aspect of the mandible. It is palpated on the lingual side of the mandible, ventrally and rostral to the angular process. Often, because of the small size of the cat mandible, it is necessary to approach this foramen from the external caudal aspect of the jaw. Skin over the site of needle entry must be appropriately clipped and prepped. The infraorbital canal in the cat is extremely shallow, so while this foramen is easily palpated, care should be taken to avoid inserting the needle more than a few millimeters into the canal. One can palpate the foramen ventral to the eye where the zygomatic arch meets the maxilla by lifting the lip and palpating along the buccal mucosa. It is important to aspirate before depositing local anesthetic at any of these foramens and not to exceed the total toxic dose of lidocaine or bupivacaine for the cat when performing multiple blocks. Occasionally, it is necessary to combine local anesthetic with saline to provide more volume.

Distal Paw Block[124]

Declawing of cats is an increasingly controversial procedure and not permitted in many countries. However, if it is performed, it is essential to provide adequate analgesia, often for several days after surgery. Preoperative and postoperative opioids are recommended in combination with an NSAID (e.g., meloxicam), as previously described. The addition of a regional block is widely used, although the postoperative benefits were not obvious in one study.[25] However, many clinicians

comment on improved quality of recovery and postoperative comfort, lower intraoperative anesthetic requirements, and fewer changes in intraoperative heart rate and blood pressure after incorporating it into their perioperative plan. Often referred to as the four-point block, the superficial branches of the radial, the palmar and dorsal cutaneous ulnar, and the median nerves are selectively blocked. The radial nerves are located proximal to the carpal joint and on the dorsomedial aspect of the paw, where they are blocked. The ulnar nerve is blocked at two points: proximal and lateral to the accessory carpal bone. The medial carpal pad provides the landmark for blocking the median nerve, which is blocked proximal to this site (Figure 6-4).

Intercostal Nerve Block[73]

This block can alleviate the pain associated with a lateral thoracotomy incision or fractured rib. For an efficacious block, it is important to remember that the innervation supplied to an individual rib has contributions from the nerve roots of the ribs cranial and caudal to the affected nerve, and therefore it is prudent to block one to two intercostal spaces cranial and one to two intercostal spaces caudal to the affected rib. The nerve is blocked near the intervertebral foramen at the caudal border of the rib, with care taken to avoid the blood vessels coursing along the caudal boarder of the rib. When a thoracotomy is performed, the nerve(s) can be directly visualized. If the technique is performed percutaneously, as opposed to directly visualized, care must be taken not to enter the thoracic cavity.

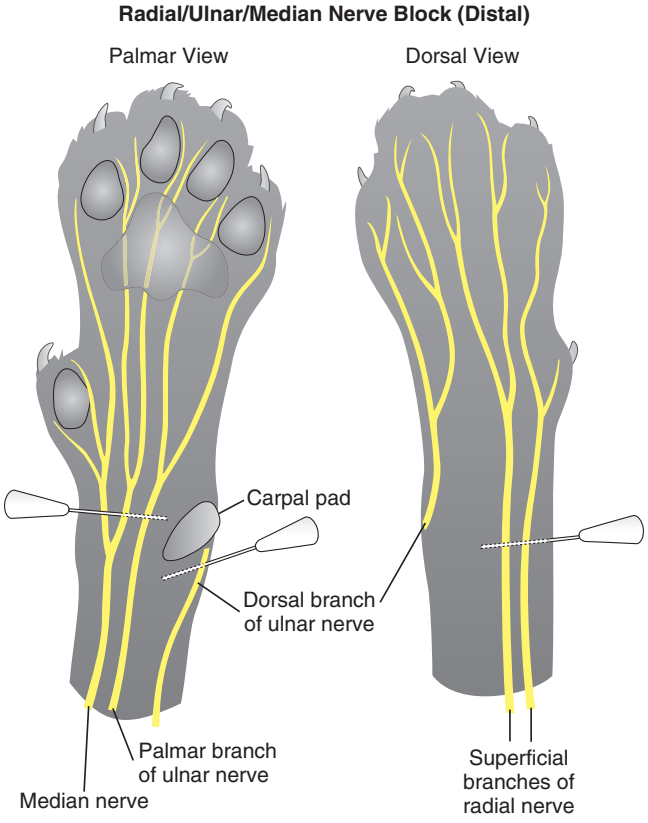

FIGURE 6-4 Targeted nerves for a distal paw block. *(Image courtesy John Spahr and Teton NewMedia.)*

Wound Infusion Catheters

Wound infusion ("soaker") catheters provide in situ continuous local analgesia of a wound. These catheters can be purchased as a "ready to use" product (ON-Q Pain Buster, I-Flow Co, Lake Forest, California) or can be made from a 5-french red rubber catheter, with alternating holes placed 5 mm apart starting 8 cm proximal to the end of the catheter. When wound infusion catheters were used as part of the pain management protocol after fibrosarcoma removal, cats were discharged from the hospital significantly earlier because they met the criteria for discharge (improved mobility and food consumption) sooner.[28] Fear of introducing infection has been cited as a reason for not using this technique, but a retrospective review of cats and dogs with wound soaker catheters did not support this concern.[1]

Alpha$_2$-Adrenergic Agonist Agents

Use of xylazine, detomidine, medetomidine, romifidine and dexmedetomidine are all reported in the cat. Dexmedetomidine (Dexdomitor) is currently the primary alpha$_2$-agonist used in cats and has market authorization in many countries. Alpha$_2$-agonists provide sedation, muscle relaxation, and analgesia. In a research model, the effects of dexmedetomidine (given as an intramuscular injection) on sedation appear to be dose related, but the analgesic effects may not be,[127] and the clinician should be aware that although sedation is obvious, analgesia may not be adequate. Dexmedetomidine also produces well-recognized cardiovascular effects, including bradycardia, decreased cardiac output, and hypertension.

Dexmedetomidine is primarily used as a premedicant before general anesthesia, for chemical restraint, and in combination with local anesthetics for minor procedures.

Oral transmucosal dexmedetomidine (40 µg/kg) provided sedation and measurable antinociceptive effects similar to the same dose given intramuscularly[128] and is a particularly useful technique when dealing with a cat that is in pain and difficult to handle.

The actions of dexmedetomidine are reversed with atipamezole (Antisedan), but it must be remembered that this reverses all effects, including analgesia. Therefore if an invasive procedure is performed, other analgesics (e.g., opioids, NSAIDs) should be given before reversal.

In an effort to utilize the analgesic properties but avoid heavy sedation and unwanted cardiovascular effects, low doses of dexmedetomidine can be given as

a CRI. This strategy has been successful in dogs and was as effective as a CRI of morphine in the postoperative period.[150] Similar studies have not been reported in cats, but infusion rates of 0.5 to 2.0 µg/kg per hour are used in clinical settings with reports of success. The cat should be evaluated for pain, including wound palpation, to ensure that any sedative effects of the drug are not masking pain. A benefit of this technique is that the infusion rate can be increased before nursing interventions, such as a bandage change, and lowered over time to assess the patient's comfort level.

N-Methyl-D-Aspartate Receptor Antagonists

Drugs in this category include ketamine, amantadine, and memantine. The latter two drugs are more commonly used in patients with long-term pain conditions, and reliable information on these drugs in cats is lacking or at best anecdotal. Ketamine, however, has a potential role to play in acute pain management.

Ketamine, classified as a dissociative anesthetic, is widely used in cats for chemical restraint or in combination with dexmedetomidine, diazepam, or midazolam to induce general anesthesia (see Chapter 7). However, because of its interaction at the NMDA receptor, there is great interest in using ketamine to provide analgesia and prevent central sensitization and "wind up." In cats arousal (as measured by electroencephalography [EEG]) and autonomic responses during nociceptive stimulation were abolished by ketamine.[141] One clinical study found that cats undergoing ovariohysterectomy with ketamine as part of their anesthesia protocol had better analgesia postoperatively.[125] Experience with sub-anesthetic infusions of ketamine given as part of a multimodal analgesic protocol in dogs undergoing major surgery suggests that it has beneficial effects on postoperative pain.[156] The clinical impression is that doses of ketamine in the range of 5 to 10 µg/kg per minute (300 to 600 µg/kg per hour) during surgery and 2 to 5 µg/kg per minute after surgery (120 to 300 µg/kg per hour for up 24 hours) improve postoperative outcome in cats, but this has not been confirmed in a well-controlled study.

Like ketamine, amantadine is also a NMDA antagonist, but in contrast to ketamine, amantadine stabilizes the NMDA channels as opposed to blocking current flow through the channel.[7] Amantadine is a somewhat new addition to the veterinary analgesic arsenal, and as such there is little information about its use in cats. It was found to enhance the effect of NSAIDs in dogs with osteoarthritis,[78] but its role in acute pain management, especially in the feline, is unclear.

Epidural administration of ketamine has been reported in cats and, when combined with lidocaine, can provide prolonged analgesia.[30] However, a preservative-free formulation of ketamine is not commercially available, and drugs containing preservatives are not recommended for epidural use. Epidural morphine provides effective analgesia and is available in a preservative-free formulation, making this the preferred drug if this route of administration is chosen.

Other Analgesic Drugs

Gabapentin is an anticonvulsant that has utility in alleviating neuropathic pain in humans.[98] There is also interest in using it in the perioperative period to prevent persistent postsurgical pain, which is thought to result from nerve damage during surgery.[68]

In the cat oral bioavailability is high (92%).[122] Oral gabapentin produced no antinociceptive effects in a thermal threshold model,[106] but this is not surprising because its mechanism of action is on damaged nerves.[26] Gabapentin has been used as an "add-on" medication in dogs that underwent intervertebral disk surgery, and beneficial effects were seen on postoperative days 3 and 4.[2] Conversely, no benefit was detected when gabapentin was used as an adjunct analgesic in dogs that underwent forelimb amputation.[155] There are no published studies on the perioperative use of gabapentin in cats.

Maropitant, a neurokinin-1 (NK-1) antagonist commonly used in the cat for prevention of emesis,[56] has shown potential as an analgesic in other species, and investigation is under way in the cat for this purpose. In a research setting there was a marked variation in individual responses to this drug; in some cats thermal antinociception could be demonstrated, but not in others.[94]

MULTIMODAL ANALGESIA

Multimodal analgesia describes the combined use of drugs that work at different receptors and pathways with the assumption this will provide superior analgesia or allow lower doses of each drug to lessen adverse side effects. Although this sounds logical, further investigation is necessary to fully validate this in the cat and to determine which drugs, dosages, and combinations will be most beneficial. Synergism has been demonstrated between the NSAID vedaprofen and tramadol.[11] Buprenorphine may have a synergistic action with carprofen; cats given both drugs exhibited fewer signs of pain than when either drug was administered alone.[137]

"SEND HOME" MEDICATIONS

When intravenous fluid support and intensive nursing are not needed, cats can go home to recuperate from surgery; most fare better in familiar surroundings, away from the stressors of a veterinary clinic. Outpatient

anesthetic and surgical techniques allow cats to return to normal function quickly; however, analgesics may be required for several days postoperatively. The liability issues associated with transdermal fentanyl patches have already been discussed. One popular take-home drug is buprenorphine (a less tightly controlled opioid), which most owners find easy to administer by the oral transmucosal route. Doses of 0.01 to 0.02 mg/kg twice or three times daily are administered depending on the severity of the surgery and the cat's behavior at home. Buprenorphine is usually no longer needed after 2 to 3 days. Oral meloxicam (0.025 to 0.05 mg/kg, once daily for 4 days) is also easy to use in a home setting because it is given once daily and is highly palatable; it is administered alone or with food.

INDIVIDUAL VARIATION IN RESPONSE TO ANALGESIC DRUGS

Pharmacogenetics (the study of genetic variation that results in different responses to drugs) is a major area of interest in the scientific community. Female humans and mice with the melanocortin-1 receptor gene (which is associated with red hair and fair skin in humans) have altered sensitivity to pentazocine compared with male subjects or female subjects with another hair color.[89] It is very likely that cats, with their many different genetic traits, also express individual variation in response to analgesic drugs. Gender differences in pain sensitivity are well documented in humans[36] but have not been well studied in animals other than rodents. Marked variations in response to butorphanol and buprenorphine have been reported in cats under well-controlled laboratory conditions.[63,81,117,135] Clinically, this is a concern because some cats may be "nonresponders" to a chosen opioid,[145] making their analgesic management more challenging. However, armed with this knowledge, good pain assessment skills, and a variety of analgesic drugs, clinicians have the ability to keep feline patients comfortable. Now that the feline genome has been mapped,[95] this opens up exciting possibilities for investigating pain and analgesia in cats.

SPECIAL POPULATIONS

There is limited information on the safety and efficacy of analgesic drugs in nursing queens, kittens, and senior cats.

Analgesics have often been withheld in young animals because of their organ immaturity and decreased ability to metabolize drugs. However, neonates do experience pain, and noxious stimuli can cause detrimental and permanent changes in the developing nervous system.[87] Carprofen can be used in kittens older than 6 weeks of age (see package insert in licensed countries), whereas meloxicam is not recommended until 16 weeks of age.[62] In kittens younger than 6 weeks, opioid agonists are the analgesic drugs of choice because they are reversible if an adverse event occurs. In neonates, cardiac output depends on heart rate; therefore opioid-related bradycardia is a concern. For this reason, and the observation that kittens may be more sensitive to the sedative and respiratory-depressant effects of opioids, it is suggested that lower doses be used initially with further treatment based on close observation. Co-administration of anticholinergics can reduce the incidence of opioid-mediated bradycardia.

Drugs administered to a dam may be excreted in milk. In species in which this has been studied, only a small percentage of the drug is detectable in milk. In cows carprofen was below detectable limits in milk after single or daily dosing[86]; no comparable study has been performed in lactating queens. There is concern that exposure of the fetus or neonates to NSAIDs may impair renal development or ductus arteriosus function[4]; therefore until more specific information becomes available, the use of NSAIDs should be restricted to a "one time only" basis in pregnant or lactating queens. It is unlikely that the concentration of opioid drugs present in milk after systemic administration to the queen will have any negative effect in nursing kittens. Epidural opioids that are hydrophilic (e.g., morphine) remain concentrated in the epidural space with minimal systemic distribution, making them a suitable choice for a queen undergoing a cesarean section. A local anesthetic line block is another simple and effective, albeit short-acting, analgesic technique for cesarean section. The review by Mathews[87] provides further information on these patient categories. With these infrequent but challenging cases, the clinician needs to tailor the analgesic plan to the specific patient.

Aging cats present a challenge in terms of treating pain because of co-existing disease(s) and Rollin reminds us that our duty is to preserve quality of life rather than just "quantity" of life in this population.[115] A full understanding of the patient's co-existing diseases and evaluation of liver and renal function are essential before a treatment regimen can be developed. Age-related neurodegeneration occurs in cats,[53] but it is not known how this relates to changes in neurotransmission, pain sensitivity, or analgesic requirements. Initially, it may be wise to use a reduced drug dose in elderly cats and base additional administration on careful evaluation.

OTHER ANALGESIC MODALITIES

Finally, not all pain management is pharmacologic. Other modalities, such as massage, physical therapy, and acupuncture, may provide benefit for the alleviation

of acute pain in the cat. These modalities have not undergone robust scientific scrutiny in this species, but individual case reports are encouraging.[21,42] In addition, the contribution of warmth, comfortable dry bedding, quiet surroundings, and gentle and considerate caretakers to a cat's overall comfort should not be underestimated.

CONCLUSION

The unique characteristics of the cat make assessing and treating these patients for pain both rewarding and challenging. However, there is no doubt that incorporating newer approaches to pain assessment, understanding individual variation, and dispelling myths about some analgesic agents have all been significant in improving the care of cats after trauma and in the perioperative period. Veterinarians have a better understanding of how to use current knowledge and have identified specific areas that require further research. Although there is still progress to be made, veterinarians are confronting the issue of pain in the cat with evidence-based, logical, compassionate choices.

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