

Preoperative analgesia— opioids and NSAIDs

B. Duncan X. Lascelles BSc, BVSc, PhD, MRCVS, CertVA, CertSAS, DipECVS
University of Cambridge, UK



Duncan Lascelles graduated from Bristol with honors in 1991 having also gained a first class intercollegiate degree in zoology. He remained at Bristol and gained an RCVS Certificate in Anaesthesia in 1994 and a PhD in experimental and clinical surgery in 1996. At the end of 1995 he started a surgical residency at the University of Cambridge and gained an RCVS Certificate in Small

Animal Surgery in 1996. He has just recently become a diplomate of the European College of Veterinary Surgeons.

KEY POINTS

- Animals probably experience pain and therefore suffer.
- Perioperative pain is disadvantageous.
- A basic understanding of pain physiology and analgesic pharmacology is required if optimum perioperative pain prevention or alleviation is to be achieved.
- Analgesic therapy is best initiated before surgery, or as soon as possible in the case of trauma.
- It is most effective to use several classes, rather than a single class, of analgesic drugs.
- Analgesic regimens must be tailored to the individual animal's requirements.

INTRODUCTION

The likelihood that animals experience pain, and that this is disadvantageous, is being increasingly accepted by veterinarians. Despite this, there is evidence that the use of analgesics in veterinary practice is suboptimal. Recent Canadian (1) and British (2) surveys have examined practitioners' attitudes to, and use of, analgesics (Table 1). Both surveys indicated that not all animals undergoing surgery, even major surgery, received analgesics. Furthermore, veterinarians considered their own knowledge of analgesia to be poor. This lack of knowledge probably accounts for the failure of many veterinarians to embrace the concept of adequate perioperative pain control.

This article reviews the relatively new, yet very simple and practical, area of preemptive analgesia, using opioids and nonsteroidal antiinflammatory drugs (NSAIDs). Clinicians should

note that local anaesthetics are useful preemptive analgesics. The practice and techniques of their use have been covered elsewhere (3).

WHY TREAT PAIN IN ANIMALS?

- Pain is suffering, and it is the duty of veterinarians to alleviate the suffering of animals in their care.
- Pain initiates adverse effects which prolong and complicate postoperative convalescence.

Although it is impossible to say with certainty whether animals feel pain in the same way as human beings, there are many similarities between the pain pathways in both species. Furthermore, animals also show signs of aversion to the same stimuli that produce pain in humans. Thus, if we are in doubt about whether or not an animal is feeling pain, or whether a particular procedure will be painful, we should give the animal the benefit of the doubt and treat the pain, or take steps to prevent it.

Many clinicians practice what amounts to pharmacological hypocrisy in the postoperative period, insofar as analgesic drugs are withheld while antibacterial agents are administered. It is illogical to withhold analgesia because one is unsure that the animal is experiencing pain, yet, at the same time, administer antibiotics without demonstrating the presence of bacterial contamination or infection! In many surgical procedures, there is more evidence for the presence of pain than there is evidence to suggest that postoperative infection is likely if antibiotics are not administered after the operation. It is also worth remembering that owners, almost without exception, believe that surgery will cause their animal discomfort, and assume their pet will receive pain relief.

It has been said that analgesics obviate the protective function of pain. However, providing that competent surgical techniques are employed (Figure 1), effective measures are taken to immobilize and/or protect damaged tissues, and animals are confined during the postoperative period, pain abolition does not usually give rise to problems.

Table 1
Summary of sample results concerning the prescription of analgesics by Canadian and UK veterinarians (1, 2)

Procedure	% of respondents who claimed to prescribe analgesics			
	Canadian survey		UK survey	
	Cat	Dog	Cat	Dog
Orthopedic	70	84	94	97
Exploratory laparotomy	44	44	56	71
Ovarohysterectomy	17	13	26	53
Castration	9	11	16	31



Figure 1
Provided competent surgical techniques are employed and effective pre- and postoperative bandages used where appropriate, postoperative pain serves no purpose.



Figure 2 *Postoperatively, animals which have not had analgesic therapy will be dull, depressed, and appear to be 'not doing as well as might be expected'.*

ASSESSMENT OF PAIN IN ANIMALS

Assessing pain in animals relies on behavioral signs (**Figure 2**). Unfortunately, these are very variable and, furthermore, they vary with species, within breeds, and with the individual. In order to recognize pain in animals the clinician must accumulate a working knowledge of normal behavior in the species he or she is dealing with. Measuring clinical variables such as heart and respiratory rates and temperature are an unreliable guide to the presence of pain (4), as are clinicopathological measurements of humoral factors such as adrenaline, nor-adrenaline, and cortisol.

A painful body area is more sensitive to touch or pressure than normal. It follows that gentle to firm palpation of the affected area can be used to determine whether or not the area being examined is painful. Indeed, mechanical thresholds such as palpation correlate well with visually assessed pain levels (5, 6). It is interesting to note that palpation is used routinely in diagnosing the cause of lameness, but usually neglected as a tool in pain assessment. Palpation may also produce exaggerated behavioral responses (i.e., aggression or avoidance) that can help the assessor to determine if the animal is in pain. An interactive method of assessing pain (which includes handling the animal) is more accurate than mere observation. One of the best ways of recognizing pain, albeit retrospectively, is to start using proven analgesics and noting the difference these make to the animal's behavior.

DISADVANTAGES OF POSTOPERATIVE PAIN

Localized pain is a valuable diagnostic tool, but once a diagnosis has been established, pain should be alleviated. Tissue injury produces a series of neurophysiological, endocrine and metabolic responses which are initiated by the local release of inflammatory mediators and the direct stimulation of nociceptive nerve endings. This inflammatory cascade and the transmission of nociceptive information to 'higher centers' results in a range of adverse responses which are not confined to the area of damage:

- There is an increased skeletal muscle tone and therefore the possibility of decreased chest wall compliance. This, and thoracic pain itself, can directly lead to impaired respiration, hypoxia and acidosis.
- Smooth muscle inhibition in the gastrointestinal and urinary tracts may result in constipation and urinary retention.
- Increases in sympathetic tone produce increases in blood pressure, cardiac output, metabolic rate and oxygen consumption, increased release of catabolic hormones, and a

shift to the inefficient use of energy substrates.

- These changes result in catabolism and possibly delayed wound healing. Pain associated with movement results in fear, anxiety, apprehension, and suffering, causing further increases in cortisol and catecholamine levels.

Pain can result in selfmutilation or traumatization of the operative site. Furthermore, acute pain may cause central hypersensitivity, resulting in chronic pain (see below). Animals in pain will be dull, depressed, and appear to be 'not doing as well as might be expected' (**Figure 2**). Obviously, this complicates the assessment of postoperative progress. We must also remember that pain probably results in greater suffering for the animal and decreased owner satisfaction.

PREEMPTIVE ANALGESIA

One of the most important advances in the control of perioperative pain has been the realization that the timing of analgesic intervention may have a significant bearing on postoperative pain. The concept was, however, formulated by Crile (7) at the beginning of the 20th century and was based on his clinical observations. Crile suggested the use of regional nerve blocks prior to surgery, in addition to general anesthesia, to prevent postoperative pain. Interest in this idea was recently revived when it was found that the changes in central processing of noxious signals occurred in response to peripheral injury (8). It was noted that these changes were suppressed to a greater extent by opioid administration preinjury, rather than postinjury (9, 10, 11). The administration of analgesics before noxious stimulation begins is known as 'preemptive analgesia'.

To understand this phenomenon, it is important to understand what happens when a 'painful' stimulus occurs (**Figures 3 and 4**). During surgery, noxious stimuli ascend peripheral nerves and activate spinal cord neurones. This activation is not prevented by general anesthetic agents. These agents induce loss of consciousness, which simply prevents the animal from perceiving the stimulus to be painful; they do not prevent the adverse changes induced by the noxious stimulus, unless the anesthetic agents are also analgesic in their own right (e.g., ketamine).

Most neuronal activation occurs in the area of the dorsal horn, where a number of processes take place:

- Rostral transmission of the noxious stimulus to the brain. This stimulus would be perceived as so-called 'fast pain' in the conscious animal.





Figure 3
The central changes ('central hypersensitivity') associated with surgery occur as soon as surgery starts and occur with even the more minor surgeries.



Figure 4 *The best time to intervene with analgesic therapy is prior to the onset of surgery. In trauma cases, it is best to intervene as soon as possible. Early intervention increases the effectiveness of the analgesic being administered and makes any subsequent pain much easier to control.*

- Dorsal horn neuronal activity is altered in such a way that there is heightened activity and responsiveness in the spinal cord. This heightened responsiveness makes it easier for signals to be perceived as painful (hyperalgesia). However, it also allows nonnoxious stimuli (both from the surgical site and from other areas) to be felt as painful when the animal regains consciousness (allodynia). These changes are known as central hypersensitivity.

The clinical implications of central hypersensitivity are that a given dose of an analgesic drug is less effective once pain is established and that the 'pain' felt by the animal appears to be greater. Furthermore, continued inflammatory input from the damaged tissues further aggravates central hypersensitivity. Clinical pain is thus a combination of central and peripheral hypersensitivity.

Preemptive analgesic administration protects the dorsal horn neurones from the sensitizing effect of noxious stimuli. Experimentally (10, 12, 13) and clinically, preemptive drug administration has been found to be effective in this regard, both with opiates (6) and NSAIDs (14, 15) in animals.

However, to gain maximum benefit, the matching of nociceptive input and analgesic medication is crucial if the clinical benefit of preemptive analgesia is to be exploited. In effect, the greater the surgical stimulus expected, the greater the degree of preemptive analgesia that must be administered. Furthermore, it must be appreciated that a single dose of an analgesic administered prior to

surgery is not necessarily all the analgesia that is going to be required. Analgesic medication will still be required in the postoperative period, although the pain may be easier to control because of the beneficial effects of preemptive analgesia outlined above (6).

'MULTI-MODAL' PAIN THERAPY

Pain transmission involves a multiplicity of pathways, mechanisms, and transmitter systems, and it is unlikely that a single class of analgesic will provide complete analgesia, irrespective of dose. Clinical experience indicates that the combination of two or more classes of analgesic—e.g., an opioid and an NSAID—is much more effective than if either is used alone. Furthermore, the effect of these drugs is often supra-additive, and smaller doses of each individual drug can be used than would be the case if one alone was used. This dose reduction decreases the likelihood of side effects from any one drug. For example, a basic regimen could consist of the preoperative use of an opioid and an NSAID. The opioid acts centrally to limit the input of nociceptive information into the CNS, and thus reduces central hypersensitivity. The NSAID also acts centrally to limit central changes induced by the nociceptive information that does 'get through' the opioid blockade. However, the NSAID also acts peripherally to decrease inflammation during and after surgery, and thus limits the nociceptive information entering the CNS. By acting on different points of the 'pain pathway', the combination is a more effective.

PHARMACOLOGICAL CONTROL OF PERIOPERATIVE PAIN USING OPIOIDS AND NSAIDS

General pharmacodynamics of opioid drugs

Analgesia

Opioids block the transmission of noxious stimuli to higher centres by acting on various (μ [OP3], δ [OP1] or κ [OP2]) pre- and post-synaptic receptors on the primary afferent sensory nerve, at the level of the spinal cord. They also act at higher centers to produce analgesia. Opioids also act peripherally via opioid receptors that are generated in inflammatory conditions. All of the opioid drugs mentioned below are satisfactory analgesics, but (specific) individual properties make some drugs more appropriate than others in certain situations (Table 2).

When an opioid is used preoperatively two points must be kept in mind. An analgesic dose must be used, and it must be administered by a route that will provide analgesia. Simply using an opioid preoperatively is not the same as ensuring that the drug will provide analgesia. Furthermore, the timing of administration must be such that surgery starts only when the opioid has achieved maximum effect:

- 20–30 minutes after i/m injection of morphine
- 10–15 minutes after i/m injection of pethidine
- 45 minutes after i/m injection of buprenorphine

The author prefers to select an analgesic first and then consider which other drugs are required, dosing accordingly.

Sedation

Sedation is particularly marked with butorphanol, buprenorphine, pethidine, and morphine. The postoperative use of opioids is often resisted by clinicians because of undesirable sedative effects (Figure 5). However, effective preemptive analgesia will lessen the requirement for postoperative opioids. Indeed, the

Table 2
Doses and routes of administration of common opioid analgesics in dogs and cats

Drug	Dog	Cat
Pethidine (pure agonist)	3–5 mg/kg IM only, as IV use is associated with histamine release and severe hypotension Provides analgesia for up to 1.5 hours Should be given 10 minutes prior to surgery Further doses should be given during surgery at 1.5 hour intervals	5–10 mg/kg IM only Provides analgesia for 1.5–2 hours Should be given 10 minutes prior to surgery Further doses should be given during surgery at 1.5 hour intervals
Morphine (pure agonist)	0.3–0.6 mg/kg IM (or slow IV) Provides analgesia for 1.5–3 hours Should be given 20 minutes prior to surgery Further doses should be given as required in the postoperative period (usually at 1–4 hour intervals)	0.1–0.3 mg/kg IM Provides analgesia for 4–6 hours Should be given 20 minutes prior to surgery Further doses should be given as required in the postoperative period (usually at 3–6 hour intervals)
Oxymorphone (pure agonist)	0.05–0.3 mg/kg IM (or slow IV) Provides analgesia for 2–4 hours Should be given 20 minutes prior to surgery Further doses should be given as required in the postoperative period (usually at 1–4 hour intervals)	0.05–0.1 mg/kg IM Provides analgesia for 4–6 hours Should be given 20 minutes prior to surgery Further doses should be given as required in the postoperative period (usually at 3–6 hour intervals)
Methadone (pure agonist)	0.1–0.5 mg/kg IM (or slow IV) Provides analgesia for 2–3 hours Should be given 20 minutes prior to surgery Further doses should be given as required in the postoperative period (usually at 1–3 hour intervals) (less nausea and sedation than morphine)	0.1–0.3 mg/kg IM (or slow IV) Provides analgesia for 4–6 hours Should be given 20 minutes prior to surgery Further doses should be given as required in the postoperative period (usually at 3–6 hour intervals)
Fentanyl (pure agonist)	0.001–0.005 mg/kg IV Rapid onset of action (1 minute) but short duration of action (15–20 minutes) Used to augment anesthesia or postoperatively as a short-term measure to provide analgesia while longer acting opioids are taking effect Cumulation can occur if multiple doses are given (less cumulation is seen with alfentanil)	0.001–0.002 mg/kg IV during anesthesia Rapid onset of action (1 minute) but short duration of action (15–30 minutes) Used to augment anesthesia
Buprenorphine (partial agonist)	0.01–0.02 mg/kg IM (or slow IV) Provides analgesia for 6–8 hours Should be given 45 minutes prior to surgery Further doses should be given as required in the postoperative period (usually at 4–8 hour intervals) Some ‘failures’ are seen and these are unpredictable Do not combine with pure agonists	0.02–0.03 mg/kg IM Provides analgesia for 8 hours Should be given 45 minutes prior to surgery Further doses should be given as required in the postoperative period (usually at 4–8 hour intervals) Do not combine with pure agonists
Butorphanol (partial agonist)	0.3–0.6 mg/kg IM (or slow IV) Provides analgesia for about 1 hour Should be given 20 minutes prior to surgery Further doses should be given throughout surgery (at 1 hour intervals) and as required in the postoperative period (usually at 1–2 hour intervals) ‘Failures’ are often seen Provides better visceral than somatic analgesia Seems to be more effective as a sedative than as an analgesic	0.3–0.6 mg/kg IM Provides analgesia for about 1 hour Should be given 20 minutes prior to surgery Further doses should be given throughout surgery (at 1 hour intervals) and as required in the postoperative period (usually at 1–2 hour intervals) ‘Failures’ are often seen Provides better visceral than somatic analgesia Seems to be more effective as a sedative than an analgesic
Naloxone (antagonist)	0.04–1.0 mg/kg For absolute or relative overdose of opioids SC, IM or IV—titrate to effect Short acting (30 minutes), may need to be repeated on a regular basis	0.04–1.0 mg/kg For absolute or relative overdose of opioids SC, IM or IV—titrate to effect Short acting (30 minutes), may need to be repeated on a regular basis

Note: Opioids must be titrated to effect—this will often mean using much larger doses than those quoted above.





Figure 5 Sedation is often viewed as undesirable postoperatively, and thus opioids are withheld. By using opioid drugs preoperatively at appropriate doses, the central nervous system can be 'protected' from the adverse changes that occur as a result of noxious stimuli input. Smaller doses will be needed postoperatively, and less sedation will be seen.

sedative effect can be utilized as part of the premedication regime, administered prior to the induction of anesthesia. Thus, the analgesic dose of the opioid can be combined with, for example, acepromazine, to provide both pre-anesthetic medication and preemptive analgesia.

Use in felidae

The notorious reputation of opiates in cats originated from the work of Joel and Arndts (1925) who used a dose of 20 mg/kg of morphine. Clinical doses of opiates (0.1–0.5 mg/kg) do not cause the same degree of sedation in cats as occurs in dogs, but neither do they cause excitement or mania. However, it is probably unwise to use opioids by the intravenous route in conscious cats as slight, transient, overstimulation of the CNS can be seen. The preoperative use of opioids in cats is very effective for analgesia.

Respiratory depression

In conscious, healthy animals, μ -agonist opioids reduce the sensitivity to CO₂ of neurones in the medulla. This results in a decreased respiratory rate, little change in tidal volume, and an increase in the blood concentration of CO₂. Equianalgesic doses of partial agonists probably produce less respiratory depression and there may also be a 'ceiling' to this effect. However, respiratory depression is not a clinical problem associated with opioid use in animals unless:

- very high doses are used, and the animal is not in pain.
- opioids are used with other sedative or anesthetic agents.

Panting is sometimes seen after the preemptive administration of moderate to large doses of morphine or pethidine to conscious animals. This may reflect stimulation of the thermoregulatory center. Animals that have sustained higher center or brain stem trauma can react unpredictably to CNS depressant drugs such as opioids. If respiratory depression does occur, it can be treated using an opioid antagonist, although this also reverses analgesia. It may be preferable to intubate and initiate positive pressure ventilation.

Cardiovascular effects

Opioids have little cardiovascular effect. Fentanyl and alfentanil will cause bradycardia and hypotension if rapidly injected intravenously, while intravenous morphine may cause hypotension and tachycardia. The bradycardia may be reversed by the administration of anticholinergics. The hypotension results from



Figure 6
There may be vomiting following opioid administration (particularly morphine) to dogs and cats, but paradoxically it is not usually seen if the animal is in pain when the drug is administered.

morphine-induced histamine release, or depression of the vasomotor center. It may be avoided by slow intravenous administration of morphine or by using the intramuscular route.

Gastrointestinal effects

Opioids stimulate gastrointestinal (GI) motility, increase nonpropulsive rhythmic contractions, increase smooth muscle tone, and close GI sphincters (including biliary and pancreatic ducts). This is followed by a period of GI stasis. Vomiting (**Figure 6**) may be seen (particularly with morphine) and is often accompanied by defecation. Preoperative morphine should be avoided where there is a risk of aspiration, where an increase in ocular pressure is undesirable, or where gastric activity is undesirable. Partial agonists such as buprenorphine exert fewer adverse GI effects. Pethidine has a spasmolytic effect on the gut due to an anticholinergic action and does not cause biliary or pancreatic spasm. It is therefore most suitable in animals undergoing biliary tract surgery.

Acute tolerance

Tolerance occurs when increasingly greater doses are required to achieve the same pharmacological effect. In veterinary practice, the reason for needing to increase the dose is uniformly due to an increase in pain. Although acute tolerance has been shown to occur after the administration of large opiate doses to pain-free laboratory animals, it does not appear to be a problem in animals receiving preemptive analgesia (6).

Routes of administration of opioids

Suggested systemic routes of administration are outlined in **Table 2**. **Table 3** outlines some special precautions to the use of opioids (**Figure 7**). The intramuscular or intravenous routes are most effective. The analgesic effect of opioids in dogs is related to plasma levels of the drug (16). Due to the differing absorption characteristics which follow the various routes of administration, a very much larger dose of drug must be given if the subcutaneous route is used. Opioids can be administered by the epidural route (17, 18) and, if given before surgery, can provide extremely good and long-lasting analgesia.

NSAIDs

Until recently, NSAIDs were regarded as less effective than opioids for treating severe pain. However, the picture has changed with the introduction of a new generation of these drugs.

NSAIDs are substances other than steroids that inhibit enzymes involved in the metabolism of arachidonic acid and the formation of eicosanoids—e.g., prostanoids (prostaglandins, prostacyclin [PGI₂], thromboxane [TXA₂]) and leukotrienes. They are a heterogeneous group of compounds, often chemically unrelated, and further



Figure 7 In young animals where hepatic function is not at adult levels, lower doses of shorter-acting (e.g., pethidine) or the safer (e.g., carprofen) analgesics should be administered, and doses titrated to effect.



Figure 8 Example of a gastric ulcer formed by the administration of a 'classic' NSAID.

research over the years has shown that the mechanism of action of some NSAIDs is highly complex and poorly understood.

Prostaglandins (particularly PGE₂ and PGI₂) play a role in the production of noxious stimuli at the periphery by sensitizing receptors on afferent nerve endings to the actions of bradykinin, histamine, and other compounds released in the inflammatory process. Prostaglandins, by virtue of their actions in the central nervous system, also facilitate the transmission of noxious stimuli travelling into and through the spinal cord to higher centers. This occurs particularly during prolonged or severe postoperative pain and in chronic pain. Thus, drugs that inhibit the production of prostaglandins (by the inhibition of cyclooxygenase [COX]) will produce analgesic effects by peripheral and central actions.

Side effects of NSAIDs

The toxicity of NSAIDs is also related to the inhibition of prostaglandin production, resulting in renal dysfunction and GI irritation and ulceration (**Figure 8**). Other adverse effects seen in animals are blood dyscrasias (e.g., with phenylbutazone), liver damage and aggravation of preexisting cardiac failure owing to water retention. It is therefore most important to consider the efficacy:toxicity ratio for any particular NSAID prior to its use in any particular species.

The kidney is active in the synthesis and metabolism of prostaglandins, where they participate in the autoregulation of renal blood flow and glomerular filtration, modulation of renin release, tubular ion transport, and water metabolism. Locally produced prostaglandins are continually active in maintaining afferent arteriolar dilation. These prostaglandins assume an important role in preserving normal renal blood flow when relative or absolute hypovolemia threatens renal blood flow. Such hypovolemia may occur during anesthesia or accompany blood loss, peritonitis, cardiac failure, septic shock, or endotoxemia, for example. If the production of these prostaglandins is inhibited under the aforementioned circumstances, renal hypoperfusion may occur, precipitating renal failure.

The gastric ulcerogenicity of NSAIDs is correlated to their ability to inhibit COX (19). Prostaglandins E₂ and I₂ promote the secretion of protective mucus along the intestinal tract, modulate the production of gastric acid, and help maintain gastric mucosal blood flow. The inhibition of prostaglandin production by steroids or classical NSAIDs can result in various degrees of GI irritation and ulceration.

COX-1 and COX-2

The COX enzyme exists in (at least) two different forms. COX-1

Table 3
Special precautions to the use of opioids

Condition	Comments
Severe respiratory disease	Opioids are contraindicated if respiratory depression is expected; however, pain (particularly thoracic or upper abdominal) can cause respiratory impairment
Cranial trauma	If opioids cause respiratory depression, the increased concentration of CO ₂ can cause dilatation of cerebral arterioles and thereby increases intracranial pressure. Also, as they cause sedation and pupillary constriction (dilation in cats), assessment of neurological status is more difficult. Patients with cranial trauma can react unpredictably to opioid drugs
Biliary obstruction	Pethidine is safe due to its spasmolytic action
Neonates	No contraindications for the perioperative use of opioids, however lower doses should be used in such patients with reduced liver function because opioids are metabolized by hepatic enzymes and often conjugated with glucuronic acid
Aged patients	
Hepatic disease	

is constantly active in most tissues, functioning to synthesize 'essential prostaglandins' which regulate normal cellular function; it has been termed the 'cellular housekeeping' enzyme. The inhibition of COX-1 leads to the toxic side effects of NSAIDs outlined above (gastric ulceration and renal toxicity). COX-2 is generally not found in resting cells in any significant amounts but concentrations increase dramatically in inflammatory states. The prostaglandin products of COX-2 activity mediate inflammation and pain. It is therefore the optimal target for NSAID activity.

Most NSAIDs block both COX-1 and COX-2 action, depriving the body of 'housekeeping' prostaglandins. Consequently, the development of specific COX-2 inhibitors has been vigorously pursued. Selective inhibition of COX-2 is claimed to improve GI tolerance, but this remains unproven in both the human and veterinary fields. As yet, no truly preferential COX-2 inhibitors are available on the veterinary market.

The perioperative use of NSAIDs

The preemptive administration of NSAIDs has been found to be beneficial in clinical cases (15). However, their use is not without risk. Potent COX inhibitors—flunixin, for example—can



Figure 9 In order to provide effective analgesia in the majority of surgical or trauma cases, as in this terrier who had its face bitten by a fox, two or more different classes of analgesic should be used—e.g., NSAIDs and opioids.

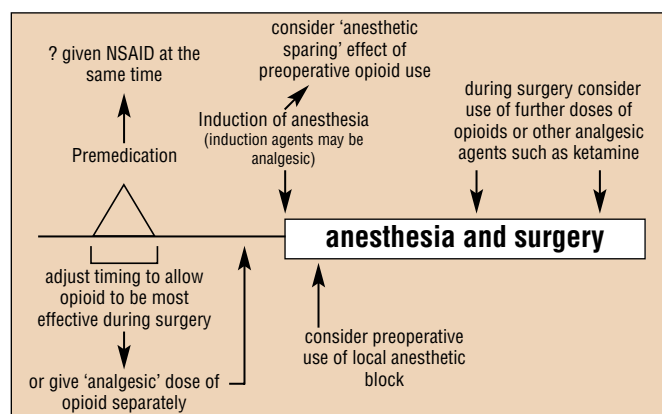


Figure 10 Diagram outlining some of the preoperative and intraoperative considerations in the use of perioperative analgesia.

occasionally precipitate acute renal failure, most notably in the dog and cat. This is due to the fact that under anesthesia, if there is a degree of relative or absolute hypovolemia, or if there is hypotension, locally produced prostaglandins help maintain renal afferent arteriolar dilation, as outlined above. The administration of a potent inhibitor of cyclooxygenase can remove the protective effect of these prostaglandins and leave the kidney vulnerable to damage. In these situations, a mild inhibitor of prostaglandin production is preferable.

Carprofen is licensed for pre- or perioperative use in companion animals in some countries. This drug appears to be a mild (dog) to moderate (cat) inhibitor of prostaglandin production (20, 21). Its mechanism of action is unknown. Experimental data and extensive clinical use have shown it to be safe and effective if given prior to anesthesia and surgery (22, 23).

A recent study has shown the preoperative administration of meloxicam is not associated with adverse changes in urea, creatinine, or ALT up to 24 hours after its injection (24).

The use of NSAIDs other than carprofen (and possibly meloxicam) for preoperative analgesia is not recommended until they have been fully investigated.

Animals receiving long-term oral NSAIDs (for chronic arthritis, for example) which require anesthesia need special attention. NSAID medication must be withdrawn 36 hours before surgery or they must be maintained on adequate rates of intravenous fluid administration to maintain normal arterial blood pressure. Intravenous fluid administration should be continued into the postoperative period, until the cardiovascular system is no longer affected by anesthetic agents and renal blood flow is considered to be normal.

PRACTICAL CONSIDERATIONS WHEN DESIGNING A 'PREEMPTIVE' ANALGESIC PROTOCOL

The three main points to bear in mind are:

- Use analgesics as early as possible.
- Use more than one class of analgesic agent (**Figure 9**).
- Match the degree of expected trauma from surgery with the doses and the duration of action of analgesics used.

First, consideration should be the choice of anesthetic agent and protocol. Only then is consideration given to which analgesics are required. For example, thiopentone provides no analgesia, but a combination of ketamine and an α adrenoceptor agonist (a combination that may be used for anesthesia during the neutering of a cat) will provide very good intra-anesthetic analgesia. However, if, in this example, the anesthetic is to be prolonged with inhalational agents, beyond the duration of action of ketamine and the α adrenoceptor agonist, provision for intra-anesthesia top-up analgesia must be made.

Second, selection of preoperative opioids. If possible, a pure μ -agonist should be chosen if severe pain is anticipated. High doses of partial agonists (such as buprenorphine) can provide very good analgesia, and top-up doses can be used. An analgesic dose should be chosen, given at the correct time prior to surgery.

- Is the single preoperative dose going to last beyond the duration of surgery, or will top-ups be required?
- Can the opioid be combined with phenothiazines to create a premedicant combination, or will a separate premedication be required?

Third, consideration is given to the preoperative use of a NSAID:

- Are there any contraindications to the use of a NSAID in the particular case? For example, concurrent steroid or NSAID therapy, preexisting renal disease or preexisting GI ulceration?
- Is the chosen drug safe when used prior to anesthesia, or is it best given after recovery from anesthesia?

Figure 10 summarizes the basic considerations to be made. A basic analgesic protocol should be worked out for each species—a protocol that is simple and workable—and then adjusted as required on an individual basis.

PRACTICAL EXAMPLES OF PERIOPERATIVE ANALGESIA

Internal fixation of femoral fracture

Approximately 20 minutes prior to surgery:

- Morphine or methadone combined with acepromazine given intramuscularly as the premedicant combination
- Carprofen given subcutaneously (or intravenously on induction of anesthesia)

During surgery:

- Doses of fentanyl used to augment the anesthetic and another dose of morphine or methadone administered 2 hours after the preoperative dose

Over the 24 hours following surgery:

- Further doses of morphine or methadone, at least every 3–4 hours if required

In the above regimen, buprenorphine could be used instead of a pure μ -agonist, but it must be administered 1 hour prior to surgery, with the rest of the premedicant. A further dose must be

administered 3 hours after the initial dose during surgery. It may be administered as required postoperatively.

Routine ovariohysterectomy

Approximately 1 hour prior to surgery:

- 20 µg/kg of buprenorphine combined with acepromazine given intramuscularly as the premedicant
- Carprofen given subcutaneously (or intravenously on induction of anesthesia)

During 24 hours following surgery:

- One more postoperative dose of buprenorphine may be required

Intussusception in a eight-week-old puppy

Approximately 20 minutes prior to surgery:

- Low dose of pethidine (1–2 mg/kg) and low dose of acepromazine given intramuscularly. The pethidine may be repeated at 2 hour intervals if required

- Low dose of carprofen (1–2 mg/kg) given subcutaneously
Over the 24 hours following surgery:

- Further doses of pethidine as required (probably every 2–3 hours)

Cesarean section in a bitch

Approximately 1–2 hours prior to surgery:

- Carprofen given subcutaneously

After the pups have been delivered:

- Buprenorphine given intravenously

- Local anesthetic injected along the site of the abdominal incision

Over the 24 hours following surgery:

- Opioids can be transferred to the pups in the milk, so further doses of opioids are usually avoided. A further half-dose of carprofen could be given within the first 24 hours if required.

REFERENCES

1. Dohoo, S. E., Dohoo, I. R. Postoperative use of analgesics in dogs and cats by Canadian veterinarians. *Canadian Veterinary Journal* 1996; **37**: 546–551.
2. Capner, C. A., Lascelles, B. D. X., Waterman-Pearson, A. E. A survey of current British veterinary attitudes to perioperative analgesia. *Veterinary Record* 1999; **145**: 95–99.
3. Quandt, J. E., Rawlings, C. R. Reducing postoperative pain for dogs: local anaesthetic and analgesic techniques. *Compendium on Continuing Education* 1996; **18**: 101–111.
4. Conzemi, M. G., Hill, C. M., Sammarco, J. L., Perkowski, S. Z. Correlation between subjective and objective measures used to determine severity of postoperative pain in dogs. *Journal of the American Veterinary Medical Association* 1997; **210**: 1619–1622.
5. Lascelles, B. D. X. Studies on the development of sensitization to acute surgical pain in the rat and dog. Doctoral Thesis, University of Bristol, 1995.
6. Lascelles, B. D. X., Cripps, P. J., Jones, A., Waterman-Pearson, A. E. Postoperative central hypersensitivity and pain: the pre-emptive value of pethidine for ovariohysterectomy. *Pain* 1997; **73**: 461–471.
7. Crile, G. W. The kinetic theory of shock and its prevention through anoci-association (shockless operation). *Lancet* 1913; **185**: 7–16.
8. Coderre, T. J., Katz, J., Vaccarino, A. L. et al. Contribution of central neuroplasticity to pathological pain: review of clinical and experimental evidence. *Pain* 1993; **52**: 259–285.
9. Woolf, C. J., Wall, P. D. Morphine-sensitive and morphine-insensitive actions of C-fibre input on the rat spinal cord. *Neuroscience Letters* 1986; **64**: 221–225.
10. Dickenson, A. H., Sullivan, A. F. Subcutaneous formalin-induced activity of dorsal horn neurons in the rat: differential response to an intrathecal opiate administration pre- or post-formalin. *Pain* 1987; **30**: 349–360.
11. Chapman, V., Dickenson, A. H. The effect of intrathecal pre- and post-treatment of lignocaine or CNQX on the formalin response of rat dorsal horn neurones. In: *Proceedings of the 7th World Meeting of the International Association for the Study of Pain*. Seattle, 1993: 469.
12. Woolf, C. J., Wall, P. D. Relative effectiveness of C primary afferent fibres of different origins in evoking a prolonged facilitation of the flexor reflex in the rat. *Journal of Neuroscience* 1986; **6**: 1433–1442.
13. Lascelles, B. D. X., Waterman, A. E., Cripps, P. J., Livingston, A., Henderson, G. Central sensitization as a result of surgical pain: investigation of the pre-emptive value of pethidine for ovariohysterectomy in the rat. *Pain* 1995; **62**: 201–212.
14. Welsh, E. M., Nolan, A. M., Reid, J. Beneficial effects of administering carprofen before surgery in dogs. *Veterinary Record* 1997; **141**: 251–253.
15. Lascelles, B. D. X., Cripps, P. J., Jones, A., Waterman-Pearson, A. E. Efficacy and kinetics of carprofen, given pre- or postoperatively, for the prevention of pain in dogs undergoing ovariohysterectomy. *Veterinary Surgery* 1998; **27**: 568–582.
16. Waterman, A. E., Kalthum, W. Pharmacokinetics of intramuscularly administered pethidine in dogs and the influence of anaesthesia and surgery. *Veterinary Record* 1989; **124**: 293–296.
17. Dodman, N. H., Clark, G. H., Court, M. H., Fikes, L. L., Boudrieau, R. J. Epidural Opioid Administration For Postoperative Pain Relief In The Dog. In: Short, C. E., Van Poznak, A. (eds.) *Animal Pain*. New York: Churchill Livingstone, 1992: 274–277.
18. Pascoe, P. J., Dyson, D. H. Analgesia after lateral thoracotomy in dogs; Epidural versus intercostal bupivacaine. *Veterinary Surgery* 1993; **22**: 141–147.
19. Konturek, S. J., Piastuki, I., Brzozowski, T. Role of prostaglandins in the formation of aspirin-induced gastric ulcers. *Gastroenterology* 1981; **80**: 4–9.
20. McKellar, Q. A., Pearson, T., Bogan, J. A. et al. Pharmacokinetics, tolerance and serum thromboxane inhibition of carprofen in the dog. *Journal of Small Animal Practice* 1990; **31**: 443–448.
21. McKellar, Q. A., Delatour, P., Lees, P. Stereospecific pharmacodynamics and pharmacokinetics of carprofen in the dog. *Journal of Veterinary Pharmacology and Therapeutics* 1994; **17**: 447–454.
22. Nolan, A., Reid, J. Comparison of the postoperative analgesic and sedative effects of carprofen and papaveretum in the dog. *Veterinary Record* 1993; **133**: 240–242.
23. Lascelles, B. D. X., Butterworth, S. J., Waterman, A. E. Postoperative analgesic and sedative effects of carprofen and pethidine in dogs. *Veterinary Record* 1994; **134**: 187–191.
24. Healy, A., Schmidt, H. Efficacy and safety of Metacam (meloxicam) in the control of perioperative pain in the dog. Poster presentation at the European Association of Veterinary Pharmacology and Therapeutics/European College of Veterinary Pharmacology and Therapeutics workshop on 'Pain and inflammation'. London, 1998.

