Many perioperative pain management protocols for cats and dogs are overly complex, some are ineffective, and still others expose patients to unnecessary risk. The purpose of this article is to provide clinicians with a basic understanding of the pathophysiology of perioperative pain and a working knowledge of the principles of effective therapy. First, the concept of multimodal analgesic therapy is discussed. Next, the pathophysiology of perioperative pain and the clinical pharmacology of the major classes of analgesic drugs are reviewed. And last, a simplified approach to managing perioperative pain in cats and dogs is presented.

Keywords: analgesia, anesthesia, pain, dogs, cats
clinical pharmacology of the major classes of analgesic drugs is required to use multimodal analgesic therapy safely and effectively in anesthetized patients.

Pathophysiology

The terminology used to describe the pathophysiology of pain is confusing, so defining a few terms relevant to the management of perioperative pain is important. Nociception is defined as the neural response to a noxious stimulus. Specifically, nociception includes signal transduction and nerve conduction in the peripheral nervous system, and synaptic transmission, projection, and modulation of nociceptive input in the central nervous system (Fig 1). Pain, on the other hand, is a complex sensation that requires integration of nociceptive and other sensory input at the cortical level. Pain is defined as an unpleasant sensory or emotional experience that is associated with actual or potential tissue damage. Pain can be further classified anatomically as somatic or visceral pain, or temporally as acute or chronic pain. Recent neuroanatomical and functional imaging studies suggest that pain is one component of an interoceptive system that is primarily responsible for maintaining internal homeostasis, and that there are significant differences among species in the neural components that make up this system.11

Most perioperative pain is due to surgical trauma and inflammation. Some patients may have preexisting tissue trauma and inflammation, and others may have pain associated with nerve injury. Although a small number of surgical patients may experience both inflammatory and neuropathic pain, inflammatory pain is by far the most common type of perioperative pain. The mechanisms of inflammatory pain are reasonably well understood and form the basis for rational, effective, multimodal analgesic therapy. Neuropathic pain is relatively uncommon in surgical patients, and the mechanisms of neuropathic pain are similar to those of inflammatory pain.12,13 Consequently, clinicians should focus on understanding the pathophysiology and management of inflammatory pain.

Nociceptive Pathways

Ascending nociceptive pathways begin in the peripheral tissues and project to the dorsal horn of the spinal cord, brainstem, thalamus, and cerebral cortex (Fig 1). The nociceptive pathways are composed of 3 general types of neurons. The first-order neurons are primary afferent neurons, and these neurons are responsible for transduction of noxious stimuli and conduction of electrical signals to the dorsal horn of the spinal cord. The second-order neurons are projection neurons, and these neurons receive input from the primary afferent neurons and project to the medulla, pons, midbrain, thalamus, and hypothalamus. Third-order supraspinal neurons integrate input from spinal neurons and project to subcortical and cortical areas where pain is finally perceived. Supraspinal processing of afferent nociceptive input is also

Figure 1. Overview of nociceptive and antinociceptive pathways. Surgical trauma activates mechanical, chemical, and thermal nociceptors. Action potentials are conducted to the dorsal horn of the spinal cord by primary afferent nerve fibers. Second-order projection neurons encode and relay signals to the brainstem and thalamus. Third-order neurons in the thalamus project to the limbic system and somatosensory cortex where pain is perceived. Descending antinociceptive pathways modulate nociceptive processing at the level of the thalamus, brainstem, and spinal cord. Different classes of analgesic drugs act at different sites in the nociceptive and antinociceptive pathways. Multimodal analgesic therapy inhibits processing of nociceptive input at 2 or more sites. PAG, periaqueductal gray; RVM, rostroventral medulla.
closely integrated with regulation of the autonomic nervous system.

Primary afferent neurons are bipolar neurons. The cell bodies of these bipolar neurons are located in the trigeminal and dorsal root ganglia, and their axons project peripherally to somatic and visceral tissues and centrally to the dorsal horn of the spinal cord. Some primary afferent neurons respond to noxious or high-threshold stimuli, and others respond to non-noxious or low-threshold stimuli (touch). Afferent nociceptive neurons have free nerve endings that change or “transduce” noxious mechanical, thermal, or chemical stimuli into electrical signals. Somatic tissues have a higher density of nociceptive nerve fibers and smaller receptive fields, whereas visceral tissues have a lower density of nociceptive nerve fibers and larger receptive fields. These anatomical differences may account for some of the qualitative differences between somatic (discrete) and visceral (diffuse) pain.

Primary afferent somatic are classified by axon diameter, the presence or absence of myelination, and their response to mechanical, thermal, and chemical stimuli. Aβ afferent neurons have large, myelinated axons that conduct impulses at a velocity of greater than 30 m/sec. The free nerve endings of these fibers respond to non-noxious mechanical stimuli (touch) but do not respond to noxious stimuli directly. Aδ nociceptive neurons have small, myelinated axons that conduct impulses at a velocity of 3 to 30 m/sec. The free nerve endings of these fibers contain membrane-bound receptors that respond primarily to intense mechanical and thermal stimuli and are called mechanothermal nociceptors. C nociceptive neurons have small, unmyelinated axons that conduct nerve impulses at a velocity of less than 3 m/sec. The free nerve endings of these fibers contain membrane-bound receptors that respond to chemical as well as thermal and mechanical stimuli and are called polymodal nociceptors. Small, myelinated Aδ fibers carry the nociceptive input responsible for the fast, sharp pain that occurs immediately after injury. The nociceptive input responsible for the prolonged dull pain that occurs several seconds later is carried by small, unmyelinated C fibers. Silent nociceptive neurons are also present in somatic tissues. The free nerve endings of these neurons only respond to mechanical and thermal stimuli after they are activated by chemical (inflammatory) mediators. This classification scheme is derived from analysis of fibers that innervate the somatic tissues (skin). Viscerale pain is qualitatively different from somatic pain and is typically dull and poorly localized. Visceral pain also lacks the fast and slow components that are characteristic of somatic pain.

Transduction of mechanical, thermal, and chemical stimuli by the free nerve endings of Aδ and C nociceptive fibers is mediated by membrane-bound receptors. Most of these receptors are nonselective cation channels that are gated by temperature, chemical ligands, or mechanical shearing forces. Activation of these channels increases inward conduction of Na⁺ and Ca²⁺ ions, which ultimately depolarizes the membrane and generates a burst of action potentials. The mechanisms of mechanical signal transduction are not well defined. Noxious mechanical stimuli may activate a mechanically gated ion channel directly, or shearing forces may release adenosine triphosphate, which acts on purine receptors (P2X). Noxious chemical stimuli (H⁺) activate acid-sensing ion channels and transient receptor potential vanilloid (TRPV1) channels. Noxious heat also activates TRPV1 channels as well as related channels (TRPV2), and noxious cold activates transient receptor potential menthol (TRPM8) channels.

Nociceptive afferent neurons synapse with second-order neurons in the dorsal horn of the spinal cord.Projection neurons and interneurons are the 2 major types of nociceptive neurons in the dorsal horn, and these neurons are organized in layers or laminae. Neurons that mediate nociception are located in laminae I, II, and V. Projection neurons are located in laminae I and V, and they have axons that cross midline and project to third-order supraspinal neurons. Projection neurons located in lamina I receive input directly from Aδ and C nociceptive fibers and are classified as nociceptive-specific and polymodal nociceptive neurons, respectively. Projection neurons in lamina V receive input from both nociceptive and non-nociceptive (Aβ) fibers and are classified as wide, dynamic-range neurons. Interneurons are located in lamina II and also receive input from nociceptive and non-nociceptive (Aβ) fibers. Inhibitory and excitatory interneurons play a central role in gating and modulating nociceptive input. Propriospinal neurons that project across several dermatomes are also present in the dorsal horn and are responsible for segmental reflexes associated with nociception.

Glutamate is the primary excitatory neurotransmitter in the dorsal horn of the spinal cord. Nociceptive as well as non-nociceptive fibers co-release glutamate and neuropeptides (substance P, neurokinin A, calcitonin gene–related peptide). With normal afferent input, glutamate binds to α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors located on the postsynaptic membrane of projection neurons. Neuropeptides bind to several types of receptors on the postsynaptic membrane. With intensive afferent input, prolonged activation of AMPA and neuropeptide receptors leads to progressive depolarization of the postsynaptic membrane and activation of additional types of glutamate receptors. Activation of a specific type of glutamate receptor, the NMDA receptor, plays a key role in the development of central sensitization.

The spinothalamic tract (STT) is the major ascending nociceptive pathway in carnivores and primates. Lamina I, nociceptive (nociceptive-specific, polymodal nociceptive) neurons are somatotopically organized, modality-selective neurons with small receptive fields that convey discrete noxious mechanical, thermal, and chemical afferent input. These neurons project to the ventromedial nucleus of the lateral thalamus, which projects to the insular cortex and the secondary somatosensory cortex. These neurons also project to the mediodorsal nucleus of the medial thalamus, which projects to the anterior cingulate cortex. Like the dorsal horn, glutamate is an important excitatory neurotransmitter within the thalamic nuclei. Lamina V, wide, dynamic-range
neurons have large receptive fields, are not somatotopically organized or modality selective, and are responsible for integration of all afferent input to the dorsal horn. These neurons project to the motor thalamus (ventrodorsal and ventrolateral nuclei), which projects to the basal ganglia and the primary somatosensory cortex. Axons from lamina I are concentrated in the lateral STT, and axons from lamina V are concentrated in the ventral STT. The thalamus relays afferent input from the STT and integrates this information with afferent input from the autonomic nervous system. Projection from neurons in the lateral thalamus to neurons in the insular and secondary somatosensory cortex appears to be responsible for the sensory-discriminative aspects of pain. Projection from neurons in the medial thalamus to neurons in the anterior cingulate cortex appears to be responsible for the motivational-affective aspects of pain. Projection from neurons in the motor thalamus to neurons in the primary somatosensory cortex appears to be responsible for sensory and motor integration. Direct connections between the lateral thalamus and the dorsal margin of the insular cortex (interoceptive cortex) are more developed in primates than in carnivores.

**Antinociceptive Pathways**

Mammals also have descending antinociceptive pathways that modulate nociceptive input at spinal and supraspinal levels (Fig 1). The antinociceptive pathways begin at the supraspinal level and project to neurons in the dorsal horn of the spinal cord. The periaqueductal gray matter (midbrain), locus ceruleus (pons), and nucleus raphe magnus (medulla) are all important structures in the modulation of nociceptive input. The periaqueductal gray matter receives direct input from the thalamus and the hypothalamus, and indirect input from the insular cortex and the anterior cingulate cortex. These neurons in the periaqueductal gray matter send projections to neurons in the nucleus raphe magnus, which project to the dorsal horn of the spinal cord. Neurons in the locus ceruleus project directly to the dorsal horn, and they may also receive input from the periaqueductal gray matter.

Endogenous opioids (endorphins, enkephalins, dynorphins), serotonin, and norepinephrine are the primary neurotransmitters in the descending antinociceptive pathways. Axons that originate in the nucleus raphe magnus release serotonin in the dorsal horn of the spinal cord and are called “serotonergic” neurons. Similarly, neurons that originate in the locus ceruleus release norepinephrine in the dorsal horn and are called “noradrenergic” neurons. Supraspinal release of endogenous opioid peptides activates both types of neurons, whereas supraspinal release of release of γ-aminobutyric acid (GABA) inhibits both types of neurons. Supraspinal inhibition of descending antinociceptive pathways is mediated by GABA_A receptors. At the supraspinal level, endogenous opioids not only activate descending antinociceptive pathways, but inhibit GABA-mediated inhibition of these same pathways, which is called “disinhibition.”

Release of norepinephrine and serotonin in the dorsal horn of the spinal cord, and subsequent release of enkephalins and GABA by local interneurons, inhibit presynaptic calcium channels that modulate neurotransmitter release. This inhibition, mediated by presynaptic noradrenergic (α₂), opioid (μ), and GABA_A receptors, limits release of glutamate and neuropeptides from primary afferent neurons, which inhibits nociceptive transmission. Release of norepinephrine, enkephalins, and GABA in the dorsal horn hyperpolarizes projection neurons, which also inhibits nociceptive transmission. This inhibition is mediated by postsynaptic noradrenergic (α₂) and opioid (μ) receptors that activate potassium channels, which leads to an outward flux of potassium ions and hyperpolarization of the postsynaptic membrane. This inhibition is also mediated by postsynaptic GABA_A receptors that activate chloride channels, which leads to an inward flux of chloride ions and hyperpolarization of the postsynaptic membrane. In summary, release of norepinephrine, endogenous opioids, and GABA inhibits synaptic transmission between primary afferent neurons and projection neurons by inhibiting neurotransmitter release and hyperpolarizing the postsynaptic membrane, which effectively shuts down the key synapse in the dorsal horn.

**Peripheral and Central Sensitization**

Neural plasticity is defined as the ability of the nervous system to modify its function in response to different environmental stimuli. Surgical trauma and inflammation produce sensitization of the peripheral nervous system, and the subsequent barrage of nociceptive input produces sensitization of neurons in the dorsal horn of the spinal cord. Peripheral and central sensitization of nociceptive pathways plays a central role in the development of pathological pain.17 Patients with no preexisting tissue trauma and inflammation experience pain that is physiological or protective in nature (Table 1). This type of inflammatory pain is well localized, proportionate to the peripheral stimulus, and subsides once the inflammatory process resolves. Patients with significant tissue trauma and inflammation experience pain that is pathological or debilitating in nature (Table 2). This type of inflammatory pain is diffuse, disproportionate to the peripheral stimulus, and continues beyond resolution of the inflammatory process. A key concept that is often lost when trying to understand the clinical relevance of neural plasticity is that central sensitization occurs secondary to surgical trauma, inflammation, and the development of peripheral sensitization.

**Table 1. Characteristics of Physiological Pain**

- Protective
- Discrete or well localized
- No peripheral or central sensitization
- Proportionate to the peripheral stimulus
- Subsides once the inflammatory response resolves
- Pain can be differentiated from touch
- Responds well to conventional analgesic therapy
Phase of central sensitization is called short-term sensitization. If the inflammatory process continues for several days, gene regulatory proteins are activated, new types receptors are expressed, and dorsal horn projection neurons become even more reactive to subsequent nociceptive input. This phase of central sensitization is called long-term sensitization. Activation of NMDA receptors and the subsequent influx of $\text{Ca}^{2+}$ also leads to the release of arachidonic acid, which is converted to prostaglandins by COX. Prostaglandins act presynaptically and postsynaptically to facilitate the development of central sensitization. Glial cells also appear to facilitate the development of central sensitization. Microglia and astrocytes normally play a supportive role in neurotransmission, but they are also activated by glutamate and neuropeptides released from primary afferent fibers. Activated glial cells release adenosine triphosphate, glutamate, nitric oxide, and cytokines, which facilitate release of neurotransmitters from afferent fibers and further sensitization of projection neurons.

**Clinical Pharmacology**

The primary goal of perioperative multimodal analgesic therapy is to limit the development of peripheral and central sensitization, and prevent the development of pathological pain. Effective analgesic therapy also blunts the neuroendocrine response, reduces major complications, and improves outcome. There are 5 major classes of analgesic drugs, and each class blocks or modulates nociceptive input at one or more sites of action (Fig 1). Alpha-2 agonists and opioids alter the central perception of pain. Activation of supraspinal and spinal alpha-2 receptors and opioid receptors also inhibits synaptic transmission in the dorsal horn of the spinal cord. Dissociative anesthetics (ketamine) block NMDA receptors on projection neurons, which inhibit the development of central sensitization. Peripheral and central neural blockade with local anesthetics also inhibits the development of central sensitization. COX inhibitors reduce inflammation, which limits the development of peripheral sensitization. COX inhibitors also reduce the synthesis of prostaglandins in the dorsal horn of the spinal cord, which limits the development of central sensitization.

**Selective Alpha-2 Agonists**

Norepinephrine is the endogenous ligand for spinal and supraspinal alpha-2 adrenergic receptors. Medetomidine and dexmedetomidine are the selective alpha-2 agonists currently available in North America. Medetomidine is supplied as a racemic mixture of 2 optical enantiomers. Dexmedetomidine is the active enantiomer, whereas levomedetomidine has no apparent pharmacological activity. As a result, dexmedetomidine is approximately twice as potent as medetomidine. The clinical effects of medetomidine and dexmedetomidine are comparable when equivalent sedative doses are administered to cats and dogs. Medetomidine has a rapid onset after parenteral injection, and the drug has a duration of action of...
Selective alpha-2 agonists induce reliable dose-dependent sedation, analgesia, and muscle relaxation in cats and dogs. The sedative and analgesic effects of selective alpha-2 agonists are mediated by activation of alpha-2 adrenergic receptors located in the pons (locus ceruleus) and the dorsal horn of the spinal cord, respectively. In addition to providing sedation and analgesia, preoperative administration of medetomidine reduces the amount of intravenous and inhalation anesthetic required to induce and maintain anesthesia. Perioperative administration of selective alpha-2 agonists also blunts the neuroendocrine response and reduces catecholamine and cortisol levels. Blood pressure increases, and heart rate and cardiac output decrease after medetomidine administration. Bradycardia and atrioventricular blockade are potential complications, and heart rate and rhythm should be monitored closely. Medetomidine does not sensitize the myocardium to catecholamines or facilitate development of ventricular arrhythmias in patients anesthetized with isoflurane. Respiratory rate and minute ventilation are well maintained after administration of medetomidine and dexmedetomidine in conscious and anesthetized dogs. Preoperative hyperthermia in cats. Morphine and hydromorphone are often administered as preanesthetics, and vomiting can occur with either drug. High doses of hydromorphone (> 0.1 mg/kg) can also cause significant postoperative hyperthermia in cats. Morphine and hydromorphone have an intermediate duration of action (2-4 hours) after parenteral administration. The preanesthetic intramuscular dose range for morphine in cats and dogs is 0.2 to 0.4 mg/kg. Hydromorphone is approximately 5 times more potent than morphine, and the preanesthetic intramuscular dose range for hydromorphone in cats and dogs is 0.05 to 0.1 mg/kg. Approximately half of the preanesthetic dose of morphine or hydromorphone can be given intraoperatively or postoperatively. Morphine can also be given epidurally alone or in combination with local anesthetics. The dose range for preoperative or postoperative epidural administration of morphine is 0.1-0.3 mg/kg. At this dose range, the onset time is slow (1-2 h), but the duration of action in long (12-24 h). Morphine can also be given postoperatively as an intravenous constant-rate infusion at a dose range of 0.1 to 0.2 mg/kg/h. Morphine has a relatively long duration of action and the drug will accumulate over time. As a result, patients should be monitored closely, and the infusion rate should be reduced as needed. Fentanyl can also be given intravenously as a preanesthetic. The drug is approximately 100 times more potent than morphine and has a relatively short duration of action (0.5 hour). The preanesthetic intravenous dose range for fentanyl in cats and dogs is 0.001 to 0.003 mg/kg. Fentanyl is less likely to accumulate over time, and the drug is often given intraoperatively to dogs as an intravenous constant rate infusion. The amount of inhalation anesthetic required to maintain adequate anesthetic depth is reduced by 30% to 50%, which improves cardiovascular function. Minute ventilation may decrease, and positive-pressure ven-
tilation may be required to prevent significant hypoventilation $(P_{\text{a}}CO_2 < 60 \text{ mm Hg})$. Intraoperatively, the dose range for fentanyl in dogs is $0.005$ to $0.01 \text{ mg/kg/h}$. Fentanyl can also be given postoperatively as an intravenous constant-rate infusion at a dose range of $0.001$ to $0.005 \text{ mg/kg/h}$. Objective clinical data on the use of intraoperative and postoperative fentanyl infusions in cats are limited.

Fentanyl patches were designed to be applied to human skin. Even in healthy cats and dogs, systemic absorption of fentanyl from transdermal patches is erratic.$^{43,44}$ In surgical patients, altered body temperature, peripheral circulation, and hydration can all compromise transdermal absorption of fentanyl. On the other hand, heating pads and forced-air warmers can dramatically increase fentanyl absorption intraoperatively and postoperatively. Consequently, preoperative and intraoperative use of fentanyl patches should be avoided. Once normal body temperature, peripheral circulation, and hydration are restored, fentanyl patches can be used postoperatively with reasonable efficacy. Onset time is very slow, and there is a 12- to 24-hour lag before effective plasma concentrations are reached. If the patch stays properly adhered to on the patient, plasma fentanyl concentrations are maintained for 3 to 5 days. Transdermal fentanyl is dosed at a rate of $0.003$ to $0.005 \text{ mg/kg/h}$ in cats and dogs.

Opioid agonist-antagonists are also used to manage perioperative pain in cats and dogs. Butorphanol is the opioid agonist-antagonist used most commonly in small animals. Butorphanol is an agonist at the $\mu$ receptor and an antagonist or partial agonist at the $\kappa$ receptor. The analgesia produced by butorphanol is not as profound as that produced by opioid agonists, and its duration of action is relatively short (1-2 hours). However, side effects (vomiting, respiratory depression, bradycardia) are less likely to occur after administration of butorphanol than after administration of morphine, hydromorphone, or fentanyl. Intraoperative administration of butorphanol also reduces isoflurane requirements by 10% to 20% in cats and dogs.$^{36,45}$ Butorphanol can be used perioperatively to manage mild to moderate pain. The preanesthetic intramuscular dose range for butorphanol in cats and dogs is 0.2 to 0.4 mg/kg. Approximately half of the preanesthetic dose can be given intraoperatively or postoperatively. Butorphanol can be given postoperatively as an intravenous constant-rate infusion at a dose range of 0.1 to 0.2 mg/kg/h. Small intravenous doses of butorphanol (0.1 mg/kg) can also be given postoperatively to reverse sedation and respiratory depression caused by administration of excessive doses of opioid agonists.

**NMDA Antagonists**

Glutamate is the endogenous agonist for spinal and supraspinal NMDA receptors. Blockade of NMDA receptors in the dorsal horn of the spinal cord prevents windup and the development of central sensitization. Ketamine is the most widely used NMDA antagonist in veterinary medicine. Ketamine is supplied as a racemic mixture of 2 optical enantiomers. $S(+)$ ketamine has 4 times the affinity of $L(-)$ ketamine for the NMDA receptor and has a shorter duration of action. The clinical analgesic potency of $S(+)$ ketamine is approximately twice that of the racemic mixture. Nonracemic mixtures of ketamine may be available for use in small animals in the near future.

Ketamine can be used to manage pain throughout the perioperative period at anesthetic and subanesthetic doses.$^{46}$ Intravenous or intramuscular administration of anesthetic doses produces “dissociative” anesthesia with poor muscle relaxation in both cats and dogs. Cardiovascular effects are limited, and ventilation is better maintained than with other anesthetic drugs. Dysphoria and seizures can also occur after administration of high doses of ketamine, but dysphoria is less severe or absent at low subanesthetic or analgesic doses. The anesthetic effects of ketamine last for approximately 30 minutes, but motor effects can persist for several hours. Intravenous administration of ketamine at an infusion rate of 0.6 mg/kg/h decreases isoflurane requirements by 25%.$^{37}$ Intraoperative and postoperative administration of ketamine also reduces pain scores in dogs after forelimb amputation.$^{47}$ Because of the potential for dysphoria, opioid infusions are a better choice for most patients than opioid-ketamine infusions or ketamine infusions alone. However, patients with significant preexisting central sensitization or those undergoing major procedures with significant surgical trauma may benefit from intraoperative and postoperative opioid-ketamine infusions. Intraoperatively, the intravenous infusion dose range for cats and dogs is 0.4 to 0.6 mg/kg/h. Postoperatively, a lower intravenous infusion dose range of 0.2 to 0.3 mg/kg/h is used to avoid dysphoria and motor effects. An intravenous bolus of 0.5 to 1.0 mg/kg can be given as a loading dose or to provide short-term analgesia.

**Local Anesthetics**

Local anesthetics have the unique ability to produce complete blockade of sensory nerve fibers and prevent the development of central sensitization. Consequently, peripheral and central neural blockade are often used in combination with other analgesic and anesthetic drugs to manage perioperative pain. Local anesthetics block the generation and conduction of nerve impulses by inhibiting voltage-gated sodium channels in nerve fibers. Lidocaine is also given systemically to manage pain and to reduce ileus after abdominal surgery. The mechanism of action of systemic administration of lidocaine is unclear, but peripheral, central, and antiinflammatory mechanisms have been proposed.$^{48}$

Lidocaine, mepivacaine, and bupivacaine are the local anesthetics used most commonly in cats and dogs. Lidocaine has a fast onset (10 minutes) and a short duration of action (1-2 hours) and is used for short diagnostic and surgical procedures. Mepivacaine is similar to lidocaine in potency and onset, but has a longer duration of action (2-3 hours), causes less tissue irritation, and has a higher therapeutic index. Bupivacaine is approximately 4 times the potency of lidocaine and mepivacaine, has a slow onset (20 minutes), and a long duration of action (4-6 hours) and is used for most
surgical procedures. Aminoamide local anesthetics are highly protein-bound and are metabolized primarily by the liver. Consequently, anemic and hypoproteinemic patients are more susceptible to local anesthetic toxicity. As a result, the clearance of lidocaine is significantly reduced in patients with low cardiac output. Local anesthetics are relatively safe if they are used correctly. Administration of an excessive dose and accidental intravenous administration are the most common causes of systemic toxicity in small animals. As a general rule, the total dose of lidocaine or bupivacaine should not exceed 8 mg/kg or 2 mg/kg, respectively. Clinicians should always consider including peripheral or central neural blockade in their perioperative pain management plans. These techniques reduce inhalation anesthetic requirements, attenuate the neuroendocrine response to surgical trauma, and improve outcome. Local anesthetic techniques for cats and dogs are described in detail in several recent articles.4,49,50

Systemic administration of lidocaine can be used perioperatively to reduce inhalation anesthetic requirements, to provide analgesia, to control ventricular arrhythmias, and to manage postoperative ileus. Intravenous administration of lidocaine at a rate of 3 mg/kg/h reduces isoflurane requirements by 20% to 30%.37,51 Intravenous loading doses of 1 to 2 mg/kg are appropriate for most dogs. Intraoperatively, the intravenous infusion dose range for dogs is 4 to 6 mg/kg/h. Postoperatively, a lower intravenous infusion dose range of 2 to 3 mg/kg/h is used to provide analgesia and to improve gastrointestinal motility. Objective clinical data on the use of intraoperative and postoperative lidocaine infusions in cats are limited.

COX Inhibitors

Prostaglandins play a central role in inflammation and the development of peripheral sensitization. Production of prostaglandins in the dorsal horn of the spinal cord also contributes to the development of central sensitization. Inhibition of constitutive (COX-1) and inducible (COX-2) cyclooxygenase inhibits the conversion of arachadonic acid to prostaglandins and thromboxanes and produces a peripheral antiinflammatory effect. In the dorsal horn, inhibition of COX produces a central analgesic effect. COX inhibitors vary in their selectivity for the different isoenzymes, as well as their ability to produce central analgesic and antiinflammatory effects.52,53

Several COX inhibitors are approved for perioperative use in cats and dogs. COX inhibitors are usually given postoperatively alone or in combination with opioids. Parenteral formulations of ketoprofen, meloxicam, and carprofen are available in Canada and the United States and are better suited for perioperative administration. Ketoprofen has a rapid onset (0.5 hour), a short half-life, and an intermediate duration of action (12 hours). The drug inhibits platelet function but does not appear to prolong bleeding time in healthy animals undergoing elective surgery.54 Ketoprofen can be given subcutaneously to cats and dogs immediately after surgery at a dose of 2 mg/kg. Therapy with ketoprofen can be continued at a dose of 0.5 mg/kg twice daily for 3 to 5 days. Meloxicam and carprofen have a slow onset time (1-2 hours) and a long duration of action (24 hours). These drugs do not appear to inhibit platelet function and do not prolong bleeding time in healthy animals. Meloxicam can be given subcutaneously to dogs immediately after surgery at a dose of 0.2 mg/kg. Therapy with meloxicam can be continued at a dose of 0.1 mg/kg once daily for 3 to 5 days. Carprofen can be given subcutaneously to dogs immediately after surgery at a dose of 4 mg/kg. Therapy with carprofen can be continued at a dose of 4 mg/kg once daily for 3 to 5 days. Deracoxib is also labeled for perioperative use in dogs, but no parenteral formulation is available. Side effects are not usually a problem in healthy animals with normal platelet, gastrointestinal, and renal function. There is little benefit to preoperative administration of COX inhibitors, and there is significant risk for patients with compromised platelet and renal function.
<table>
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<tr>
<th>Surgical Procedure</th>
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<tr>
<td>Castration (Protocol 1)</td>
<td>Premedication: Acepromazine: 0.1-0.2 mg/kg, IM; Butorphanol: 0.2-0.4 mg/kg, IM</td>
<td>Induction and maintenance: Ketamine: 10-15 mg/kg, IM</td>
<td>Ketoprofen: 2.0 mg/kg, SC immediately after recovery from anesthesia</td>
<td>Mild pain</td>
</tr>
<tr>
<td>Castration (Protocol 2)</td>
<td>Premedication: Medetomidine: 0.01-0.02 mg/kg, IM†; Butorphanol: 0.2-0.4 mg/kg, IM</td>
<td>Induction and maintenance: Ketamine: 5-10 mg/kg, IM</td>
<td>Ketoprofen: 2.0 mg/kg, SC immediately after recovery from anesthesia</td>
<td>Mild pain</td>
</tr>
<tr>
<td>Ovariohysterectomy (Protocol 1)</td>
<td>Premedication: Acepromazine: 0.1-0.2 mg/kg, IM; Hydromorphone: 0.05-0.1 mg/kg, IM</td>
<td>Induction: Thiopental: 8-12 mg/kg, IV to effect; Isoflurane: 3%; Maintenance: Isoflurane: 1.5%-2.5%</td>
<td>Ketoprofen: 1.0 mg/kg, PO once daily for 2-3 days</td>
<td>Moderate pain; Some patients may require additional hydromorphone postoperatively.</td>
</tr>
<tr>
<td>Ovariohysterectomy (Protocol 2)</td>
<td>Premedication: Medetomidine: 0.01-0.02 mg/kg, IM†; Hydromorphone: 0.05-0.1 mg/kg, IM; Glycopyrrolate: 0.01 mg/kg, IM</td>
<td>Induction: Thiopental: 4-6 mg/kg, IV to effect; Isoflurane: 3%; Maintenance: Isoflurane: 1.0%-2.0%</td>
<td>Ketoprofen: 1.0 mg/kg, PO once daily for 2-3 days</td>
<td>Moderate pain; Some patients may require additional hydromorphone postoperatively.</td>
</tr>
<tr>
<td>Onychectomy (Protocol 1)</td>
<td>Premedication: Acepromazine: 0.1-0.2 mg/kg, IM; Hydromorphone: 0.05-0.1 mg/kg, IM</td>
<td>Induction: Propofol: 4-6 mg/kg, IV to effect; Isoflurane: 3%; Maintenance: Isoflurane: 1.5%-2.5%; Digital nerve block: 0.5% bupivacaine: 0.5-1.0 mL; Do not exceed a total dose of 2 mg/kg.</td>
<td>Ketoprofen: 2.0 mg/kg, SC immediately after recovery from anesthesia</td>
<td>Moderate pain; Digital nerve block reduces anesthetic requirements and improves analgesia postoperatively.</td>
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Clinical Management

Multimodal analgesia is not a difficult concept to understand, nor is it a difficult concept to put into practice. In the perioperative setting, a multimodal analgesic protocol is simply a balanced anesthetic and pain management protocol (Fig 2). At first glance, the notion that analgesic drugs should be given to anesthetized patients that are unable to consciously perceive pain seems irrational. However, most intravenous (propofol) and inhalation (isoflurane, sevoflurane) anesthetics simply produce unconsciousness and do not substantially alter nociceptive processing. In fact, autonomic responses (sudden changes in respiratory rate, heart rate, and blood pressure) that occur during surgery as a result of noxious stimulation usually reflect inadequate analgesia rather than insufficient anesthetic depth. The safest approach for most patients is to limit the amount of inhalation anesthetic required by providing supplemental intraoperative analgesic therapy with opioids and local anesthetic techniques.

After initial assessment of analgesic requirements and identification of major anesthetic risk factors, drugs are selected to minimize risk and to provide optimal anesthetic and pain management throughout the perioperative period. Patient monitoring and supportive care are also selected to optimize cardiopulmonary function and to minimize anesthetic risk. Hypoventilation ($P_{CO_2} > 60$ mm Hg), hypotension (mean arterial pressure < 60 mm Hg), and bradycardia are common perioperative complications. Care should be taken to avoid or reduce doses of anesthetic and analgesic drugs that have similar side effects. Opioids and inhalation anesthetics can induce significant respiratory depression. Acepromazine, inhalation anesthetics, and epidural anesthesia can cause significant hypotension. Alpha-2 agonists and opioids can cause bradycardia and enhance oculovagal and viscerovagal reflexes triggered by surgical manipulation. Given the potential for significant intraoperative complications, there is no substitute for diligent patient monitoring by a qualified, experienced anesthetist.

The type of surgery (invasive vs minimally invasive) and the surgical site (somatic vs visceral) should also be considered when developing anesthetic and pain management plans. Pain must be managed aggressively throughout the perioperative period in patients scheduled for invasive surgical procedures, whereas postoperative administration of COX inhibitors may be appropriate for patients scheduled for minimally invasive procedures. Peripheral or central neural blockade is appropriate for most patients scheduled for surgical procedures of the front or hind limbs and for those scheduled for dental procedures. Conversely, complete blockade of nociceptive input from somatic and visceral afferents may be impossible to achieve in patients scheduled for thoracic or abdominal surgical procedures.

Perioperative use of analgesic drugs and techniques reduces the doses of intravenous and inhalation anesthetics required to induce and maintain anesthesia, improves cardiopulmonary function during surgery, and promotes a smooth recovery from anesthesia after surgery. These analgesic drugs

<table>
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<tr>
<th>Surgical Procedure</th>
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<th>Intraoperative Management</th>
<th>Postoperative Management</th>
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</thead>
<tbody>
<tr>
<td>Onychectomy</td>
<td>Medetomidine: 0.01-0.02 mg/kg, IM†</td>
<td>Propofol: 2-3 mg/kg, IV to effect</td>
<td>Ketoprofen; 2.0 mg/kg, SC immediately after recovery from anesthesia</td>
<td>Ketoprofen; 1.0 mg/kg, PO once daily for 2-3 days</td>
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<td></td>
<td>Hydromorphone: 0.05-0.1 mg/kg, IM†</td>
<td>Isoflurane: 3%</td>
<td>Digital nerve block 0.5% Bupivacaine: 0.5-1.0 mL</td>
<td>Do not exceed a total dose of 2 mg/kg.</td>
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<tr>
<td></td>
<td>Glycopyrrolate: 0.01 mg/kg, IM†</td>
<td>Maintenance: 1.0%-2.0%</td>
<td>Digital nerve block</td>
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<td>Ketoprofen: 0.01-0.02 mg/kg, SC, IM†</td>
<td>Isoflurane: 0.5-0.1 mg/kg, IM†</td>
<td>Do not exceed a total dose of 2 mg/kg.</td>
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Abbreviations: IM, Intramuscularly; IV, intravenously; SC, subcutaneously; PO, by mouth.

*Some of these drugs are not approved for use in cats in Canada or the United States.
†Dexmedetomidine can be substituted at approximately half the medetomidine dose.

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<td>Castration (Protocol 1)</td>
<td>Premedication: Acepromazine: 0.05-0.1 mg/kg, IM, Butorphanol: 0.2-0.4 mg/kg, IM</td>
<td>Induction: Propofol: 4-6 mg/kg, IV to effect Isoflurane: 3%</td>
<td>Ketoprofen: 2.0 mg/kg, SC immediately after recovery from anesthesia</td>
<td>Mild pain</td>
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<td>Castration (Protocol 2)</td>
<td>Premedication: Medetomidine: 0.005-0.01 mg/kg, IM†, Butorphanol: 0.2-0.4 mg/kg, IM</td>
<td>Induction: Propofol: 2-3 mg/kg, IV to effect Isoflurane: 3%</td>
<td>Ketoprofen: 2.0 mg/kg, SC immediately after recovery from anesthesia</td>
<td>Mild pain</td>
</tr>
<tr>
<td>Ovariohysterectomy (Protocol 1)</td>
<td>Premedication: Acepromazine: 0.05-0.1 mg/kg, IM, Hydromorphone: 0.05-0.1 mg/kg, IM</td>
<td>Induction: Thiopental: 8-12 mg/kg, IV to effect Isoflurane: 3%</td>
<td>Meloxicam: 0.2 mg/kg, SC immediately after recovery from anesthesia Meloxicam: 0.1 mg/kg, PO once daily for 2-3 days</td>
<td>Moderate pain Some patients may require additional hydromorphone postoperatively</td>
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<tr>
<td>Ovariohysterectomy (Protocol 2)</td>
<td>Premedication: Medetomidine: 0.005-0.01 mg/kg, IM†, Hydromorphone: 0.05-0.1 mg/kg, IM, Glycopyrrolate: 0.005-0.01 mg/kg, IM</td>
<td>Induction: Thiopental: 4-6 mg/kg, IV to effect Isoflurane: 3%</td>
<td>Meloxicam: 0.2 mg/kg, SC immediately after recovery from anesthesia Meloxicam: 0.1 mg/kg, PO once daily for 2-3 days</td>
<td>Moderate pain Some patients may require additional hydromorphone postoperatively</td>
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<td>Dentistry with an upper canine extraction</td>
<td>Premedication: Midazolam: 0.1-0.2 mg/kg, IM, Hydromorphone: 0.05-0.1 mg/kg, IM</td>
<td>Induction: Propofol: 4-6 mg/kg, IV to effect Isoflurane: 3%</td>
<td>Ketoprofen: 2.0 mg/kg, SC immediately after recovery from anesthesia Ketoprofen: 1.0 mg/kg, PO once daily for 2-3 days</td>
<td>Moderate pain Infraorbital nerve block reduces anesthetic requirements and improves analgesia postoperatively</td>
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and techniques also have the potential to reduce major complications and improve outcome. In a busy practice setting, simple, straightforward anesthetic and pain management protocols are the best choice for most patients. Pain can be managed safely and effectively in the vast majority of surgical patients with opioids, COX inhibitors, and peripheral or central neural blockade. Alpha-2 agonists, NMDA antagonists, and other adjunctive drugs are helpful in patients with significant short-term or long-term central sensitization. And last, atraumatic surgical technique is the first, and most important, step in the prevention of peripheral and central sensitization and the development of pathological pain. Examples of balanced anesthetic and pain management protocols for routine surgical procedures in healthy cats and dogs are outlined in Tables 3 and 4, respectively.

References

2. Lemke KA: Understanding the pathophysiology of perioperative pain. Can Vet J 45:405-413, 2004