Chapter 10

Opioids, Nonsteroidal Anti-inflammatories, and Analgesic Adjuvants

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Introduction

There are three major classes of analgesic agents employed in veterinary medicine for the management of pain: opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), and local anesthetics. In addition to these three traditional drug classes, another diverse group of agents used to manage pain is known collectively as analgesic adjuvants. This chapter reviews the pharmacology of the opioids, NSAIDs, and analgesic adjuvants. For a complete discussion of the local anesthetics, the reader is referred to Chapter 14.

Opioids

All opioid analgesics are chemically related to a group of compounds that have been purified from the juice of a particular species of poppy: *Papaverum somniferum*. The unrefined extract from the poppy is called *opium* and contains approximately 20 naturally occurring pharmacologically active compounds, including familiar ones like morphine and codeine. This group of purified natural agents is specifically referred to as *opiates*. In addition, numerous semisynthetic and synthetic analogs of the opiates have been developed for clinical use. The word *opioid* is used broadly to cover all drugs that are chemical derivatives of the compounds purified from opium and is the term that is used throughout this chapter.

The opioids continue to be the cornerstone of effective pain treatment in veterinary medicine. They are a versatile group of drugs with extensive applications in the management of pain in patients with acute trauma, in patients undergoing surgical procedures, in patients with painful medical conditions or disease processes, and in patients suffering from chronic pain that require long-term therapy. In order for today's practitioner to be in a position to exploit this class of drugs to their fullest potential, a discussion encompassing the current state of knowledge of opioid pharmacology is appropriate.

Receptors

It is well known that exogenously administered opioids such as morphine or heroin exert their effects by interacting with specific opioid receptors and mimicking naturally occurring molecules known as *endogenous opioid peptides*. Based on work carried out over the past 20 years, it is now accepted that there are three well-defined types of opioid receptors, most commonly known by their Greek letter designations as μ (mu), δ (delta), and κ (kappa).[1–4] This classic system of nomenclature has been under reconsideration for a number of years and, during this time, several alternative naming systems have been proposed, leading to considerable confusion. In addition, a fourth type of opioid receptor, the nociceptin receptor (also known as the orphanin FQ receptor) has been characterized.[5,6] According to the most recent recommendations of the International Union of Pharmacology Subcommittee on Nomenclature, variations based on the Greek letters remain acceptable. Thus, mu, μ, or MOP (for *mu opioid peptide*); delta, δ, or DOP (for *delta opioid peptide*); kappa, κ, or KOP (for *kappa opioid peptide*); and NOP (for *nociceptin opioid peptide*) are considered interchangeable abbreviations. Distinct complementary DNA (cDNA) sequences have been cloned for all four opioid receptor types, and each type appears to have a unique distribution in the brain, spinal cord, and periphery.[7]

The diversity of opioid receptors is further extended by the existence of several subtypes of μ, δ, and κ receptors. Based on pharmacological studies, there are thought to be at least three μ-receptor subtypes, μ_1, μ_2, and μ_3; two δ-receptor subtypes, δ_1

and δ_2; and perhaps as many as four κ-receptor subtypes, κ_{1a}, κ_{1b}, κ_2, and κ_3.[7] The discovery of opioid receptor subtypes generated great enthusiasm among researchers and introduced the possibility of developing subtype-specific therapeutic agents with favorable side-effect profiles. At this point, however, the functional significance of these receptor subtypes remains unclear, and distinct cDNA sequences corresponding to these subtypes have not yet been identified.[7]

In general, it appears that the μ receptor mediates most of the clinically relevant analgesic effects, as well as most of the adverse side effects associated with opioid administration.[2] Drugs acting at the δ receptor tend to be poor analgesics, but may modify μ receptor–mediated antinociception under certain circumstances and mediate opioid receptor "crosstalk." The κ receptor mediates analgesia in several specific locations in the central nervous system (CNS) and the periphery, but distinguishing μ- and κ-mediated analgesic effects has proven to be difficult.[2,7] In contrast to the classic opioid receptors, the nociceptin receptor does not mediate typical opioid analgesia,[3,6] but instead produces antiopioid (pronociceptive) effects.[5,6] Because of the considerable structural homology among the three classically described opioid receptors, it is likely that there are significant interactions among these receptors in different tissues, and the loosely defined physiological roles ascribed to each receptor type still require further clarification.

Endogenous Receptor Ligands

The aforementioned opioid receptors discussed are part of an extensive opioid system that includes a large number of endogenous opioid peptide ligands. *Endogenous opioid peptides* are small molecules that are naturally produced in the CNS and in various glands throughout the body, such as the pituitary and the adrenal.[3] Three distinct families of endogenous opioid peptides have been identified: the enkephalins, the dynorphins, and β-endorphin. Each of these is derived from a distinct precursor polypeptide: proenkephalin, prodynorphin, and proopiomelanocortin, respectively.[3] These endogenous opioid peptides are expressed throughout the CNS, and their presence has been confirmed in peripheral tissues, as well.[3] There are considerable structural similarities among these three groups of peptides, and each family demonstrates variable affinities for μ, δ, and κ receptors. None of them bind exclusively to a single opioid receptor, and none of them have any significant affinity for the nociceptin receptor. The physiological roles of these peptides are not completely understood at this time. They appear to function as neurotransmitters, neuromodulators and, in some cases, as neurohormones. They mediate some forms of stress-induced analgesia and also play a role in analgesia induced by electrical stimulation of discrete regions in the brain, such as the periaqueductal gray area of the mesencephalon.[4]

Nociceptin (also known as orphanin FQ) is the endogenous ligand for the more recently discovered nociceptin receptor. Nociceptin is derived from pronociceptin, and its amino acid sequence is closely related to that of the aforementioned endogenous opioid peptides.[3,5] Despite this homology, nociceptin binding is specific for the nociceptin receptor, and the peptide does not appear to interact with μ, δ, or κ receptors. Furthermore, the physiological effects of nociceptin are in direct contrast to the actions of the classical endogenous opioid peptides, with nociceptin producing a distinctly pronociceptive effect.[3,5,6] The functional significance of nociceptin and its receptor remains to be elucidated, but additional insight into this novel opioid peptide may have substantial implications in future therapeutic drug development.

In addition to the enkephalins, dynorphins, β-endorphin, and nociceptin, there are now two other recently discovered endogenous opioid peptides called endomorphin 1 and endomorphin 2.[8] These peptides are putative products of an, as yet, unidentified precursor and have been proposed to be the highly selective endogenous ligands for the μ receptor.[3,8] The endomorphins are small tetrapeptides that are structurally unrelated to the endogenous opioid peptides.[8] Their identification has heralded a new era in research of the μ opioid system, which may contribute to our understanding of the neurobiology of opioids and provide new avenues for therapeutic interventions.

Signaling and Mechanisms of Analgesia

Binding of an opioid agonist to a neuronal opioid receptor, regardless of whether the agonist is endogenous or exogenous, typically leads to several events that serve to inhibit the activation of the neuron. Opioid receptors are part of a large superfamily of membrane-bound receptors that are coupled to G proteins.[7] As such, they are structurally and functionally related to receptors for many other neurotransmitters and neuropeptides that act to modulate the activity of nerve cells. Opioid receptor binding, via activation of various types of G proteins, may inhibit adenylyl cyclase (cyclic adenosine monophosphate) activity, activate receptor-operated phosphate ion (K^+) currents, and suppress voltage-gated calcium ion (Ca^{2+}) currents.[4]

At the presynaptic level, decreased Ca^{2+} influx will reduce release of transmitter substances, such as substance P, from primary afferent fibers in the spinal cord dorsal horn thereby inhibiting synaptic transmission of nociceptive input.[4] Postsynaptically, enhanced K^+ efflux causes neuronal hyperpolarization of spinal cord projection neurons and inhibits ascending nociceptive pathways. A third potential mode of opioid action involves upregulation of supraspinal descending antinociceptive pathways in the periaqueductal gray matter. It is now known that this system is subject to tonic inhibition mediated by GABAergic neurons, and opioid receptor activation has been shown to suppress this inhibitory influence and augment descending antinociceptive transmission.[4,9] The proposed cellular basis for this involves μ receptors that activate voltage-dependent K ions present on presynaptic GABAergic nerve terminals that inhibit γ-aminobutyric acid (GABA) release into the synaptic cleft.[9] It is important to note that although our collective understanding of opioid receptor–mediated signaling has increased dramatically in recent years, the relationship of such subcellular events to clinical analgesia at the level of the organism continues to require further clarification.

Distribution and Therapeutic Implications

Although cellular and molecular studies of opioid receptors and ligands are invaluable in understanding their function, it is criti-

cal to place opioid receptors in their anatomical and physiological context to fully appreciate the opioid system and its relevance to pain management. It has long been a principle tenet of opioid analgesia that these agents are centrally acting, and this understanding has shaped the way we use opioid analgesics clinically. It has been well established that the analgesic effects of opioids arise from their ability to directly inhibit the ascending transmission of nociceptive information from the spinal cord dorsal horn, and to activate pain-control circuits that descend from the midbrain via the rostral ventromedial medulla to the spinal cord. Within the CNS, evidence of μ, δ, and κ opioid receptor messenger RNA and/or opioid peptide binding has been demonstrated in supraspinal sites, including the mesencephalic periaqueductal gray matter, the mesencephalic reticular formation, various nuclei of the rostral ventromedial medulla, and forebrain regions including the nucleus accumbens, as well as spinally within the dorsal horn.[10,11] The interactions between groups of opioid receptors at various spinal and supraspinal locations, as well as interactions among different receptor types within a given location are complex and incompletely understood at this time.

Systemic administration of opioid analgesics via intravenous, intramuscular, or subcutaneous injection will induce a relatively rapid onset of action via interaction with these CNS receptors. Oral, transdermal, rectal, or buccal mucosal administration of opioids will result in variable systemic absorption, depending on the characteristics of the particular agent, with analgesic effects being mediated largely by the same receptors within the CNS. In addition, neuraxial administration, either into the subarachnoid or epidural space, is a particularly efficacious route of administration. Small doses of opioids introduced via these routes readily penetrate the spinal cord and interact with spinal and/or supraspinal opioid receptors to produce profound and potentially long-lasting analgesia, the characteristics of which will depend on the particular drug used.

Even though opioids have long been considered the prototype of centrally acting analgesics, a body of evidence has emerged that clearly indicates that opioids can produce potent and clinically measurable analgesia by activation of opioid receptors in the peripheral nervous system.[12] Opioid receptors of all three major types have been identified on the processes of sensory neurons,[13,14] and these receptors respond to peripherally applied opioids and locally released endogenous opioid peptides when upregulated during inflammatory-pain states.[12,15,16] Furthermore, although sympathetic neurons and immune cells have also been shown to express opioid receptors, their functional role remains unclear.[14] Although the binding characteristics of peripheral and central opioid receptors are similar, the molecular mass of peripheral and central μ opioid receptors appears to be different, suggesting that selective ligands for these peripheral receptors could be developed that would produce opioid analgesia without the potential to induce centrally mediated adverse side effects.[12,14,17–19]

Side Effects

Although opioids are used clinically primarily for their pain-relieving properties, they also produce a host of other effects on a variety of body systems. This is not surprising in light of the wide distribution of endogenous opioid peptides and their receptors in supraspinal, spinal, and peripheral locations. Some of these side effects, such as sedation, may be classified as either desirable or undesirable depending on the clinical circumstances. The following is a brief summary of these major side effects as they relate to opioids as a class of drugs.

Central Nervous System

Arousal There are considerable species differences in the CNS response to opioid analgesics that cannot be attributed to pharmacokinetic variations alone. CNS depression (i.e., sedation) is typically seen in dogs, monkeys, and people, whereas CNS stimulation (i.e., excitement and/or spontaneous locomotor activity) may be elicited in cats, horses, goats, sheep, pigs, and cows after systemic administration of various opioids, most notably morphine.[20] Reasons for these different responses are not entirely clear at this time, but are presumably related to differing concentrations and distributions of μ, δ, and κ receptors in various regions of the brain in these species.[21] Despite these fundamental differences, it must be remembered that there are numerous factors that may affect the CNS response to opioids within a given species, including the temperament or condition of the patient; the presence or absence of pain; the dose, route, and timing of drug administration; and the specific opioid administered.

Thermoregulatory Center The hypothalamic thermoregulatory system is also affected by opioid administration. Hypothermia tends to be the most common response, particularly when opioids are used during the perioperative period in the presence of other CNS-depressant drugs.[10,20] Under some clinical circumstances, however, opioid administration causes hyperthermia in cats, horses, swine, and ruminants. Part of this increase in body temperature may be attributed to an increase in muscle activity associated with CNS excitation in these species; however, a specific central hypothalamic mechanism has also been implicated, but remains poorly understood.[20] Panting is seen commonly after opioid administration, most often in dogs, but this effect tends to decrease with the onset of hypothermia.

Emetic Center Nausea and vomiting associated with opioid administration are caused by direct stimulation of the chemoreceptor trigger zone for emesis located in the area postrema of the medulla.[10,22] As with the other centrally mediated side effects, species plays a role in determining an individual's tendency to vomit after an opioid is administered. Horses, rabbits, ruminants, and swine do not vomit with opioid administration. Cats may vomit, but usually at doses that are greater than those which stimulate vomiting in dogs. Dogs will commonly vomit after opioid administration, especially with morphine. Emesis is rarely seen when opioids are administered in the immediate postoperative period or in any patient that may be experiencing some degree of pain.

Cough Center Opioids have variable efficacy in depressing the cough reflex, at least in part by a direct effect on a cough center

located in the medulla.[10] Certain opioids are more effective antitussives than others, and drugs like codeine, hydrocodone, and butorphanol are occasionally prescribed specifically for this indication.

Pupillary Diameter As a general rule, opioids tend to produce mydriasis in those species that exhibit CNS excitation, and miosis in those that become sedated after opioid administration.[20,23–25] Miosis is produced by an excitatory action of opioids on neuronal firing in the oculomotor nucleus.[22,24,25] In cats, and presumably in other species that exhibit mydriasis, this increase in activity in the oculomotor nuclear complex still occurs, but the miotic effect is masked by increased release of catecholamines, which produces mydriasis.[25]

Respiratory System

Opioids produce dose-dependent depression of ventilation, primarily mediated by μ_2 receptors, leading to a direct depressant effect on brain-stem respiratory centers.[10,22] This effect is characterized by decreased responsiveness of these centers to carbon dioxide and is reflected in an increased resting arterial carbon dioxide partial pressure and displacement of the carbon dioxide response curve to the right. This effect is compounded by the coadministration of sedative and/or anesthetic agents, meaning that significant respiratory depression and hypercapnia are much more likely to occur in anesthetized patients that receive opioids compared with those that are conscious. It should be noted that, in general, humans tend to be more sensitive to the respiratory-depressant effects of opioids when compared with most veterinary species, and the risk of hypoventilation would rarely constitute a legitimate reason for withholding opioid treatment in clinical practice.

Cardiovascular System

Most opioids have minimal effects on cardiac output, cardiac rhythm, and arterial blood pressure when clinically relevant analgesic doses are administered. Bradycardia may be caused by opioid-induced medullary vagal stimulation and will respond readily to anticholinergic treatment if warranted. Particular opioids (morphine and meperidine) can cause histamine release, especially after rapid intravenous administration, which may lead to vasodilation and hypotension.[20,26] Because of their relatively benign effects on cardiovascular function, opioids commonly form the basis of anesthetic protocols for patients with preexisting cardiovascular disease.

Gastrointestinal System

The gastrointestinal effects of the opioids are mediated by μ and δ receptors located in the myenteric plexus of the gastrointestinal tract.[10,20] Opioid administration will often stimulate dogs and, less frequently, cats to defecate. After this initial response, spasm of gastrointestinal smooth muscle predisposes patients to ileus and constipation. Horses and ruminants in particular may be predisposed to gastrointestinal complications associated with opioid administration, such as colic and ruminal tympany, respectively. These side effects tend to be most significant with prolonged administration of opioids in dogs and cats experiencing chronic pain, and such patients may require dietary modifications and stool-softening medications to manage these adverse effects.

In human patients, opioids (most notably fentanyl and morphine) have been shown to increase bile duct pressure through constriction of the sphincter of Oddi.[27] The incidence of this side effect in people is, however, quite low.[28] Despite anatomical differences, this observation has led to concerns about opioid administration to dogs and cats with pancreatitis and/or cholangitis. A study reviewing the body of human literature found that, despite widespread clinical practice, there was no evidence to indicate that morphine is contraindicated for use in acute pancreatitis.[29] As there are no studies that specifically evaluate the effects of opioids in dogs and cats with pancreatitis, it does not at this time seem appropriate to withhold this class of drugs from this subset of severely painful patients.

Genitourinary System

Opioids, particularly when administered neuraxially, may cause urinary retention through dose-dependent suppression of detrusor contractility and decreased sensation of urge.[30,31] Manual expression of the urinary bladder or catheterization may be required in certain individuals until urodynamic function returns to normal.

Urine volume may also be affected by opioids, and the mechanism of this effect appears to be multifactorial. μ-Agonists tend to produce oliguria in the clinical setting, and this is in part a due to increased antidiuretic hormone release leading to altered renal tubular function.[22,32] Elevations in circulating plasma atrial natriuretic peptide may also play a role in morphine-induced antidiuresis.[32] Conversely, κ-agonists tend to produce a diuretic effect, possibly through inhibition of antidiuretic hormone secretion.[22,32] Other peripheral mechanisms involving stimulation of renal α_2-adrenergic receptors may also contribute to this κ-agonist effect.[32]

Agonists

Almost all clinically useful opioids exert their analgesic effects by acting as agonists at μ receptors. Although a few opioids act as κ-agonists, these drugs also tend to have antagonist or partial agonist effects at μ and/or δ receptors and are thus not classified as *pure* agonists. Pure or full opioid agonists can elicit maximal activation of the receptor when they bind it, and the subsequent downstream processes produce a maximal analgesic effect (Fig. 10.1). Clinically, the full μ-agonists are superior analgesics and are the drugs of choice for pain of moderate to severe intensity in many veterinary species (see Table 10.1 for recommended dosages). The following section contains brief descriptions of full μ-agonists that are in current clinical use.

Morphine (Morphine Sulfate)

Morphine is the prototypical opioid analgesic and acts as a full agonist not only at μ receptors, but also at δ and κ receptors.[10] Despite the development of numerous synthetic opioids, many of which are more potent than morphine and may have other characteristics that make them desirable alternatives to morphine in certain circumstances, no other drug has been shown to be more

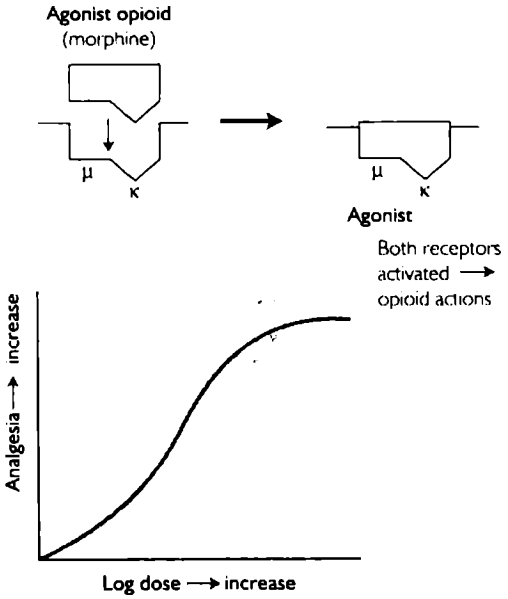

Fig. 10.1. A lock-and-key analogy is used to illustrate full agonist drug interactions at opioid receptors, with a relative dose-response curve for analgesic efficacy shown below. A full opioid agonist (in this case, morphine) stimulates both μ- and κ-receptor types, which produces increased analgesic effect with increased dose. Modified from Nicholson and Christie,[270] p. 273, with permission from Elsevier.

Table 10.1. Dosage ranges (mg/kg) for opioid agonists in several domestic species

Opioid	Dogs	Cats	Horses	Cattle	Swine
Morphine	0.3–2.0 IM, SC 0.1–0.5 IV 0.1–0.3/h IV CRI 0.1–0.2 epidural[a] 1.5–3 PO[b]	0.05–0.2 IM, SC 0.1–0.2 epidural[a]	0.1–0.3 IM, SC 0.1–0.2 epidural[a]	?	0.5–2.0? IM, SC
Oxymorphone	0.05–2.0 IV, IM, SC	0.05–0.1 IV, IM, SC	0.01–0.03 IV, IM, SC	NR	0.05–0.2? IM, SC
Hydromorphone	0.05–2.0 IV, IM, SC	0.05–0.1 IV, IM, SC	0.01–0.03 IV, IM, SC	NR	0.05–0.2? IM, SC
Meperidine	3–5 IM, SC	3–5 IM, SC	1–3 IM, SC 0.2–1.0 IV	3–4? IM, SC	1–2? IM, SC
Fentanyl	0.002–0.01 IV 0.002–0.03c/h IV CRI 0.001–0.005/h epidural[a] CRI 0.002–0.005/h transdermal[d]	0.001–0.005 IV 0.002–0.03[c]/h IV CRI 0.001–0.005/h epidural[a] CRI 0.002–0.005/h transdermal[d]	0.001–0.002/h transdermal[d]	0.001–0.002/h transdermal[d]	NR
Alfentanil	?	?	NR	NR	?
Sufentanil	0.001–0.005 IV loading dose 0.001–0.01[c]/h IV CRI	?	NR	NR	?
Remifentanil	0.004–0.01 IV loading dose 0.004–0.06[c]/h IV CRI	?	NR	NR	?
Methadone	0.05–0.2 PO, IM, SC	0.05–0.2 PO, IM, SC	NR	NR	NR
Codeine	1–2 PO	0.1–1.0 PO	NR	NR	NR
Oxycodone	0.1–0.3? PO	?	NR	NR	NR
Hydrocodone	?	?	NR	NR	NR

CRI, continuous-rate infusion; IM, intramuscular(ly); IV, intravenous(ly); NR, not recommended for administration in this species; PO, per os (orally); SC, subcutaneous(ly); ?, reliable doses have not been established for this species.

[a]Preservative-free formulations are recommended for epidural administration.

[b]Doses are for sustained-release product (MS Contin), which should be dosed q 12 h.

[c]Lower IV infusion rates are suitable for management of most types of pain, whereas higher rates will produce profound analgesia suitable for surgery.

[d]Fentanyl transdermal patches are available in 0.025-, 0.05-, 0.075-, or 0.1-mg/h sizes.

efficacious than morphine at relieving pain. Compared with the synthetic opioid agonists, morphine is relatively hydrophilic and crosses the blood-brain barrier more slowly than fentanyl or oxymorphone, thereby delaying the peak effect somewhat even after intravenous administration.[10,22] Clinically, this lag is not likely to be significant under most circumstances, with the onset of analgesia occurring reasonably promptly after a single dose of morphine and typically lasting 3 to 4 h.[33,34] Morphine's poor lipid solubility means that it can produce long-lasting analgesia when administered into the epidural or subarachnoid space, with effects persisting for 12 to 24 h. The first-pass effect is significant after oral administration, and the bioavailability of oral morphine preparations is only in the range of 25%. If dose adjustments are made, adequate pain relief can be achieved with oral morphine administration, and the duration of action tends to be somewhat longer with this route.

In most species, the primary metabolic pathway for morphine involves conjugation with glucuronic acid leading to the formation of two major metabolites: morphine 6-glucuronide and morphine 3-glucuronide.[10,35] Despite the low levels of glucuronyl transferase in cats, the pharmacokinetics of morphine in this species seem to be broadly comparable to those in dogs and people, though clearance rates may be marginally slower.[33–35] This suggests that morphine must undergo a different type of conjugation reaction in this species. Morphine 6-glucuronide has pharmacological activities that are indistinguishable from those of morphine in animal models and in people, whereas morphine 3-glucuronide appears to have little affinity for opioid receptors, but may contribute to the excitatory effects of morphine in some situations.[10,36] With chronic morphine administration, it is likely that the active metabolite, morphine 6-glucuronide, contributes significantly to clinical analgesia.

Very little morphine is excreted unchanged in the urine. The major metabolites—morphine 3-glucuronide and, to a lesser extent, morphine 6-glucuronide—are eliminated almost entirely via glomerular filtration. In human patients, renal failure may lead to accumulation of morphine 6-glucuronide and persistent clinical effects, whereas liver dysfunction seems to have minimal impact on morphine clearance.[10,22]

The side effects associated with morphine administration are typical of most opioid agonists and have been discussed previously in this chapter. In particular, the increased incidence of vomiting after morphine administration, as well as its potential to cause histamine release after intravenous administration, helps to distinguish morphine from other full opioid agonists.

Clinically, morphine is a useful analgesic in dogs, cats, horses, and rats. It is often administered to dogs and cats at fixed dosing intervals via the intramuscular, subcutaneous or, less commonly, intravenous routes to manage pain associated with a variety of traumatic injuries and disease processes. Morphine has also been used extensively throughout the perioperative period in these species to manage pain associated with surgical procedures. In dogs and cats, the sparing effect of morphine on both injectable and inhalant anesthetic requirements can be significant.[37,38] Morphine is particularly effective in dogs when administered intravenously as a continuous infusion, which facilitates more precise dose titration to achieve optimal analgesic effects.[38,39] Subcutaneous infusions of morphine and other opioids are being employed in human patients experiencing cancer pain,[40–43] and, as subcutaneous infusion devices are developed that are applicable to dogs and cats, this route of administration may be accessed by veterinarians in the future. Administration of the drug into the epidural or, less commonly, subarachnoid space is a common analgesic technique employed in both dogs and cats in a variety of clinical situations.[44,45] More recently, the discovery of peripheral μ opioid receptors has led to the clinical practice of instilling morphine locally into inflamed joints[46,47] and even topically onto damaged corneas[48] to supplement analgesia in canine patients.

The analgesic benefits of morphine use in horses are less clear-cut than in dogs and cats. Low doses of morphine can be administered systemically without adverse side effects and may relieve pain in conscious horses, though the analgesic response has been difficult to demonstrate in numerous clinical studies.[49] A 2003 study showed that morphine, in the absence of other drugs, actually increased the minimum alveolar concentration (MAC) of isoflurane in horses anesthetized in an experimental setting.[50] While this finding would appear to discourage routine use of morphine in the perioperative period, another retrospective study failed to demonstrate any adverse effects associated with perioperative morphine administration in a typical clinical setting in the presence of other drugs, such as α_2-agonists and ketamine.[51] Thus, the routine systemic administration of morphine to horses, especially those undergoing surgery, remains controversial.

Regional administration of morphine to horses, however, is becoming increasingly common, and a growing body of evidence seems to support this practice. Morphine produces significant analgesia with few adverse side effects when administered epidurally or intra-articularly and is often combined with other analgesic agents, such as α_2-agonists and local anesthetics, when administered via these routes.[49,52,53]

Morphine is used infrequently in ruminants and swine in the clinical setting, and its effects have not been well studied in these species. It is likely that regional and perhaps even systemic administration of morphine may play a role in pain management of these species in the future.

Oxymorphone (Oxymorphone Hydrochloride [Numorphan])

Oxymorphone is a synthetic opioid that acts as a full agonist at μ receptors and is comparable to morphine in its analgesic efficacy and duration of action. It is a more lipid soluble drug than morphine and is readily absorbed after intramuscular or subcutaneous administration. Oxymorphone is not available as an oral formulation.

When compared with morphine, oxymorphone is less likely to cause dogs and cats to vomit, and tends to produce more sedation when administered to these species. Its respiratory-depressant effects are similar to those induced by morphine, but oxymorphone seems more likely to cause dogs to pant. It does not produce histamine release, even when administered intravenously.[26] Oxymorphone's other side effects are typical of other full μ-agonist opioids and have been discussed previously.

Oxymorphone has been used extensively in dogs and cats, and is most often administered at fixed dosing intervals, either intramuscularly, subcutaneously, or intravenously, to manage pain in a variety of clinical settings. It is also commonly used in the preanesthetic, intraoperative, and postoperative periods in surgical patients. Oxymorphone has been administered epidurally in dogs, but its relative lipid solubility means that its analgesic action is briefer when administered by this route compared with the action of morphine.[54]

Oxymorphone is not commonly administered to horses, ruminants, or swine, and little data exist in these species to make any therapeutic recommendations.

Hydromorphone (Hydromorphone Hydrochloride [Dilaudid])

Hydromorphone is a synthetic opioid that acts as a full agonist at μ receptors and is used in both human and veterinary medicine. Clinically, hydromorphone and oxymorphone have similar efficacy, potency, duration of analgesic action, and side-effect profiles, but hydromorphone remains significantly less expensive. Like oxymorphone, hydromorphone is not associated with histamine release, so bolus intravenous administration is considered safe.[26]

In dogs and cats, hydromorphone can be used in any clinical situation where oxymorphone is used. Evidence from the human literature suggests that hydromorphone may be suitable for administration via a continuous infusion, either intravenously, subcutaneously, or epidurally,[42,55,56] and these routes of administration may further expand the use of hydromorphone in veterinary patients in the future. There is little published on the use of hydromorphone in large animal species at this time.

Meperidine (Meperidine Hydrochloride or Pethidine [Demerol])

Meperidine is a synthetic opioid that exerts its analgesic effects through agonism at μ receptors. Interestingly, it also appears able to bind other types of receptors, which may contribute to some of its clinical effects other than analgesia. Meperidine can block sodium channels and inhibit activity in dorsal horn neurons in a manner analogous to local anesthetics.[57,58] Meperidine also exerts agonist activity at α_2 receptors, specifically the α_{2B} subtype, suggesting that it may possess some α_2-agonist-like properties.[59,60]

Meperidine has a shorter analgesic action compared with morphine, oxymorphone, or hydromorphone, typically not extending beyond 1 h.[20] Metabolic pathways vary among different species, but, in general, most of the drug is demethylated to normeperidine in the liver and then undergoes further hydrolysis and ultimately renal excretion.[20,34,61] Normeperidine is an active metabolite and has approximately one-half the analgesic efficacy of meperidine.[10,20] Normeperidine has produced toxic neurological side effects in human patients receiving meperidine for prolonged periods, especially in the presence of impaired renal function.[22,62]

Unlike most of the other opioids in clinical use, meperidine has been shown to produce significant negative inotropic effects when administered alone to conscious dogs.[63] Because of its modest atropine-like effects, meperidine tends to increase heart rate rather than predispose patients to bradycardia, as is often seen with other opioids.[20,22] The clinical significance of these cardiovascular effects in the perianesthetic period has never been clearly ascertained. Like morphine, meperidine also causes histamine release when administered intravenously.[20]

A rare, but life-threatening, drug interaction that may have relevance in veterinary medicine has been reported in human patients receiving meperidine. The combination of meperidine (and perhaps other opioids) with a monoamine oxidase inhibitor may lead to *serotonin syndrome*, which is characterized by a constellation of symptoms, including confusion, fever, shivering, diaphoresis, ataxia, hyperreflexia, myoclonus, and diarrhea.[64–67] A monoamine oxidase inhibitor, selegiline (Deprenyl), has been used in canine patients to treat pituitary-dependent hyperadrenocorticism or to modify behavior in patients with canine cognitive dysfunction. Though there have not, to date, been any scientific studies of adverse meperidine-selegiline interactions in dogs, veterinarians must be aware of the potential for complications if analgesia is required in patients receiving monoamine oxidase inhibitors. A recent study that evaluated the effects of other opioids (oxymorphone and butorphanol) in selegiline-treated dogs did not identify any specific adverse drug interactions in these animals.[68]

Clinically, meperidine has been used primarily in dogs and cats during the preanesthetic period, often in combination with sedatives or tranquilizers. In patients undergoing surgery, administration of another full μ-agonist opioid with a longer duration of action is recommended for use postoperatively. Meperidine appears to offer few, if any, advantages over other opioids, such as oxymorphone or hydromorphone, in these species during the perioperative period.

Meperidine is not commonly used in large animals, but may, like morphine, produce useful analgesic effects when administered into the epidural space in these species.[69] Because of its local anesthetic-like effects, caudal epidural meperidine may offer advantages over other epidural opioids when perineal analgesia is specifically indicated.

Fentanyl (Fentanyl Citrate [Sublimaze])

Fentanyl is a highly lipid soluble, short-acting synthetic μ opioid agonist. A single dose of fentanyl administered intravenously has a more rapid onset and a much briefer action than morphine. Peak analgesic effects occur in about 5 min and last approximately 30 min.[10,22] Rapid redistribution of the drug to inactive tissue sites, such as fat and skeletal muscle, leads to a decrease in plasma concentration and is responsible for the prompt termination of clinical effects. In most veterinary species, the elimination half-life after a single bolus or a brief infusion is in the range of 2 to 3 h.[70–72] Administration of very large doses or prolonged infusions may cause saturation of inactive tissues, with termination of clinical effects becoming dependent on hepatic metabolism and renal excretion.[10,22] Thus, the context-sensitive half-life of fentanyl increases significantly with the duration of the infusion, and clinical effects may persist for an extended period following termination of a long-term intravenous infusion.

Side effects associated with fentanyl administration are similar to those of the other full μ-agonist opioids. In general, cardiovascular stability is excellent with fentanyl, and intravenous administration is not associated with histamine release.[10,22] Bradycardia may be significant with bolus doses, but readily responds to anticholinergics if treatment is warranted.[10,20] In human patients, muscle rigidity, especially of the chest wall, has been noted after administration of fentanyl or one of its congeners.[65,73,74] The potential significance of this adverse effect in animal patients is not clear at this time, and the risk is considered minimal if large, rapid bolus administrations are avoided.

Clinically, fentanyl is used most frequently in dogs and cats, but is also a potentially useful analgesic in other species, including horses, cows, sheep, goats, and pigs. Historically, fentanyl was available in combination with the butyrophenone tranquilizer, droperidol, in a product called Innovar-Vet, which was typically administered in the preanesthetic period to provide sedation and analgesia. This product is no longer available, and systemic administration of fentanyl today is usually via the intravenous route.

Because of its shorter action, fentanyl is typically administered as a continuous infusion to provide analgesia. Intravenous fentanyl can be infused at relatively low doses to supplement analgesia intraoperatively and/or postoperatively in dogs and cats. It is also useful for management of nonsurgical pain, such as that associated with pancreatitis. Alternatively, larger doses can be administered, often in combination with a benzodiazepine like midazolam, to induce general anesthesia in canine patients with cardiovascular or hemodynamic instability. Similarly, higher infusion rates of fentanyl can be used as the primary anesthetic agent for surgical maintenance in patients who will not tolerate significant concentrations of volatile inhalant anesthetics.[75–77] In the clinical setting, there are few reports of intravenous fentanyl administration in large animal species, though fentanyl infusions have been employed in a variety of surgical animal research models involving calves, sheep, and pigs.[78,79]

In addition to intravenous administration, fentanyl may be deposited into the epidural space to produce analgesia. Because of its high lipid solubility, epidural fentanyl, unlike morphine, is rapidly absorbed into the systemic circulation. Consequently, the clinical effects associated with a single bolus of epidural fentanyl resemble those of an intravenous injection. However, the benefits of neuraxial administration can be achieved by administering epidural fentanyl as a continuous infusion through an indwelling epidural catheter, often in combination with other analgesic agents. This technique is typically used in canine patients for management of severe acute pain, but it may have additional applications for the management of chronic pain as well.

The development of novel, less invasive, routes of opioid administration for use in human patients led to the marketing of transdermal fentanyl patches (Duragesic). The patches are designed to release a constant amount of fentanyl per hour that is then absorbed across the skin and taken up systemically. Fentanyl patches are designed for human skin and human body temperature, but their use has been evaluated in a number of veterinary species.[70,72,80–86] Though transdermal fentanyl appears to be an effective means of providing analgesia in a number of clinical settings, substantial variations in plasma drug concentrations have been documented, and significant lag times after patch placement are common prior to onset of analgesia.[70,71,83,84] Furthermore, changes in body temperature have been shown to affect fentanyl absorption significantly in anesthetized cats,[87] and it is likely that other factors associated with skin preparation and patch placement have the potential to alter plasma fentanyl levels and analgesic efficacy substantially. Two recent studies evaluating the efficacy of pluronic lecithin organogel (PLO gel) delivery of fentanyl through skin in dogs and cats concluded that this method of administration did not result in measurable plasma concentrations and thus could not be justified as an effective means of systemic administration.[88,89]

Alfentanil, Sufentanil, and Remifentanil (Alfenta, Sufenta, and Ultiva)

Alfentanil, sufentanil, and remifentanil are all structural analogs of fentanyl that were developed for use in human patients in an effort to create analgesics with a more rapid onset of action and predictable termination of opioid effects. All three are similar with regard to onset, and all have context-sensitive half-lives that are shorter than that of fentanyl after prolonged infusions.[22] Remifentanil is unique among opioids because it is metabolized by nonspecific plasma esterases to inactive metabolites.[90,91] Thus, hepatic or renal dysfunction will have little impact on drug clearance, and this, in combination with the robust nature of the esterase metabolic system, contributes to the predictability associated with remifentanil infusion.[10,22]

All three of these drugs are used during general anesthesia for procedures requiring intense analgesia and/or blunting of the sympathetic nervous system response to noxious stimulation. As yet, they have limited applications for postoperative or chronic pain management. Like fentanyl, they can be administered at relatively low infusion rates as adjuncts to general anesthetic protocols based on volatile inhalant or other injectable agents, or they can be administered at higher rates as primary agents for total intravenous anesthesia. The minimum alveolar-sparing properties of these agents have been demonstrated in both dogs[91,92] and cats.[77,93,94] In horses, systemic infusions of alfentanil did not have significant effects on MACs of inhalant anesthetics and, when administered to conscious horses, were associated with increases in locomotor activity.[95–97] There is little evidence to suggest that any of the fentanyl analogs offer advantages over morphine when administered into the epidural space for analgesia.[52]

Methadone (Methadone Hydrochloride [Dolorphine])

Methadone is a synthetic μ opioid agonist with pharmacological properties qualitatively similar to those of morphine, but possessing additional affinity for *N*-methyl-D-aspartate (NMDA) receptors.[98,99] Methadone's unique clinical characteristics include excellent absorption after oral administration, no known active metabolites, high potency, and an extended duration of action.[10,20,99] In human patients, the drug has been used primarily in the treatment of opioid-abstinence syndromes, but is being used increasingly for the management of chronic pain. Though

there are reports of intramuscular or intravenous administration of methadone in the perioperative period in dogs, cats, and horses,[100–102] the drug is not commonly used in this setting in North America at this time. Additional studies may identify a role for oral methadone in the management of chronic pain syndromes in veterinary patients.

Codeine (Codeine Phosphate)

Codeine is the result of substitution of a methyl group onto morphine, which acts to limit first-pass hepatic metabolism and accounts for codeine's high oral bioavailability.[10,22] Codeine is well known for its excellent antitussive properties and is often combined in an oral formulation with a nonopioid analgesic, such as acetaminophen, for the management of mild to moderate pain in human patients. Codeine, alone or in combination with acetaminophen (Tylenol 3), has been used in dogs for the management of mild pain on an outpatient basis.

Oxycodone and Hydrocodone (Oxycodone Hydrochloride and Hydrocodone Bitartrate)

Oxycodone and hydrocodone are opioids that are typically administered orally for the treatment of pain in human patients. Though oxycodone is available as a single-drug continuous-release formulation (Oxycontin), these drugs are most often prepared in combination with nonopioid analgesics, such as aspirin and acetaminophen (e.g., Percocet, Percodan, Lorcet, and Vicodan). Little has been published regarding the use of these opioids in veterinary patients, and thus specific recommendations regarding their use cannot be made at this time.

Etorphine and Carfentanil (M-99 and Wildnil)

These two opioids are discussed together because they are both used exclusively for the restraint and capture of wild animals rather than as analgesic agents. They are extremely potent opioids, and the immediate availability of a suitable antagonist is mandatory before these drugs are to be used, not only to reverse drug effects in animal patients, but also as a safety precaution in the event of accidental human injection. Though etorphine and carfentanil are most often injected intramuscularly (usually using a remote drug-delivery technique), studies suggest that carfentanil is useful when administered orally in a variety of species.[103–106] A number of different drugs have been used in combination with etorphine or carfentanil to enhance muscle relaxation, including acepromazine, xylazine, and medetomidine.[107–110] For more detailed information on the use of these agents for immobilization of free-ranging wildlife, readers are referred to Chapters 12, 31, and 32 in this text.

Agonist-Antagonists and Partial Agonists

This group includes drugs that have varying opioid receptor–binding profiles, but that have one thing in common: They all occupy μ opioid receptors, but do not initiate a maximal clinical response. Drugs such as butorphanol and nalbuphine are classified as agonist-antagonists. They are competitive μ-receptor antagonists, but exert their analgesic actions by acting as agonists at κ receptors (Fig. 10.2). Buprenorphine, on the other hand, is classified as a partial agonist and binds μ receptors, but produces only a limited clinical effect (Fig. 10.3). These mixed agonist-antagonist drugs were developed for the human market in an attempt to create analgesics with less respiratory depression and addictive potential. Because of their opioid receptor–binding affinities, the side effects associated with these drugs demonstrate a so-called ceiling effect, whereby increasing doses do not produce additional adverse responses. Unfortunately, the benefits of this ceiling effect on ventilatory depression come at the expense of limited analgesic efficacy and only a modest ability to decrease anesthetic requirements.

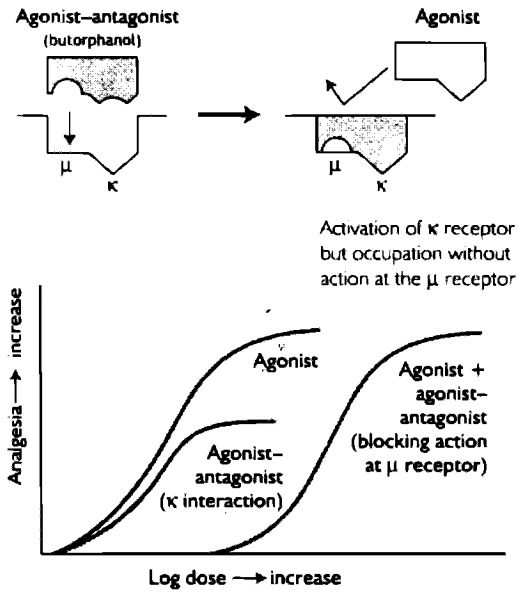

Fig. 10.2. A lock-and-key analogy is used to illustrate agonist-antagonist drug interactions at opioid receptors, with a relative dose-response curve for analgesic efficacy shown below. An agonist-antagonist opioid (in this case, butorphanol) has agonist activity at κ receptors and antagonist activity at μ receptors. In the presence of a full μ-agonist, these opioids tend to have antagonistic effects and will increase the dose of full agonist required to achieve maximal analgesic effect. Modified from Nicholson and Christie,[270] p. 273, with permission from Elsevier.

The coadministration of opioids with differing receptor-binding profiles is currently an active area of research that deserves further attention. The interactions in this setting are complex, and opioid coadministration appears to have the potential to produce additive, synergistic, or antagonistic analgesic effects, depending on the particular species, dosage, drugs, and pain model being evaluated. The following section contains brief descriptions of opioid agonist-antagonists and partial agonists that are currently in clinical use (see Table 10.2 for recommended dosages).

Butorphanol (Butorphanol Tartrate [Torbugesic])

Butorphanol is a synthetic agonist-antagonist opioid and has been used extensively in a wide variety of veterinary species. The drug was originally labeled as an antitussive agent in dogs and,

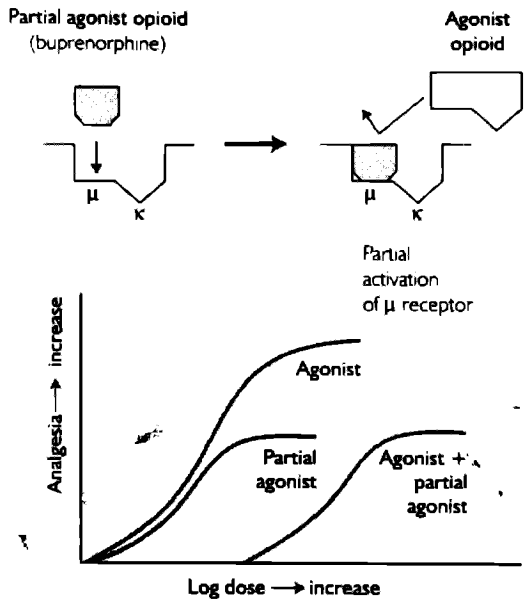

Fig. 10.3. A lock-and-key analogy is used to illustrate partial agonist drug interactions at opioid receptors, with a relative dose-response curve for analgesic efficacy shown below. A partial opioid agonist (in this case, buprenorphine) weakly stimulates μ receptors, which produces a reduced maximal analgesic effect compared with a full agonist. A large dose of partial agonist will block the receptor actions of a full agonist, moving its dose-response curve to the right and depressing its maximal analgesic effect. Modified from Nicholson and Christie,[270] p. 273, with permission from Elsevier.

even now, is approved as an analgesic in cats and horses only.[20] Butorphanol exerts its relevant clinical effects through its interactions at κ receptors and acts as an antagonist at μ receptors. The duration of butorphanol's analgesic effects remains somewhat debatable and likely varies with species, type and intensity of pain, dosage, and route of administration.[111–113] In general, its effects are shorter-lived than those of morphine and are probably in the range of 1 to 3 h. Butorphanol is typically administered via the intramuscular, subcutaneous, or intravenous route, though an oral formulation is available and is occasionally prescribed for outpatient analgesia in dogs.

Butorphanol does not induce histamine release when administered intravenously and has minimal effects on cardiopulmonary function. There is conflicting evidence regarding the effects of butorphanol on inhalant anesthetic requirements in the dogs, cats, and horses. Earlier studies failed to demonstrate a significant sparing effect on MAC when butorphanol was coadministered with halothane in dogs and ponies.[114–116] More recently, isoflurane MAC reductions have been documented after administration of clinically relevant doses of butorphanol in both dogs and cats.[37,117] Reasons for these discrepancies are probably related to differences in study techniques, and, in dogs and cats specifically, it seems that butorphanol can induce at least modest reductions in inhalant anesthetic requirements.

When administered alone to healthy dogs and cats, butorphanol produces minimal sedation only. However, the drug is commonly used in combination with a variety of sedatives and tranquilizers, such as acepromazine, medetomidine, or midazolam, to produce sedation and analgesia for minimally invasive procedures.[118] It is also used during the preanesthetic and postoperative periods to provide analgesia for surgical procedures associated with mild to moderate pain.[85,119,120] Butorphanol does not appear to be an effective monoanalgesic for moderate to severe pain in these species, especially when pain is orthopedic in origin.[121–123]

Butorphanol, which is the opioid most commonly used in horses, is almost always coadministered with an α_2-agonist or, occasionally, acepromazine. It is administered intravenously for a variety of standing procedures or prior to induction of general anesthesia. Butorphanol has been shown to be an effective, though short-lived, analgesic for visceral pain in this species, but the α_2-agonists still seem to be superior for treatment of this type of pain in horses.[124,125] One study has documented the safety and apparent efficacy of a continuous intravenous infusion of butorphanol that maintained therapeutic plasma levels of drug while minimizing the potential for adverse gastrointestinal and behavioral effects.[113] Butorphanol has not been shown to be particu-

Table 10.2. Dosage ranges (mg/kg) for opioid agonist-antagonists and partial agonists in several domestic species

Opioid	Dogs	Cats	Horses	Cattle	Swine
Butorphanol	0.1–0.4 IV, IM, SC 0.5–2.0 PO[a]	0.1–0.8 IV, IM, SC 0.5–1.0 PO[a]	0.02–0.04 IV, IM, SC 0.02–0.04/h IV CRI 0.04 epidural	0.01–0.04 IV, IM, SC	0.1–0.5 IV, IM, SC
Nalbuphine	0.3–0.5 IM, SC 0.1–0.3 IV	0.2–0.4 IM, SC 0.1–0.2 IV	?	?	?
Pentazocine	1–3 IV, IM, SC	1–3 IV, IM, SC	0.1–1.0 IV, IM, SC	?	?
Buprenorphine	0.005–0.02 IV, IM, SC	0.005–0.02 IV, IM, SC 0.01–0.02 PO[b]	0.005–0.01 IV, IM, SC	0.005–0.01 IV, IM, SC	0.01–0.1 IV, IM, SC

CRI, continuous-rate infusion; IM, intramuscularly; IV, intravenously; PO, per os (orally); SC, subcutaneously; ?, reliable doses have not been established for this species.

[a]Butorphanol's oral bioavailability remains uncertain.

[b]Buprenorphine injectable solution has been shown to be effective when administered to the buccal mucosa in cats.

larly effective when administered into the caudal epidural space in horses, and other opioids, such as morphine, produce superior analgesia when given by this route.[52,126]

Butorphanol is occasionally administered to cattle, sheep, goats, and pigs to provide analgesia, but there is limited information in the literature on its analgesic efficacy in these species. The combination of butorphanol with xylazine or detomidine appears to enhance and prolong the sedation induced by the α_2-agonist. Additional studies evaluating the analgesic potential of butorphanol and other opioids in these species are certainly warranted.

Traditionally, it was thought that the simultaneous or sequential administration of butorphanol with a pure μ opioid agonist such as morphine or hydromorphone would be counterproductive from an analgesic standpoint because butorphanol's ability to antagonize μ receptors could inhibit or even reverse the effects of the agonist drug. Certainly, it has been clearly demonstrated that excessive sedation associated with a pure μ-agonist can be partially reversed by the administration of low doses of butorphanol, and it was presumed that butorphanol would similarly reverse the μ-mediated analgesic effects, as well. It would now appear that the potential interactions between butorphanol and full μ opioid agonists are more complex than originally believed. One study demonstrated that coadministration of butorphanol and oxymorphone to cats subjected to a visceral noxious stimulus enhanced analgesic effects.[127] A more recent feline study, however, which evaluated the combination of butorphanol and hydromorphone in a thermal threshold-pain model, failed to demonstrate enhanced analgesia and suggested that butorphanol actually did inhibit hydromorphone's analgesic effects.[128]

These contradictory findings illustrate that we still have much to learn about coadministration of opioid agents with differing receptor-binding profiles, and the clinical effects produced by such coadministration likely depend on many factors, including species, type of pain, dose, and the specific drugs involved.

Nalbuphine and Pentazocine (Nalbuphine Hydrochloride [Nubain] and Pentazocine Hydrochloride [Talwin])

Nalbuphine and pentazocine are classified as agonist-antagonist opioids and are clinically similar to butorphanol. They induce mild analgesia accompanied by minimal sedation, respiratory depression, or adverse cardiovascular effects. In human patients, nalbuphine is used more commonly than butorphanol, whereas, in veterinary medicine, butorphanol is used far more frequently. In the past, pentazocine was used in equine patients for management of colic pain, but it has largely been replaced by the α_2-agonists (xylazine and detomidine), nonsteroidal anti-inflammatories (flunixin meglumine), and butorphanol. Like butorphanol, nalbuphine is occasionally used to partially reverse the effects of a full μ-agonist opioid while maintaining some residual analgesia.

Buprenorphine (Buprenex [Temgesic])

Buprenorphine is a semisynthetic, highly lipophilic opioid derived from thebaine. Unlike other opioids in this category, buprenorphine is considered to be a partial agonist at μ opioid receptors. The drug binds avidly to, and dissociates slowly from, μ receptors, but cannot elicit a maximal clinical response. Because of its receptor-binding characteristics, buprenorphine has a delayed onset of action and takes at least 1 h to attain peak effect after intramuscular administration. It also has a relatively long action, with clinical analgesic effects persisting for 6 to 12 h in most species. Also, its high affinity for the μ receptor means that it may be difficult to antagonize its effects with a drug such as naloxone. Buprenorphine has most often been administered intravenously or intramuscularly; however, because of the long lag time before clinical effects are achieved after intramuscular administration, the intravenous route is preferred. A recent study has documented comparable plasma drug levels and analgesic efficacy with oral transmucosal administration in cats.[129] This route seems to be well tolerated by feline patients and is becoming increasingly popular in clinical practice. A transdermal buprenorphine patch (Transtec) is now commercially available and currently being evaluated in cats.

In dogs and cats, buprenorphine is used most often in the postoperative period to manage pain of mild to moderate intensity.[130–132] As with the other opioids in this category, buprenorphine may not be adequate for management of severe pain such as that associated with thoracotomies or invasive orthopedic procedures.[133] The drug is a popular analgesic in laboratory-animal species because it can be formulated with a variety of foodstuffs and given orally to rodents.

In horses, buprenorphine is occasionally administered in combination with an α_2-agonist to enhance and prolong sedation and analgesia.[134] There is little information published on the use of buprenorphine in cattle, and, though the drug is commonly used as an analgesic agent in research laboratories in sheep and swine, few reports actually evaluate its analgesic efficacy in these species.

Antagonists

These drugs have high affinities for the opioid receptors and can displace opioid agonists from μ and κ receptors. After this displacement, the pure antagonists bind to and occupy opioid receptors, but do not activate them (Fig. 10.4). Under ordinary circumstances, in patients that have not received exogenous agonist opioids, the opioid antagonists have few clinical effects when administered at clinically relevant dosages.[10] It is important to recognize that these drugs will rapidly reverse all opioid-induced clinical effects, including analgesia (see Table 10.3 for recommended dosages). Therefore, use of pure opioid antagonists should be reserved for emergency situations such as opioid overdose or profound respiratory depression. Their routine use for reversal of excessive sedation in patients experiencing prolonged anesthetic recoveries or in patients that develop bradycardia secondary to opioid administration is inappropriate and may cause the development of intense acute pain and activation of the sympathetic nervous system.

Naloxone (Naloxone Hydrochloride [Narcan])

The use of this pure opioid antagonist can reverse all opioid agonist effects, producing increased alertness, responsiveness, coordination and, potentially, increased perception of pain. Naloxone's effects are shorter than that of many of the opioid agonists, with recommended intravenous doses lasting between 30

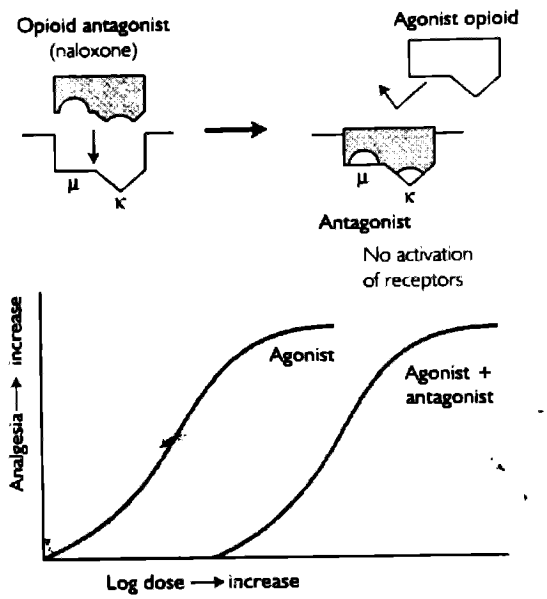

Fig. 10.4. A lock-and-key analogy is used to illustrate pure antagonist drug interactions at opioid receptors, with a relative dose-response curve for analgesic efficacy shown below. A pure opioid antagonist (in this case, naloxone) blocks both μ- and κ-receptor types, but has no intrinsic activity at these receptors. Receptor binding is competitive, so more agonist is required in the presence of antagonist to produce a maximal analgesic effect. Modified from Nicholson and Christie,[270] p. 273, with permission from Elsevier.

and 60 min. Consequently, animals need to be closely monitored for renarcotization after a dose of naloxone. Occasionally, excitement or anxiety may be seen after naloxone reversal of an opioid agonist. Premature ventricular contractions have also been documented after reversal, but are not common and seem to be more likely if there are high levels of circulating catecholamines. This drug is sometimes administered sublingually to neonatal patients exhibiting respiratory depression that have been delivered by cesarean section after maternal administration of an opioid agonist.

Naloxone has also been shown in animal models and human patients to produce a dose-related improvement in myocardial contractility and mean arterial blood pressure during shock.[135–137] Further studies are needed to clarify the role of the endogenous opioid system in the pathophysiology of various forms of shock.

Nalmefene and Naltrexone (Revex and Trexonil)

Both of these drugs are pure opioid antagonists with clinical effects that last approximately twice as long as those of naloxone.[138] Though little is published about the use of these drugs in veterinary patients, they may be advantageous in preventing renarcotization when used to antagonize the effects of a long-acting opioid.

Nonsteroidal Anti-inflammatories

The nonsteroidal anti-inflammatory drugs (NSAIDs) relieve mild to moderately severe pain, with efficacy dependent on the particular NSAID administered. This class of analgesics dates back thousands of years, with the salicylates being among the oldest and still most commonly used analgesics.[139] *Salicylate* is a naturally occurring substance found in willow bark and, prior to production of the synthetic compound, was used for centuries to manage pain associated with rheumatism. In 1878, Felix Hoffman, working at Bayer in Germany, made the acetylated form of salicylic acid that has come to be known as aspirin.[139] Although aspirin (acetylsalicylic acid or ASA) has been found to be effective in the management of acute and chronic mild discomfort, the newer injectable NSAIDs appear to have comparable efficacy to the pure μ-agonist opioids in controlling moderate to severe soft tissue and orthopedic pain. The NSAIDs appear to confer synergism when used in combination with opioids and may demonstrate an opioid-sparing effect should lower dosages of opioid be required. Their extended duration of action, in addition to their analgesic efficacy, make the NSAIDs ideal for treating acute and chronic pain in veterinary patients. Careful patient and drug selection is critical, however, because of their potential for harmful side effects.

Cyclooxygenases and Prostaglandin Synthesis

In 1971, Vane discovered the mechanism by which aspirin exerts its anti-inflammatory, analgesic, and antipyretic actions. He proved that aspirin and other NSAIDs inhibited the activity of a cyclooxygenase (COX) enzyme that produced prostaglandins (PGs) involved in the pathogenesis of inflammation, swelling, pain, and fever.[140] Twenty years later, a second COX enzyme was discovered and, more recently, a newly identified COX-3 has been identified.[141–143] *Cyclooxygenase* (previously termed *prostaglandin synthase*) oxidizes arachidonic acid (previously termed *eicosatetraenoic acid*) to various eicosanoids (including PGs and other related compounds) (Fig. 10.5).[144] Oxidation of arachidonic

Table 10.3. Dosage ranges (mg/kg) for opioid antagonists in several domestic species

Opioid	Dogs	Cats	Horses	Cattle	Swine
Naloxone	0.002–0.02 IV	0.002–0.02 IV	0.002–0.02 IV	[a]	[a]
Nalmefene	0.025–0.03? IV	0.025–0.03? IV	?	?	?
Naltrexone	0.0025–0.003? IV	0.0025–0.003? IV	?	?	?

IV, intravenously; ?, reliable doses have not been established for this species.

[a]Doses have not been specifically reported for these species; however, 0.01 mg/kg IV is probably appropriate

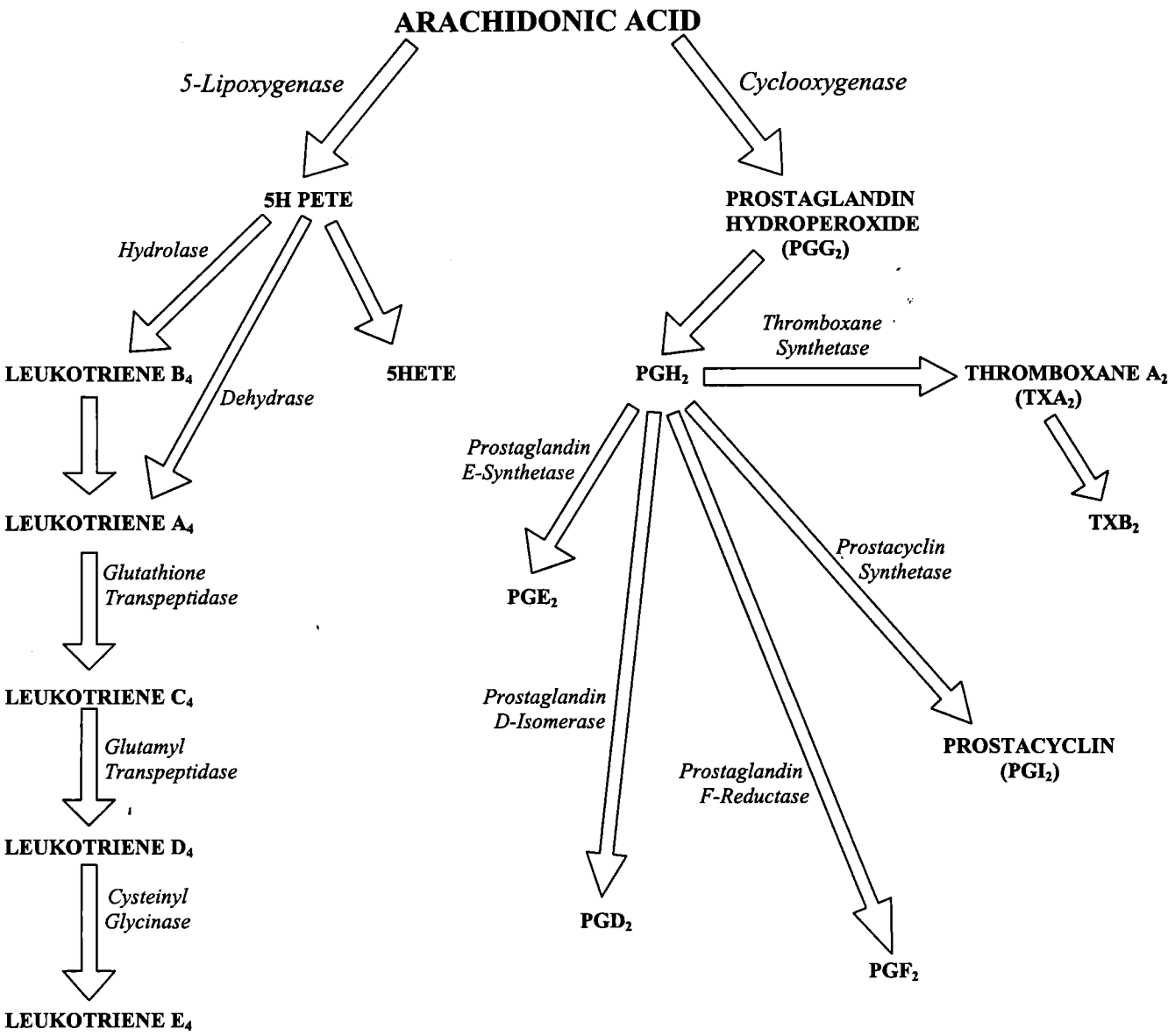

Fig. 10.5. The arachidonic acid cascade: eicosanoid synthesis. 5-HETE, 5-hydroxy-6,8,11,14-eicosatetraenoic acid; and 5-HPETE, 5-hydroperoxy-6,8,11,14-eicosatetraenoic acid.

acid by 5-lipoxygenase (5-LOX), the most biologically important of the mammalian oxygenases, produces the series of eicosanoids termed *leukotrienes* (Fig. 10.5). The release of arachidonic acid from membrane phospholipid is catalyzed by the enzyme phospholipase A_2 and is the rate-limiting step in PG and leukotriene synthesis. Prostaglandin G_2 is the initial prostenoid formed, followed by prostaglandin H_2, which serves as a substrate for prostaglandin E synthetase, prostaglandin D isomerase, prostaglandin F reductase, prostacyclin synthetase, and thromboxane synthetase for conversion to a variety of other prostenoids ubiquitous throughout cells and tissues in the body.[144] These include the PGs PGE_2, PGD_2, PGF_2, and PGI_2 (prostacyclin), and the thromboxanes TXA_2 and TXB_2, all with diverse functions.[145] The PGs are not stored, but are synthesized at a constant rate. They have short half-lives of 4 to 6 min at 37°C and act locally at the site of production.

The PGs produced by both COX-1 and COX-2 are ubiquitous throughout the body and serve to facilitate many physiological functions during both health and illness. Consequently, the clinical use of NSAIDs has the potential to disrupt these functions, with the possibility of significant organ dysfunction. Thus, in addition to their role as analgesics, the effects of NSAIDs on the constitutive functions of the PGs must always be considered. There are several key points to note: (a) COX-1 generates PGs that are responsible for *mucosal defense* (i.e., secretion of bicarbonate and mucus, mucosal blood vessel attenuation of constriction, and mucosal epithelial regeneration), as well as TXA_2, which is necessary for platelet function; (b) COX-2 produces

PGs that function in the prevention and promotion of healing of mucosal erosions, and exert anti-inflammatory effects by inhibiting leukocyte adherence, as well as play a role in renal protection and maturation;[145] and (c) COX-3 produces PGs that exert a protective function by initiating fever.[143]

Thus, depending on the NSAID selected, primary plug formation of platelets, modulation of vascular tone in the kidney and gastric mucosa, cytoprotective functions within the gastric mucosa, smooth muscle contraction, and regulation of body temperature will all be affected.[145] In this regard, however, not all NSAIDs are created equal. As already noted, the COX-1, COX-2, and COX-3 enzymes make variable contributions to these functions, and individual NSAIDs inhibit each of these enzymes differently. Some NSAIDs inhibit both COX-1 and COX-2 (i.e., aspirin, phenylbutazone, ketoprofen [Anafen], ketorolac [Toradol], and flunixin meglumine [Banamine]); other NSAIDs preferentially inhibit COX-2 with only weak inhibition of COX-1 (i.e., meloxicam [Metacam], carprofen [Rimadyl], etodolac [Etogesic], vedaprofen [Quadrisol-5], and tolfenamic acid [Tolfedine]); and others inhibit COX-2 exclusively (i.e., deracoxib [Deramaxx] and firocoxib [Previcox]); whereas still another drug, acetaminophen, only weakly inhibits both COX-1 and COX-2 while inhibiting COX-3 activity preferentially.[141]

Several in vitro studies investigating NSAID selective inhibition of the COX-1 and COX-2 isoenzymes have been published, but their findings are very difficult to interpret because of inconsistencies in the assays used.[146] Clinically, this information is confusing because it does not consider the pharmacokinetics of particular drugs and their concentrations in various tissues.[147] Most NSAIDs that inhibit COX have been shown to result in diversion of arachidonate to the 5-LOX pathway. The 5-LOX is principally found in polymorphonuclear cells, mast cells, monocytes, basophils, and B lymphocytes that are recruited during inflammatory and immune reactions.[147] This enzyme catalyzes the initial step in leukotriene biosynthesis, which subsequently produces various eicosanoids, with leukotriene B_4 (LTB_4) being the most notable potent mediator of inflammation. The excessive production of leukotrienes has been implicated in the creation of NSAID-induced ulcers.[148,149] As always, however, the biological system is not clear-cut. Although the LOX pathway is proinflammatory, there is also an anti-inflammatory pathway,[150] which is discussed in more detail later.

The contribution of the leukotrienes to the inflammatory process would seem to suggest that inhibition of both the COX and 5-LOX pathways by a therapeutic agent would enhance the safety profile and may confer even greater analgesic efficacy because of broader anti-inflammatory and antinociceptive effects.[151] Data available show that dual acting compounds are effective in arthritic models, where they also retain antithrombotic activity, produce little or no gastrointestinal damage, and do not adversely affect the asthmatic state.[147] A dual COX–5-LOX inhibitor (tepoxalin [Zubrin]) has undergone clinical trials and is now approved for veterinary use.[151,152] Tepoxalin has demonstrated gastrointestinal anti-inflammatory activity in mice,[153] which supports the theory that 5-LOX inhibition can play a vital role in preventing NSAID-induced gastric inflammation.

Mechanisms of Analgesia

Prostaglandins, notably PGE_2 and prostacyclin, are potent mediators of inflammation and pain. These molecules exert hyperalgesic effects and enhance nociception produced by other mediators, such as bradykinin. The NSAIDs' analgesic mechanism of action is through inhibition of COX-1, COX-2, and COX-3 activity, with subsequent prevention of PG synthesis.

The antinociceptive effects of the NSAIDs are exerted both peripherally and centrally.[154] The NSAIDS penetrate inflamed tissues, where they have a local effect, which makes them excellent analgesic choices for treatment of injuries with associated inflammation, as well as conditions such as synovitis, arthritis, cystitis, and dermatitis.[154] The central action is at both the spinal and the supraspinal levels, with contributions from both COX-1 and COX-2.[154–158] This central effect may account for the overall well-being and improved appetite that are often observed in patients receiving parenterally administered NSAIDs for relief of acute pain.

The rational use of NSAIDs as analgesics should be based on an understanding of pain physiology and pathophysiology. Nociceptive pathways may involve either the COX-1 or COX-2 gene, and these genes are expressed in different locations and under different circumstances. The COX-2 isoenzyme, which is known as the inducible isoform because it is upregulated in inflammatory states, is known to play a key role in nociception. Although the COX-1 gene has traditionally been thought of as being expressed constitutively, this isoenzyme also plays an integral role in the pain experience.[142] The COX-1-selective NSAIDs are superior to COX-2-selective NSAIDs at inhibiting visceronociception caused by chemical pain stimulators in a mouse peritoneal model.[159] This has been confirmed by visceronociception being greatly reduced in COX-1, but not COX-2, knockout mice.[160] These studies concluded that peripheral COX-1 mediates nociception in slowly developing pain in mice, such as in visceral pain, and that central COX-1 may be involved in rapidly transmitted, nonvisceral pain, such as that caused by thermal stimulation.[160] Visceral pain may be mediated, at least in part, by stimulation of intraperitoneal receptors located on sensory fibers by COX-1-produced prostacyclin.[143] There may even be gender differences as in Ballou's mouse model, which demonstrated that spinal COX-2 did in fact contribute to visceral nociception, but only in female mice.[160] The analgesic potency of a range of NSAIDs in relieving tooth-extraction pain in human patients correlates closely with increasing selectivity toward COX-1 rather than COX-2. These findings highlight the importance of both COX-1 and COX-2 contributions to pain and the selective efficacy of the NSAIDs in treating various painful conditions and syndromes.

The COX-2 or inducible isoenzyme can increase by 20-fold over baseline in the presence of tissue injury and inflammation.[155] Proinflammatory cytokines and mitogens, such as interleukin 1β (IL-1β), interferon γ, and tumor necrosis factor α (TNF-α), induce COX-2 expression in macrophages, as can platelet-activating factor and PGE_2.[147] These events may also occur in chondrocytes, osteoblasts, and synovial microvessel endothelial cells. Higher COX levels increase prostenoid produc-

tion where these compounds serve as amplifiers of nociceptive input and transmission in both the peripheral and central nervous systems.[155] The COX-2-selective NSAIDs have been shown to be clinically useful in managing inflammatory pain in human and animal patients. This has been a focus of the pharmaceutical industry as a more selective COX-2 inhibitor might show efficacy in alleviating pain and hyperalgesia while sparing COX-1-constitutive activity and potential adverse effects traditionally associated with NSAID administration. Unfortunately, this biological system is not as simple as first envisioned. Although COX-2 is induced during inflammation, it has also been shown to be induced during resolution of the inflammatory response where the anti-inflammatory PGs (PGD_2 and $PGF_{2\alpha}$), but not proinflammatory PGE_2, are produced. Potentially, inhibition of COX-2 during this phase may actually prolong inflammation.[147] As is the case for COX-1, it now appears that the COX-2 isoenzyme also has important constitutive functions. Studies indicate there may be a protective role for COX-2 in maintenance of gastrointestinal integrity,[161] in ulcer healing,[162] and in experimental colitis in rats.[163] In addition, the COX-2 isoenzyme appears to have constitutive functions associated with nerve, brain, ovarian and uterine function, and bone metabolism.[161] Therefore, the potential for NSAID-associated side effects with these systems is of concern. Of major importance are the COX-2-constitutive functions within the kidney, which differ from those of COX-1 in hypotensive and hypovolemic states.[164] Also, COX-2 appears to be important in nephron maturation.[165] The canine kidney is not fully mature until 3 weeks after birth,[166] and administration of a NSAID during this time, or to the bitch prior to birth, may cause a permanent nephropathy. In fact, in COX-2 null mice, which lack the gene for COX-2, all animals die of renal failure before 8 weeks of age.[167] Renal failure does not occur in COX-1-null–developing mice, and they do not develop gastric pathology.[167]

When considering the COX selectivity of a particular NSAID, the concentration (i.e., dose) of the NSAID may also influence its actions. A drug may function as a competitive, nonpreferential, or selective COX inhibitor (COX-1 or COX-2) at higher concentrations, and as a COX-2-selective inhibitor at lower concentrations.[168] The significance of this is the potential for inhibition of COX-1 with administration of an allegedly COX-2-selective NSAID. The COX selectivity may be present in vitro; however, at the dosing required to achieve analgesia, such selectivity may be lost. Cloning studies comparing canine COX isoenzymes with human COX isoenzymes found that they are highly homologous.[169] Canine COX-1 and COX-2 had a 96% and 93% DNA-sequence homology, respectively, with their human counterparts. This suggests that they would be similarly affected by pharmaceuticals such as NSAIDs designed to inhibit their function. However, the distribution of the COX enzymes may differ among species. When reviewing the adverse effects of NSAIDs (e.g., gastrointestinal ulceration, renal perturbations, and hemorrhage), hemorrhage is the only pathology that appears to be clinically diminished by the use of the more COX-2-selective NSAIDs.

COX 2 is reduced after administration of glucocorticoids, which may partially explain the anti-inflammatory and analgesic effects of this class of medications. Of interest, in addition to the COX-2 role in inflammation, aberrantly upregulated COX-2 expression is increasingly implicated in the pathogenesis of a number of epithelial cell carcinomas, including colon, esophagus, breast, and skin, and in Alzheimer's disease and other neurological conditions.[170–172] For this reason, the COX-2 inhibitors are being researched as potential anticarcinogenic agents.[173]

Dissecting out the details of the derivation and specific actions of COX-1 and COX-2 continues to provide important insight into the management of pain with NSAIDs. The picture, however, remains incomplete because some NSAIDS do not significantly inhibit these enzymes. This finding stimulated the search for a potential COX-3 isoenzyme. Based on studies using canine cortex, a COX-3 isoenzyme was discovered that was derived from the same gene as COX-1.[142] The COX-3 isoenzyme is also present in human brain and heart tissues. It is distinct from COX-1 and COX-2 as demonstrated in studies using common analgesic-antipyretic NSAIDS in suppressing COX production. Acetaminophen inhibited COX-3 activity, but not COX-1 and COX-2, as does dipyrone.[142] Both of these agents are frequently used to reduce fever in animals. Other analgesic-antipyretic NSAIDs found to be effective COX-3 inhibitors are diclofenac (the most potent) and aspirin and ibuprofen (which preferentially inhibit COX-3 over COX-1 and COX-2). The overall conclusion of this particular study was that COX-3 possesses COX activity that differs pharmacologically from both COX-1 and COX-2, but is more similar to COX-1.[142] These findings indicate that the COX-3 isoenzyme is more susceptible to inhibition by drugs that are analgesic and antipyretic, but that lack anti-inflammatory activity. This observation again emphasizes the potential utility of administering NSAIDs with different COX selectivities for managing pain of different etiologies. As the COX-3 isoenzyme genetic profile is derived from the COX-1 gene, it appears that the COX-1 gene plays an integral role in pain and/or fever, depending on the physiological context.[142] This has been confirmed by the aforementioned studies.[143,159,160] The COX-1-selective NSAIDs with poor CNS penetration (i.e., ketoprofen and ketorolac) that are used in veterinary and human patients may, in fact, reach sufficient concentrations in the brain to inhibit COX-3.[174] It is also recognized that the analgesic effects of these NSAIDs frequently occur at lower dosages than those required to inhibit inflammation.

Fever Inhibition

Just as the relationship between pain and the various activities of the COX system is complex, so too is the association between fever and the COX isoenzymes. The mechanisms leading to the generation of fever vary depending on the inciting factor, which may be peripheral (i.e., endotoxin) or central (i.e., endogenous pyrogens, such as interleukin 1). Interspecies variation is also substantial, and the definitive role of the COXs in pyresis remains to be clearly elucidated. Evidence suggests that COX-2 plays a role in endotoxin pyrexia, whereas, based on the antipyretic effects of acetaminophen and aspirin, COX-1 and COX-3 appear to function in endogenous pyrexia.[141–143] Both of these drugs are effective in reducing fever in dogs. As an alternative in feline patients, ketoprofen[175] and meloxicam[176] have been

shown to be effective antipyretic agents. Ketoprofen appears to be a good antipyretic in both cats and dogs, and this action can often be achieved at a relatively low dose.

Endogenous Anti-inflammatory Mechanisms

Endogenously generated small chemical mediators, or *autacoids*, play a key role in controlling inflammation by inhibiting polymorphonuclear cell recruitment and enhancing monocyte activity in a nonphlogistic manner.[149] Arachidonic acid–derived lipoxins, particularly lipoxin A_4, have been identified as anti-inflammatory mediators, indicating that the LOX pathway has a dual proinflammatory and anti-inflammatory function.

The NSAIDs may amplify or decrease this endogenous anti-inflammatory system. Aspirin is more COX-1 selective and can impair many components of mucosal defense and enhance leukocyte adherence within the gastric and mesenteric microcirculation.[177] However, with chronic use of aspirin, an adaptation of the gastric mucosa is associated with a marked upregulation of COX-2 expression and lipoxin production. This lipoxin is specifically termed *aspirin-triggered lipoxin* (ATL). Aspirin is unique among current therapies because it acetylates COX-2, thereby enabling the biosynthesis of 15(R)-hydroxyeicosatetraenoic acid from arachidonic acid, which is subsequently converted to ATL by 5-LOX. Inhibition of either the COX-2 or 5-LOX enzymes causes blockade of ATL synthesis.[177] Lipoxin A_4 and ATL (a carbon-15 epimer of lipoxin) attenuate aspirin-induced leukocyte adherence, whereas administration of selective COX-2 inhibitors blocks ATL synthesis and has been shown to augment aspirin-induced damage and leukocyte adherence to the endothelium of mesenteric venules in rats.[177]

In addition to the lipoxins, aspirin-induced COX-2 acetylation generates numerous other endogenous autacoids derived from dietary omega-3 fatty acids.[178] Some of these local autacoids are potent inhibitors of neutrophil recruitment, thereby limiting the role of these cells during the resolution phase of inflammation, and thus are referred to as *resolvins*.[178] The identification of both the lipoxins and the resolvins has introduced new potential therapeutic avenues for the treatment of inflammation, cardiovascular disease, and cancer.

Pharmacological Considerations

The NSAIDs are effective analgesics as indicated by the human consumption of 120 billion aspirin tablets per year in addition to the many other NSAIDs currently on the market. Despite this, the safety profile of these analgesics remains a concern. A search for the NSAID without adverse gastrointestinal effects is still ongoing. Incorporation of a nitric oxide–generating moiety into the molecule of several NSAIDs has shown attenuation of the ulcerogenic effects of these drugs. However, nitric oxide has also been implicated in the pathogenesis of arthritis and subsequent tissue destruction.[147]

Because of their high protein binding, NSAIDs can displace other drugs from their plasma protein-binding sites and potentially increase their plasma concentration. This is rarely a concern unless NSAIDs are administered to patients with organ dysfunction or in those receiving other highly protein-bound medications with a narrow therapeutic index. Interference with the metabolism and excretion of certain coadministered drugs may occur; therefore, verifying the safety of combination therapy is always mandatory.

Some NSAIDs may induce the syndrome of inappropriate secretion of antidiuretic hormone (ADH). Renal water reabsorption depends on the action of ADH mediated by cyclic adenosine monophosphate (cAMP). As PGs exert a controlled negative-feedback action on cAMP production, inhibition of PG synthesis produces above-normal levels of cAMP with potential for enhanced ADH activity. In addition, the administration of a COX-2-selective NSAID may enhance sodium and water reabsorption. Clinically, both mechanisms may result in high-specific-gravity urine with dilutional hyponatremia. Urine volume may be decreased through this mechanism, but without renal injury.[179,180]

NSAID-induced renal insufficiency is usually temporary and reversible with drug withdrawal and administration of intravenous fluids. Accidental ingestion of NSAIDs should be managed with gastric lavage (if within 1 h) followed by administration of activated charcoal and gastric protectants. If evidence of gastric ulcers exist, aggressive sucralfate therapy is necessary. Intravenous fluid therapy should continue for at least 1 day. Therapy beyond this period will depend on the renal and gastric status of the individual patient.

Patient Selection and Therapeutic Considerations

The general health of a patient greatly influences the decision to use NSAIDs. Cats and dogs are more susceptible than people to the adverse effects of this class of drugs. Thus, the reported safety of any one NSAID in human patients should not be assumed to be so in veterinary patients. Most NSAIDs have a narrow safety margin, so accurate dosing is absolutely necessary.

The administration of NSAIDs for perioperative pain management should be restricted to animals older than 6 weeks that are well hydrated and normotensive. Patients should have normal hemostatic function, no evidence or concern for gastric ulceration, and normal renal and hepatic function. Although these are general guidelines, future studies may indicate that short-term management of acute pain by using COX-1-sparing and, to some degree, COX-2-sparing NSAIDs may prove safe in animals with minimally compromised liver or renal function. Patients should not receive corticosteroids and NSAIDs concurrently,[181] nor should different NSAIDs be administered concurrently.

The preemptive use of NSAIDs is controversial because of their potential for harm. An earlier study assessing the effects on the kidney of preoperative administration of ketorolac, ketoprofen, or carprofen resulted in variable alterations in parameters measured. The conclusions of the study were that, in clinically normal dogs undergoing elective surgery, the use of these NSAIDs was not contraindicated, although renal function was not measured and two dogs in each of the ketoprofen and ketorolac groups were azotemic.[182] Another study assessing effects of preoperative administration of ketoprofen on whole blood

platelet aggregation, buccal mucosal bleeding time, and hematologic indices in dogs undergoing elective ovariohysterectomy showed a decrease in platelet aggregation for at least 1 day after surgery. Mucosal bleeding time and hematologic indices did not change.[183] Other studies, specifically assessing efficacy and safety of NSAIDs given preoperatively in a variety of surgical procedures where intraoperative fluid therapy was administered and patient monitoring was conducted, noted adverse reactions with some of the NSAIDs.[123,184,185] A study conducted at the Ontario Veterinary College demonstrated no adverse effects with the administration of meloxicam or carprofen prior to orthopedic or soft tissue surgery in both cats (meloxicam) and dogs (meloxicam or carprofen) (unpublished data). In these studies, the preoperative administration of a NSAID provided very good to excellent analgesia. A laboratory study investigating potential adverse effects on glomerular filtration rate in dogs receiving meloxicam, carprofen, or saline prior to anesthesia and a painful stimulus failed to demonstrate a reduced glomerular filtration rate, and intravenous fluids were not administered in this study.[186] The benefit of preoperative administration of NSAIDs is the potential for a preemptive effect and the presence of analgesia upon recovery. When NSAIDs are administered postoperatively, opioids are often given concurrently, as 45 min is required to obtain a therapeutic effect with a NSAID, regardless of route. Another potential approach could be to administer the NSAID parenterally prior to completing the surgical procedure at least 45 min prior to extubation. Often it is difficult to distinguish the difference in the analgesic effects produced by preoperative versus intraoperative NSAID administration. For prolonged operative procedures, the benefit of a longer postoperative effect may be seen with administration of the NSAID upon completion, rather than at the start, of the procedure.

Effective plasma levels of NSAIDs are reached within 1 h after oral administration.[187–189] When NSAIDs are administered per os, they must be given with food to protect the gastric mucosa. If food is not present in the stomach, the contact area of the tablet on the mucosa results in a high localized concentration of the drug, increasing the potential for localized ulcer formation. It is important to remember that the potential for ulceration exists with all NSAIDs regardless of the route of administration.

Pain Management

The indications proposed here assume there are no contraindications to their use.

Postoperative Pain

The NSAIDs are extremely valuable in selected orthopedic[123,182,190,191] and soft tissue surgical procedures,[184,192–197] especially where extensive inflammation or soft tissue trauma is present. Opioid administration is preferred immediately after any surgical procedure, because the sedative-analgesic effects of this class of drugs help to ensure a smooth recovery. Injectable NSAIDs (carprofen, ketoprofen, meloxicam, or tolfenamic acid) can be coadministered initially with an opioid and subsequently used alone following orthopedic and selected soft tissue surgery; however, this depends on the degree of pain an animal is experiencing. Oral NSAIDs may be administered when an animal is able to eat. The initial dose of NSAID depends on the expected severity of pain. For example, a difficult fracture repair would require the recommended loading dose, but a laparotomy without complications could be successfully treated with half this dose. A sliding-scale approach similar to that used with the opioids for managing varying degrees of anticipated pain is also recommended for the NSAIDs; however, the upper dosing limit must not be exceeded.

Inflammatory Conditions

For relief of pain caused by meningitis, bone tumors (especially after biopsy), soft tissue swelling (mastitis), polyarthritis, cystitis, otitis, or severe inflammatory dermatologic diseases or injury (e.g., degloving and animal bites), the NSAIDs may be more efficacious than opioids. However, as many of these patients may be more prone to NSAID toxicity, careful patient selection and management are advised. The combination of an opioid with a low dose of NSAID is also effective in these conditions. An exception is necrotizing fasciitis, where NSAIDs may actually increase morbidity and mortality.[198]

Osteoarthritis

Few long-term studies evaluating the adverse effects of NSAIDs have been completed. A short-term study (12 days) assessing the effect of carprofen on platelet aggregation and activated partial thromboplastin time in Labrador retrievers showed, after 5 days of treatment, a reduction in platelet aggregation that persisted after treatment was discontinued for 7 days. The activated partial thromboplastin time was similarly affected as times were prolonged over baseline during this period, although they remained within normal range. The conclusions of this study, however, were that these alterations were minor and not clinically important.[199] The major adverse effects associated with long-term use of carprofen,[200] meloxicam,[201] or etodolac[202] for osteoarthritis are predominantly associated with the gastrointestinal tract. Gastroduodenal pathology associated with buffered aspirin, carprofen, etodolac, and placebo has been evaluated in healthy dogs after a 4-week course of administration. Two independent studies concluded that the administration of carprofen, etodolac, or placebo produced significantly fewer gastroduodenal lesions in dogs than did buffered aspirin.[203,204] Similar studies comparing ketoprofen with aspirin and placebo,[205] and comparing carprofen, meloxicam, and ketoprofen to aspirin and placebo,[206] noted that these NSAIDs produced mild to moderate gastrointestinal lesions that were similar to placebo, but significantly less severe than those produced by aspirin. A sliding-scale approach of NSAID administration for chronic use is highly recommended. As many patients with osteoarthritis are geriatric, a rapid reduction of the dose to affect a comfortable state is advised to reduce potential toxicity. For example, alternating to every-third-day therapy of meloxicam with half the recommended label dose proved efficacious in some dogs during a 1-year period.[201] If an individual patient requires persistent high doses of a particular NSAID to manage pain, prescribing a different NSAID may be more effective because of individual vari-

ation in response and effect, as previously discussed. When the adverse effects of a NSAID are a concern, reducing the dose and adding an analgesic of a different class (e.g., tramadol) may be equally effective for the treatment of chronic severe pain. However, for many geriatric animals with renal insufficiency, NSAIDs may be the only effective class of analgesic. For these animals, quality of life is a major issue. In this situation, meloxicam (in both cats and dogs) or carprofen (in dogs only) titrated down to the lowest effective dose has been used in patients with renal insufficiency with minimal or no worsening of renal function over time (personal communication).

During NSAID therapy, all patients should be monitored for hematochezia or melena, vomiting, increased water consumption, and nonspecific changes in demeanor. If any of these occur, the owner should be instructed to stop the medication and consult a veterinarian. Intermittent monitoring of creatinine and alanine aminotransferase (ALT) is recommended when the use of NSAIDs is prescribed on a chronic basis. Another important consideration for chronic use is the potential effect of NSAID therapy on joint and cartilage metabolism. Studies investigating the effects of carprofen[207,208] and meloxicam[209] at therapeutic doses found no toxicological or pharmacological actions on cartilage proteoglycan metabolism. In addition, meloxicam may have the potential for controlling cellular inflammatory reactions at inflamed sites in the joints of patients with osteoarthritis.[209]

Miscellaneous Conditions

Other indications for the use of NSAIDs are panosteitis, hypertrophic osteodystrophy (HOD), cancer pain (especially of bone), and dental pain. The NSAIDs with selective COX-1 inhibition should be used with caution after dental extractions where bleeding is, or may be, of concern. Meloxicam and carprofen have minimal, if any, antithromboxane activity and should, therefore, not interfere with platelet adhesion. For severe panosteitis and HOD, the full loading dose of a NSAID is required to obtain a suitable effect. The HOD of Weimaraners is poorly responsive to NSAID therapy and is better treated with high-dose, short-term corticosteroids, provided infectious disease has been ruled out and clinical signs are consistent with HOD alone.[210]

Contraindications

NSAIDs should not be administered to patients with acute renal insufficiency, hepatic insufficiency, dehydration, hypotension, or conditions associated with low *effective circulating volume* (e.g., congestive heart failure or ascites), coagulopathies (e.g., factor deficiencies, thrombocytopenia, or von Willebrand's disease), or evidence of gastric ulceration (i.e., vomiting with or without the presence of "coffee ground material" or melena). Administration of NSAIDs following gastrointestinal surgery must be determined by the overall health of the gut at the time of surgery. As the COX-2 isoenzyme is important for healing, intuitively NSAIDs producing potent COX-2 enzyme inhibition would be contraindicated where compromised bowel is noted. Concurrent use of other NSAIDs (e.g., aspirin) or corticosteroids is not recommended. The use of COX-1-preferential NSAIDs is contraindicated in patients with spinal injury (including herniated intervertebral disc) because of the potential for hemorrhage and neurological deterioration, and because of excessive bleeding at the surgical site should surgical treatment be pursued. The NSAIDs should never be administered to patients in shock, trauma patients upon presentation, or patients with evidence of hemorrhage (e.g., epistaxis, hemangiosarcoma, or head trauma). The condition of patients with severe or poorly controlled asthma, such as feline asthma, or other types of moderate to severe pulmonary disease, may deteriorate with NSAID administration. Aspirin administration has been documented to exacerbate asthma in human patients, but the administration of COX-2-specific NSAIDs did not worsen clinical signs.[211] It is unknown whether animals may be affected in this way. Although administration of NSAIDs in head trauma, pulmonary diseases, or thrombocytopenia is generally contraindicated, the use of COX-2-preferential NSAIDs (i.e., meloxicam, etodolac, carprofen, tolfenamic acid, firocoxib, or deracoxib) may prove to be safe with further study. Because of inhibition of PG activity, the NSAIDs may be detrimental to reproductive function. Indomethacin may block prostaglandin activity in pregnant women, causing cessation of labor, premature closure of the ductus arteriosus in the fetus, and disruption of fetal circulation.[161] These effects may also occur in animals, so NSAIDs should not be administered during pregnancy. As COX-2 induction is necessary for ovulation and subsequent implantation of the embryo,[161] the use of NSAIDs should also be avoided in breeding females during this stage of the reproductive cycle. As previously mentioned, the COX-2 isoenzyme is required for maturation of the embryological kidney, so COX-2 administration to lactating mothers should be avoided.

Topical NSAIDs do not appear to be associated with the same adverse gastrointestinal effects noted when these same drugs are taken orally,[212] and topical administration has proven to be significantly more effective than placebo in many human clinical trials involving acute and chronic painful conditions.[213] A liposomal topical cream formulation of 1% diclofenac sodium (Surpass) has recently been approved by the U.S. Food and Drug Administration as a topical anti-inflammatory cream for the control of joint pain and inflammation associated with osteoarthritis in horses. The results of clinical field trials indicate that the product is safe, easy to use, and effective in reducing lameness caused by degenerative joint disease in this species. When applied topically (a 5-inch strip of cream) for 10 consecutive days to a single fetlock, diclofenac was present in all serum samples up to 2 days after the final application.[214] The term *locally enhanced topical delivery* (LETD) has been used to describe the local accumulation of drug to the target tissues. This effect has been documented in horses when using the 1% diclofenac liposomal formulation.[215] Consistent with its prolonged effect at the target tissue, diclofenac was slowly absorbed and eliminated following its application. When compared with other conventional topical creams and ointments, liposomal preparations provide better penetration and a more sustained release of agent. There are no well controlled published studies investigating the clinical use of topical formulations of NSAIDs in dogs and cats at the date of this writing.

Specific NSAIDs

Recommended dosages are listed in Tables 10.4 through 10.6.

Meloxicam (Oral Liquid and Parenteral Formulations)

Meloxicam is a COX-2-preferential NSAID approved for oral use in dogs in Australasia, Europe, and North America. The parenteral formulation is approved for cats in Australasia and the United States. Its use in cats in Canada is under investigation at the time of this writing, with completed studies indicating safety and efficacy. Its use in horses is also under investigation, with pharmacokinetic studies indicating that the half-life is shorter and clearance greater than in dogs, which suggests that dosing more than once a day may be necessary.[216]

Studies indicate no renal or hepatic abnormalities with acute administration[184] and minimal to no antithromboxane activity,[217] suggesting that hemostasis in normal animals may not be a problem. Very few adverse reactions have been documented, and most involve the gastrointestinal tract. A 2003 study showed no difference in gastric erosions over saline placebo when meloxicam was administered at 0.1 mg/kg for 3 days after electrical stimulation (i.e., surgical simulation) under anesthesia. However, the administration of corticosteroids plus meloxicam caused significant gastric erosions.[181] A case report of the administration of a combination of aspirin and meloxicam in a dog detected duodenal perforation.[218] This case illustrates the importance of COX-2 in intestinal protection when aspirin is coadministered, and rein-

Table 10.4. Dosage ranges (mg/kg unless otherwise indicated) for NSAIDs in dogs and cats

NSAID[a]	Indication	Species/Dose/Route	Frequency
Ketoprofen	Surgical pain	Dogs, ≤ 2.0 IV, SC, IM, PO	Once
		Cats, ≤ 2.0 SC	Once
		then dogs and cats, ≤ 1.0 IV, SC, IM, PO	q 24 h
		Dogs and cats, ≤ 2.0 PO	
	Chronic pain	then ≤ 1.0	Once
Meloxicam	Surgical pain	Dogs, ≤ 0.2 IV, SC	Once
		then ≤ 0.1 IV, SC, PO	q 24 h
	Chronic pain	Dogs,≤ 0.2 PO	Once
		then ≤ 0.1 PO	q 24 h
	Surgical pain	Cats, ≤ 0.2 SC, PO	Once
		then ≤ 0.1 SC, PO lean weight	q 24 h for 2–3 days
	Chronic pain	Cats, ≤ 0.2 SC, PO	Once
		then ≤ 0.1 PO lean weight	q 24 h for 2–3 days
		then 0.025 PO or (0.1 mg/CAT max) lean weight	3–5 × weekly
Carprofen	Surgical pain	Dogs, ≤ 4.0 IV, SC, IM	Once at induction
		then ≤ 2.2 PO	Repeat q 12–24 h
		Cats, ≤ 4.0 SC lean weight	Once at induction only
	Chronic pain	Dogs, ≤ 2.2 PO	q 12–24 h
Etodolac	Chronic pain	Dogs, ≤ 10–15 PO	q 24 h
Tolfenamic acid	Acute, chronic pain	Dogs and cats, ≤ 4 SC, PO	q 24 h for 3 days, 4 days off, then repeat cycle
Firocoxib	Chronic pain	Dogs, 5.0 PO	q 24 h
Flunixin meglumine	Surgical pain	Dogs, ≤ 1.0 IV, SC, IM	Once
		Cats, 0.25 SC	q 12–24 h PRN × 1 or 2 doses
	Pyrexia	Dogs and cats, 0.25 SC	q 12–24 h PRN × 1 or 2 doses
	Ophthalmologic procedures	Dogs, 0.25–1.0 SC, IM	q 12–24 h PRN × 1 or 2 doses
Ketorolac	Surgical pain	Dogs, 0.3–0.5 IV, IM	q 8–12 h × 1 or 2 doses
		Cats, 0.25 IM	q 12 h × 1 or 2 doses
	Panosteitis	Dogs, 10-mg total dose in dogs ≥ 30 kg PO 5-mg total dose in dogs > 20 kg < 30 kg PO	q 24 h for 2–3 days
Deracoxib	Surgical pain	Dogs, ≤ 3–4 PO	q 24 h for 3–7 days
	Chronic pain	Dogs, ≤ 1–2 PO	q 24 h
Tepoxalin	Chronic pain	Dogs, 10 PO	q 24 h
Piroxicam	Inflammation of the lower urinary tract	Dogs, 0.3 PO	q 24 h × 2 doses then q 48 h
Acetaminophen	Acute, chronic pain	Dogs, 15 PO (contraindicated in cats)	q 8 h
Aspirin	Acute, chronic pain	Dogs, 10 PO	q 12 h

CAT max, maximal dose in cats; IM, intramuscularly; IV, intravenously; NSAID, nonsteroidal anti-inflammatory drug; PO, per os (orally); PRN, as necessary; SC, subcutaneously.

[a]See the text for details on contraindications for use.

Table 10.5. Dosage ranges (mg/kg) of NSAIDs in horses

NSAID[a]	Dose	Route	Frequency	Notes
Phenylbutazone	2–4	PO, IV	q 12 h	Reduce to 2 mg/kg on day 2
Flunixin meglumine	1	PO, IV, IM	q 12–24 h	
Ketoprofen	2–3	IV	q 24 h	
Carprofen	0.7	IV	q 24 h	
Eltenac	0.5	IV	q 24 h	
Diclofenac	5-inch ribbon of cream	Transdermal	q 12 h	Apply liposomal cream over 1 joint only twice daily
Vedaprofen	1	IV	q 24 h	
Meloxicam	0.6	IV	q 12 h	

IM, intramuscularly; IV, intravenously; NSAID, nonsteroidal anti-inflammatory drug; PO, per os (orally).
[a]See text for details on contraindications for use.

Table 10.6. Dosage ranges (mg/kg) of NSAIDs in ruminants

NSAID[a]	Dose	Route	Frequency	Notes
Phenylbutazone	2–6	PO, IV	q 24 h	Prohibited in dairy cattle >20 months of age
Flunixin meglumine	1	PO, IV, IM	q 12 or 24 h	
Ketoprofen	3	IV, PO	q 24 h	
Carprofen	0.7	IV	q 24–48 h	Sheep
Aspirin	100	PO	q 12 h	

IM, intramuscularly; IV, intravenously; NSAID, nonsteroidal anti-inflammatory drug; PO, per os (orally).
[a]See text for details on contraindications for use.

forces the concept that different NSAIDs should not be administered concurrently. Analgesia is excellent when meloxicam is combined with an opioid. Meloxicam has proven to be beneficial in the treatment of sodium urate–induced synovitis[219] and panosteitis[220] in dogs, and radiation-induced stomatitis in cats.[221]

Carprofen (Tablet and Parenteral Formulations)

Although classified as a NSAID, carprofen administration to beagles did not inhibit PGE_2, 12-hydroxyeicosatetraenoic acid, or TXB_2 synthesis in an experimental study using subcutaneous tissue cage fluids.[222] It was concluded that the principle mode of action of carprofen must be by mechanisms other than COX or 12-lipoxygenase inhibition. However, more recent studies indicate that it is a COX-2-preferential NSAID.[146,223] Carprofen is approved for perioperative and chronic pain management in dogs in Australasia, Europe, and North America. Carprofen is approved for single-dose, perioperative use in cats in Europe and is licensed for use in horses in the United Kingdom. In sheep, carprofen (0.7 mg/kg intravenously) produced plasma concentrations of 1.5 μg/mL, similar to those required to confer analgesia in horses, for up to 48 h.[224] However, analgesia was not assessed in this sheep study.[224] Antithromboxane activity is minimal,[217,225] suggesting that induced coagulopathy may not be a problem in patients with intact hemostatic mechanisms.

According to the European literature, potential adverse effects of NSAIDs, such as nephrotoxicity, hepatotoxicity, gastrointestinal bleeding, or hemostatic deficiencies have not been reported with carprofen use.[198] Acute hepatotoxicity and death after carprofen administration have been reported among dogs with previously reported normal liver function (with Labrador retrievers highly represented).[226] Carprofen provides good analgesia from 12 h[182,192] to 18 h after a variety of orthopedic procedures. In cats undergoing ovariohysterectomy, carprofen administration provided profound analgesia between 4 and 20 h postoperatively.[193]

Ketoprofen (Tablet and Parenteral Formulations)

Ketoprofen is approved for treatment of postoperative and chronic pain in both dogs and cats in Europe and Canada. It is also approved for use in horses and ruminants. As ketoprofen is an inhibitor of both COX-1 and COX-2, adverse effects are a potential problem requiring careful patient selection. Although several studies using ketoprofen preoperatively indicate its effectiveness in controlling postoperative pain,[182,184,190] a general consensus among practitioners has restricted its use primarily to the postoperative period to reduce the potential for hemorrhage. Ketoprofen should not be administered to patients with risk factors for hemorrhage. It is often administered to animals immediately after orthopedic procedures (e.g., fracture repair, cruciate repair, or onychectomy); however, it is advised to restrict administration after laparotomy or thoracotomy until such time that hemorrhage is not a concern and when intracavitary drainage tubes have been removed.

In a study investigating the efficacy of NSAIDs in controlling postoperative pain, ketoprofen conferred a very good to excellent analgesic state for up to 24 h when compared with butorphanol.[184] Ketoprofen administration has also been suggested for management of pain associated with hypertrophic osteodystrophy and panosteitis in dogs. Gastroprotectants should be coadministered. Occasional vomiting may be seen when ketoprofen is administered chronically. It has also been recommended in horses.[227] In foals less than 1 day old, the volume of distribution is larger and the clearance is reduced, which indicate that this drug has a longer elimination half-life in foals.[228] In ponies, synovial concentrations of ketoprofen are achieved after intravenous injection and will last for up to 4 h.[229] After oral administration, ketoprofen was an effective analgesic in 4- to 8-week-old calves undergoing dehorning,[230] and in 8- to 16-week-old calves when administered intravenously in conjunction with lidocaine injection of the testicles for castration.[231]

Etodolac (Tablet Formulation)

Etodolac is a COX-2-preferential NSAID approved in the United States for use in dogs for the management of pain and inflammation associated with osteoarthritis,[202,232] but is also useful in other painful conditions. The adverse effects appear to be primarily restricted to the gastrointestinal tract.

Deracoxib and Firocoxib (Tablet Formulations)

Deracoxib is a coxib-type COX-2-specific inhibitor approved in the United States and Canada for control of postoperative pain and inflammation associated with orthopedic surgery and chronic osteoarthritic pain in dogs. Firocoxib is the most COX-2 selective NSAID available in veterinary medicine and the most recently approved NSAID for the control of osteoarthritic pain in dogs in the United States. The incidence of vomiting and diarrhea were similar in dogs receiving deracoxib and those receiving placebo in a perioperative field trial, and overall the drug was well tolerated and effective.[233] It was also shown to be effective in attenuating lameness in dogs with urate crystal–induced synovitis after prophylactic and therapeutic administration.[234,235] The coxib group of NSAIDs were originally marketed as being more gastroprotective in human patients when compared with the less COX-1-sparing NSAIDs such as aspirin.[236] However, more recent findings and large-scale usage in human patients have indicated that coxib NSAIDs do not necessarily guarantee gastroprotection with chronic use. In a more recent canine study comparing the gastrointestinal safety profile of licofelone (a dual COX-LOX inhibitor) with rofecoxib (a similar coxib-type COX-2 inhibitor to deracoxib and firocoxib), rofecoxib was found to induce significant gastric and gastroduodenal lesions.[237] It has been recommended by some investigators that coxib-type NSAIDs not be administered for a period of 1 week after a previously administered NSAID or steroid has been discontinued.

Tepoxalin (Dissolvable Wafer)

Tepoxalin is a COX-1, COX-2, and LOX inhibitor of varying degrees with efficacy comparable to meloxicam or carprofen and safety comparable to placebo.[238] Tepoxalin has been approved for management of osteoarthritic pain in dogs. The safety profile of tepoxalin showed no difference from that of placebo when administered prior to a 30-min anesthesia period and a minor surgical procedure in dogs.[239]

Tolfenamic Acid (Tablet and Parenteral Formulations)

Tolfenamic acid is approved for use in cats and dogs in Europe and Canada for controlling acute postoperative and chronic pain. The dosing schedule is 3 days on and 4 days off, which must be strictly adhered to. Reported adverse effects are diarrhea and occasional vomiting. Tolfenamic acid has significant anti-inflammatory and antithromboxane activity,[240] so posttraumatic and surgical hemostasis may be compromised during active bleeding after administration of this NSAID.

Flunixin Meglumine (Parenteral Formulation)

Flunixin meglumine, which is a COX-1 and COX-2 inhibitor, is approved for use in dogs in Europe, but not in North America. It is also approved for use in ruminants and horses. Flunixin is commonly used to treat colic pain in horses. In foals less than 1 day old, pharmacokinetic data suggest increasing the dose by as much as 1.5 times the adult dose to achieve comparable therapeutic concentrations; however, longer dosing intervals are necessary to avoid toxicity.[241] Dosages for cattle are similar to those in horses. In dogs, it is reported to be an effective analgesic for surgical pain;[123,195] however, the potential for side effects such as increased ALT,[123] nephrotoxicity,[123,185,242] and gastric ulceration[243] is a major concern. Flunixin is also used as an anti-inflammatory in selected ophthalmologic surgical procedures, but safer NSAIDs appear to be as effective in this setting.

Phenylbutazone (Powder and Parenteral Formulations)

Phenylbutazone is approved for use in horses, cattle, and dogs in North America. Since safer NSAIDs are approved for dogs, phenylbutazone is not recommended for this species. In horses, there is high risk of gastric ulceration and nephrotoxicity,[244] where signs of toxicity may progress from inappetence and depression to colic, gastrointestinal ulceration, and weight loss.[245,246] In horses recovering from arthroscopic surgery, phenylbutazone administered prior to surgery and for 21/2 days afterward improved analgesic outcome when compared with a placebo group.[247] Phenylbutazone has a prolonged elimination half-life in cattle, ranging from 30 to 82 h.[248,249] Phenylbutazone administration to dairy cattle 20 months of age or older is prohibited by the U.S. Food and Drug Administration to avoid the presence of residues that are toxic to people.

Eltenac (Parenteral Formulation and Topical Gel)

In horses, eltenac induced minimal side effects when 0.5 mg/kg was used during an investigative study.[250] When used in an endotoxemic horse model, eltenac improved outcome parameters when compared with placebo, and it was proposed that this NSAID may provide clinical benefit in horses with naturally occurring endotoxemia.[251]

Vedaprofen (Oral and Parenteral Formulations)
The oral form is approved for use in dogs in Europe and Canada. The parenteral form is approved for use in horses in Europe and North America and has very similar pharmacokinetic and pharmacodynamic properties to those of ketoprofen.[252,253]

Ketorolac (Parenteral Formulation)
Ketorolac, which is a COX-1 and COX-2 inhibitor, is not approved for use in veterinary patients, but is included for the benefit of those working in the research setting where the availability of ketorolac is more likely than other NSAIDs. Ketorolac is comparable to oxymorphone in efficacy and to ketoprofen in duration and efficacy in managing postlaparotomy and orthopedic pain in dogs.[123] Only one to two doses should be administered to dogs or cats. Ketorolac has been used successfully for treatment of severe panosteitis in dogs where all other therapies had failed. It is recommended that ketorolac be administered with food or gastroprotectants to decrease the incidence of gastric irritation.

Piroxicam (Capsule Formulation)
Piroxicam is not approved for use in veterinary patients, but has proven valuable for its anti-inflammatory effects on the lower urinary tract in dogs with transitional cell carcinoma or cystitis and urethritis. The administration of gastroprotectants is recommended.[254]

Acetaminophen (Tablet and Oral Suspension Formulations)
Acetaminophen is a COX-3 inhibitor with minimal COX-1 and COX-2 effects. It is not approved for use in veterinary patients. It should not be administered to cats because of deficient glucuronidation of acetaminophen in this species.[255] It may be administered to dogs as an antipyretic and analgesic for mild pain and can be used in combination with opioids for a synergistic analgesic effect or opioid-sparing effect.[141,142] It can be prescribed as an individual drug that can be coadministered with an opioid (this approach allows more flexibility in dosing of the opioid), or in a proprietary combined formulation with an opioid (e.g., codeine plus acetaminophen, or oxycodone plus acetaminophen).

Aspirin (Tablet Formulation)
Aspirin, which is primarily a COX-1 inhibitor, is most commonly used as an analgesic for osteoarthritic pain in dogs. It is also available in proprietary combinations with various opioids (aspirin plus codeine, or aspirin plus oxycodone) to achieve a synergistic effect for the treatment of moderate pain. It is also used as an antipyretic and anticoagulant in dogs and cats. Aspirin has also been evaluated as an analgesic in cattle.[256]

Dipyrone (Tablet and Parenteral Formulations)
Dipyrone, which is a COX-3 inhibitor, is approved for use in cats and dogs in Europe and Canada. It should be given intravenously to avoid the irritation experienced when given intramuscularly. The analgesia produced is not usually adequate for moderate to severe postoperative pain, and dipyrone is reserved for use as an antipyretic in cases where other NSAIDs are contraindicated. Nephrotoxicity or gastric ulceration is not a major concern in the short term even in critically ill patients. Dipyrone administration induces blood dyscrasias in human patients, but this has not been reported in animals.

Diclofenac (Topical Liposomal Cream Formulation)
Diclofenac is a phenylacetic acid NSAID that is a nonselective cyclooxygenase inhibitor commonly used in human patients. There is no oral or parenteral formulation available in veterinary medicine, but a topical cream has recently been approved by the Food and Drug Administration for use in horses. This liposomal cream formulation of 1% diclofenac provides a novel therapeutic modality for the local application of NSAID-type anti-inflammatory drugs. Dosing is achieved by applying a 5-inch ribbon of topical cream to only one affected joint twice daily for no more than 10 consecutive days. Rubber gloves should be worn when applying and rubbing the cream into the skin covering the painful joint. The cream is stored at room temperature and should not be frozen. Simultaneous multiple-joint application can result in excessive absorption and high serum concentrations with an increased potential for severe NSAID-type adverse reactions.

Analgesic Adjuvants

Analgesic adjuvants are defined as drugs that have primary indications other than pain, but that possess analgesic actions in certain painful conditions. This definition encompasses a very diverse group of drugs and distinguishes the analgesic adjuvants from the so-called traditional analgesics, which include the opioids, the NSAIDs, and the local anesthetics. It is only recently that analgesic adjuvants have begun to be used in veterinary medicine, and most therapeutic recommendations have been extrapolated from experience with human patients and subsequently applied to companion animals.

As the name implies, these agents are typically coadministered with the traditional analgesics. They have been used most often in the management of chronic pain states; however, their use in acute pain settings is increasing, and certain adjuvant agents have become common analgesic supplements during the perioperative period. In the chronic pain setting, the adjuvant analgesics are administered (a) to manage pain that is refractory to traditional analgesics, (b) to enable the dose of traditional analgesics to be reduced in order to lessen side effects, and (c) concurrently to treat a symptom other than pain. In some clinical settings, such as chronic neuropathic pain syndromes, adjuvant analgesics have become so well accepted that they are administered as the first-line therapy in human patients.

When contemplating administration of an adjuvant analgesic, veterinarians must be aware of the drug's clinical pharmacology and its particular use in patients with pain. The following information about the drug is necessary: (a) approved indications, (b) unapproved indications (e.g., for analgesia) that are widely accepted in veterinary medical practice, (c) common side effects and uncommon but potentially severe adverse effects, (d) important pharmacokinetic features, and (e) specific dosing guidelines for pain.

Table 10.7. Potential analgesic adjuvants in veterinary clinical practice

α_2-Agonists	NMDA receptor antagonists
Medetomidine	Ketamine
Detomidine	Amantadine
Romifidine	Methadone
Antidepressants	Memantine
Amitriptyline	Anticonvulsants
Imipramine	Gabapentin
Paroxetine	Carbamazepine
Oral local anesthetics	Clonazepam
Mexiletine	Miscellaneous analgesics
Tocainide	Tramadol
Flecainide	
Others	
Capsaicin	
Calcitonin	
Magnesium	
Bisphosphonates	
Radiopharmaceuticals	

NMDA, *N*-methyl-D-aspartate.

Table 10.8. Dosage ranges (mg/kg) for analgesic adjuvants in selected domestic species

Analgesic Adjuvant	Dogs	Cats
Ketamine	0.5 IV loading dose 0.1–0.5/h IV CRI	0.5 IV loading dose 0.1–0.5/h IV CRI
Medetomidine	0.002–0.015 IV, IM	0.005–0.02 IV, IM
Gabapentin	2–10 PO q 8–12 h	2–10 PO q 8–12 h
Amantadine	3–5 PO q 24 h	3–5 PO q 24 h
Tramadol	2–10 PO q 12–24 h	?

CRI, continuous-rate infusion; IM, intramuscular(ly); IV, intravenous(ly); PO, per os (orally); ?, reliable doses have not been established for this species.

Numerous drugs may be considered as analgesic adjuvants in veterinary medicine today (Table 10.7). Some of these, such as ketamine and the α_2-agonists, are familiar to practitioners, whereas others have not been used historically in veterinary medicine. Much of the evidence substantiating the use of these agents comes from laboratory-animal research, clinical trials in humans, or anecdotal reports in human or animal patients. The following section briefly reviews the current state of knowledge regarding selected analgesic adjuvants in veterinary medicine (see Table 10.8 for recommended dosages).

Ketamine

Ketamine is a dissociative anesthetic and has been used for decades in veterinary medicine. More recently, it has been recognized as an NMDA receptor antagonist and, at very low doses, can contribute substantially to analgesia by minimizing CNS sensitization.

α_2-Agonists

Xylazine and, more recently, medetomidine, detomidine, and romifidine have been used extensively to provide sedation in a variety of veterinary species. Medetomidine and detomidine in particular have considerable analgesic potential, even in microdoses, and can be administered via a number of novel routes and techniques to supplement analgesia and enhance the analgesic actions of other agents in various painful conditions.

Gabapentin

Gabapentin is a human anticonvulsant drug that has been approved by the U.S. Food and Drug Administration since 1993.[10] Several years later, reports of its antihyperalgesic effects in rodent experimental pain models, as well as case reports and uncontrolled clinical trials involving human patients suffering from neuropathic pain, began to appear in the literature. Gabapentin's mechanism of analgesic action is unknown, but there is evidence to suggest that it may increase central inhibition or reduce the synthesis of glutamate, even though it does not appear to interact directly with NMDA receptors.[99]

Despite the lack of controlled data available at this time, gabapentin administration has been advocated for the management of a variety of human neuropathic pain syndromes[99,257] and more recently for management of incisional pain and arthritis.[258–261] In human clinical trials, side effects occur in approximately 25% of patients, are usually mild and self-limiting, and include drowsiness, fatigue, and weight gain with chronic administration. There are only anecdotal reports of its use in veterinary patients. Dosing guidelines in dogs and cats have been extrapolated from human dosing recommendations. Dosage modifications are often based on the clinical efficacy achieved in individual veterinary patients. Though it is not possible to make specific scientific recommendations of dosage and indication in specific species, with owner consent, both gabapentin and pregabalin have been increasingly used by veterinary practitioners striving to better manage chronic neuropathic pain of both malignant and nonmalignant origins in companion animals.

Amantadine

Amantadine is an antiviral agent developed to inhibit the replication of influenza A in human patients.[10] It has also been shown to have efficacy in the treatment of drug-induced extrapyramidal effects and in the treatment Parkinson's disease. More recently, amantadine administration has been advocated for the treatment of various types of pain. The drug appears to exert its analgesic effects through antagonism of NMDA receptors in a manner analogous to ketamine. Though controlled clinical human trials are lacking, amantadine seems most efficacious in the management of chronic neuropathic types of pain characterized by hyperalgesia and allodynia.[262,263] Patients suffering from opioid tolerance may also respond favorably to amantadine therapy, and some studies suggest that the drug may even find a place in peri-

operative pain management.[264] There are, at this writing, no well-controlled published studies evaluating the analgesic effects of amantadine in veterinary patients, and dosing recommendations are based largely on anecdotal reports. As the management of chronic pain in companion animals continues to receive much attention in veterinary medicine, the use of amantadine and other drugs with a similar mechanism of action is likely to become more prevalent.

Tramadol

Tramadol is a synthetic codeine analog that is a weak μ-receptor agonist.[10] In addition to its opioid activity, tramadol also inhibits neuronal reuptake of norepinephrine and 5-hydroxytryptamine (serotonin), and may actually facilitate 5-hydroxytryptamine release.[22] It is thought that these effects on central catecholaminergic pathways contribute significantly to the drug's analgesic efficacy.[266] Tramadol is recommended for the management of acute and chronic pain of moderate to moderately severe intensity associated with a variety of conditions, including osteoarthritis, fibromyalgia, diabetic neuropathy, neuropathic pain, and even perioperative pain in human patients.[266–268]

A study published in 2003 compared the effects of intravenous tramadol and morphine administered prior to ovariohysterectomy in dogs.[269] In this particular study, tramadol was comparable to morphine in its analgesic efficacy for this type of surgical pain. Clearly, additional studies are necessary before definitive therapeutic recommendations can be made for the management of perioperative pain in a variety of species. There are also anecdotal reports of singular oral tramadol administration for the management of chronic pain in dogs and cats when NSAID usage is contraindicated because of advanced renal disease. Because of its inhibitory effect on 5-hydroxytryptamine uptake, tramadol should not be used in patients that may have received monoamineoxidase inhibitors (MAOIs) such as selegiline (see also the section on meperidine) or in those patients with a recent history of seizure activity.

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