The Clinical Pharmacology of Cyclooxygenase-2–Selective and Dual Inhibitors

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BIOLOGY OF CYCLOOXYGENASE

As mediators of biologic processes, prostaglandins were first extracted from tissues in the 1930s and were demonstrated to exert an effect on blood pressure and smooth muscle contraction [1]. Much later, arachidonic acid (AA) was identified as the common precursor to prostaglandins [2,3], followed by the identification of cyclooxygenase (COX) as the enzyme that cyclized and oxygenated AA to yield prostaglandin [4]. The first purification of a COX enzyme from tissue was later achieved in sheep [5] and bovine seminal vesicles [6]. It is now well established that a variety of isomerases and oxidoreductases produce an array of biologically important prostaglandins from a COX-derived common intermediate. The collision between prostaglandin research and pharmacology occurred in 1971, when Vane [7] demonstrated that aspirin, indomethacin, and salicylate, common nonsteroidal anti-inflammatory drugs (NSAIDs), exerted their effect by inhibiting COX. Before this time, NSAIDs were commonly used in clinical medicine to alleviate pain, inflammation, and fever without an understanding of the underlying mechanism.

Shortly after the recognition that NSAIDs work through COX inhibition, it was proposed that there existed more than one COX enzyme. In particular, an acetaminophen-inhibitable form of COX was hypothesized to exist in canine brain that was not present in other tissues or species [8]. The most compelling evidence that more than one COX existed was the timing of prostaglandin appearance in various tissues after mitogen stimulation. For example, Habenicht and colleagues [9] demonstrated early (10 minutes) and late (2–4 hours) peak inductions in prostaglandin synthesis in a fibroblast cell line. It was only the late peak induction that required protein synthesis, and thus was considered inducible. Finally, in 1991, two laboratories independently reported a gene sequence that coded a new inducible COX enzyme [10,11]. It is now clear that the original
COX isolated from seminal vesicles was noninducible, identified as COX-1, whereas the newly identified isoform was inducible and referred to as COX-2.

More recently, a brain-specific splice variant of COX-1 has been identified in dogs, termed COX-3 by the authors [12]. This enzyme results from the COX-1 gene that retains an additional 90 nucleotides from intron-1. Thus, unlike COX-2, which is encoded from a unique gene, COX-3 is considered a variant of COX-1. It is, however, biologically different from COX-1; COX-3 contains less prostaglandin synthesis activity and the analgesic and antipyretic drugs acetaminophen and dipyrone preferentially inhibit its activity.

COX enzymes have important biologic and pathophysiologic roles. A common adverse reaction observed with classic NSAIDs is gastrointestinal (GI) ulceration, which can now be better explained with a fuller understanding of COX. Prostaglandin synthesis generally attributable to COX-1 has been documented in all portions of the GI tract, with a rank order from highest to lowest synthesis being gastric muscle, gastric mucosa, colon, rectum, ileum, cecum, duodenum, jejunum, and esophagus [13]. Prostaglandins are considered cytoprotective, and insults to the gastric mucosa can be reduced or eliminated by coadministration with various prostaglandins [14]. This cytoprotective effect is brought about by three general mechanisms. First, prostaglandins reduce the secretion of gastric acid by the parietal cells of the stomach [15]. Second, prostaglandins exert a direct vasodilatory effect on the gastric mucosa, thereby increasing mucosal blood flow and maintaining the integrity of the gastric tissue [16]. Finally, prostaglandins stimulate the production of viscous mucus and bicarbonate by the epithelial and smooth muscle cells of the stomach, which likely plays a defensive role in mucosal injury [17]. These observations have led to the general notion that preserving the function of COX-1 should minimize GI adverse reactions attributable to NSAIDs.

In addition to their cytoprotective effect on the gastric mucosa, prostaglandins play an important physiologic role in the kidney, central nervous system (CNS), reproductive system, and cardiovascular system. In the kidney, vasodilatory prostaglandins play a key role in regulating renal blood flow, diminishing vascular resistance, dilating renal vascular beds, and enhancing organ perfusion [18]. In the CNS, COX-1 is found in neurons throughout the brain, where it may be involved in complex integrative functions [19]. COX-1 is also expressed in fetal, amniotic, and uterine tissues, where it establishes implantation, maintains pregnancy, and contributes to placental development [20,21]. Blood platelets contain only COX-1, which converts AA to the potent proaggregatory and vasoconstrictor prostaglandin thromboxane (TBX) A2; this is the rationale for using COX-1–selective compounds (eg, aspirin) in human beings to prevent myocardial infarction. A special note regarding the cardiovascular safety of COX-2–selective drugs should be considered. Recent regulatory and legal action has been taken for some COX-2–selective drugs in human health as the result of apparent adverse cardiovascular events. The concern in human medicine is that the use of COX-2 inhibitors can lead to heart ailments or strokes [22]. Whereas this continues to be examined in human
health, the US Food and Drug Administration (FDA) Center for Veterinary Medicine (CVM) does not believe there is compelling data to merit concern for cardiovascular events in dogs or cats [23]. Therefore, in addition to improved GI safety, NSAIDs that preserve COX-1 activity may presumably spare other important organ system functions.

A primary reason for the clinical use of NSAIDs in veterinary medicine is to treat inflammation, pain, and fever by reducing prostaglandin synthesis brought about by inducible COX-2. Proinflammatory cytokines and mitogens elaborated as the result of noxious stimuli induce COX-2. A key role for COX-2 in joint inflammation was demonstrated through the induction of COX-2 expression in chondrocytes, osteoblasts, and synovial microvessel endothelial cells [24]. Taken together, it has been proposed that selective inhibition of COX-2 should result in anti-inflammatory activity, whereas sparing COX-1 should minimize GI, renal, and other toxicities associated with NSAIDs [25].

**CYCLOOXYGENASES AND DRUG DISCOVERY AND DEVELOPMENT**

Even before the discovery of COX-2, pharmaceutical companies were searching for NSAIDs with a more favorable GI safety profile. This work resulted in the development of three drugs intended for human health that were later developed for veterinary medicine: carprofen, etodolac, and meloxicam. After the discovery of COX-2 in 1991, these new NSAIDs with greater GI safety were shown to selectively inhibit COX-2, thus accounting for their improved GI safety profile. After these early introductions, screens for drugs with even higher selectivity toward COX-2 were developed, with the presumption being that a higher safety profile could be achieved by further minimizing COX-1 inhibition. As a result of this work, newer compounds were introduced to veterinary medicine, including deracoxib and firocoxib. Importantly, each of these drugs is approved by the FDA for use in dogs or cats and should be considered safe and effective when used according to the label. Since their introduction, however, some new information and concerns have been raised.

On the basis of experimental information and clinical data, the correlation of COX-2 selectivity with safer NSAIDs was widely supported. Emerging information supports a role for COX-2 in the stomach that may have an impact on the GI safety of COX-2–selective NSAIDs, however. For example, COX-2 induction has been documented in Helicobacter pylori gastritis, inflammatory bowel disease, and bacterial infections of the gastric mucosa; thus, administration of a COX-2 inhibitor may become harmful in the presence of GI inflammation. This is supported in studies in which transgenic animals lacking the COX-1 gene did not develop gastric ulcers spontaneously [26] and administration of a COX-2–selective inhibitor exacerbated mucosal injury [27]. In another study in a rat model of colitis, administration of a selective COX-2 inhibitor at doses that do not inhibit COX-1 resulted in significant inhibition of mucosal prostaglandin synthesis and a marked increase in colonic damage [28]. When treatment continued with a COX-2–selective drug for 1 week in these
rats, colonic injury was exacerbated to perforation, resulting in 100% death. Taken together, COX-2 may also be required for GI defense, and ulcers may result from the inhibition of COX-2 and COX-1.

This pathophysiology may have played a role in recent results that examined GI tract perforation reported in dogs administered deracoxib, a highly selective COX-2 inhibitor [29]. In a retrospective evaluation of the records of 29 dogs treated with deracoxib in which GI tract perforation was documented, 20 dogs died or were euthanized and 9 survived. Sixteen (55%) of the 29 dogs had received deracoxib at a dosage higher than that approved by the FDA for the particular indication being treated. Seventeen (59%) dogs had received at least one other NSAID or a glucocorticoid in close temporal association (within 24 hours) with deracoxib administration (ie, immediately before or after). Altogether, 26 (90%) dogs had received deracoxib at a higher than approved dosage or had received at least one other NSAID or glucocorticoid in close temporal association with deracoxib administration. Perforation and death seemed to be related to higher than approved doses of deracoxib or coadministration with other NSAIDs or glucocorticoids. The authors concluded that deracoxib should only be used at approved dosages and that glucocorticoids and other less selective NSAIDs should not be coadministered in close temporal association with selective COX-2 inhibitors.

Subsequent to the discovery of COX-2–selective NSAIDs, it has been established that COX-2 plays a role in the maintenance of renal function. Consequently, another concern that has been raised is the safety of COX-2–selective NSAIDs in relation to renal function and ischemia [30]. To date, the evidence does not support the notion that COX-2–selective NSAIDs raise the risk of renal injury when used chronically for osteoarthritis. In addition, renal safety is further supported when they are used to control perioperative pain in otherwise healthy animals in conjunction with standard intraoperative supportive care. For example, in a blind multicenter study of 454 dogs undergoing various soft tissue procedures, dogs were administered carprofen (2 mg/lb) approximately 2 hours before surgery and then once daily after surgery as needed [31]. Relevant renal clinical pathologic variables evaluated included, in part, clinical chemistries, urinalysis, and urinary gamma glutamyl transpeptidase (GGT)/creatinine ratio. None of the dogs developed renal impairment. These results have been repeated in numerous small and large studies using laboratory Beagles and client-owned dogs with several different COX-2–selective NSAIDS. The safety of hypotensive or volume-depleted dogs undergoing surgery that were treated with a COX-2–selective drug has not been reported.

Importantly, greater inhibition of COX-2 over COX-1 has been linked to greater GI safety. Therefore, as a drug discovery tool, compounds with limited COX-1 inhibition (COX-1 sparing) in in vitro screens are brought forward for further evaluation by pharmaceutical companies. Although it is tempting to equate an in vitro COX-2/COX-1 inhibition ratio to overall in vivo safety, the data do not support this approach. The true overall safety for any individual compound is based on its evaluation in laboratory margin-of-safety studies,
reproductive safety studies and blind multicenter field studies in client-owned animals. Therefore, when choosing a COX-2–selective compound for clinical use, all in vivo data must be taken into account to understand comparative safety and continued use must be based on the drug’s performance in the individual being treated. Therefore, to support a full understanding of NSAID selection and continued use in a clinical setting, the following discussion on the individual drugs focuses on evidence-based medicine supporting their safe and effective use in companion animals.

INDIVIDUAL CYCLOOXYGENASE-2–SELECTIVE DRUGS

Carprofen

Carprofen was the first COX-2–selective NSAID approved for use in dogs new animal drug application ([NADA] 141-053). Its selective inhibition of COX-2 has been demonstrated in vitro and ex vivo [32,33]. Carprofen is indicated for the relief of pain and inflammation associated with osteoarthritis and for the control of postoperative pain associated with soft tissue and orthopedic procedures in dogs. It is available as caplets, chewable tablets, or a solution for subcutaneous injection. The approved dose is 2 mg/lb (4.4 mg/kg) administered once daily or 1 mg/lb (2.2 mg/kg) administered twice daily. When used for postoperative pain, the dose should be given 2 hours before surgery.

As stated previously, early development of carprofen preceded the discovery of COX-2. Therefore, shortly after its introduction, the notion that carprofen does not work through COX inhibition was put forth, based on studies using in vivo models of inflammation. First, it was observed in early data that carprofen had no effect on prostaglandin synthesis in mice [34]. We now know, however, that data from murine systems must not be extrapolated to potency and efficacy in dogs for two reasons: there can be inherent differences between species in potency and selectivity against COX-1 and COX-2 enzymes, and there are significant differences in metabolism between mice and dogs that make interpretation of in vivo data difficult. Second, carprofen did not inhibit ex vivo platelet TBX B2 synthesis at a dose of 0.7 mg/kg (1.54 mg/lb) in dogs [35]. Since the discovery of COX-2, ex vivo synthesis of TBX B2 is now considered an accepted assay for COX-1 inhibition, and given carprofen’s COX selectivity [32], these data are consistent with carprofen’s mechanism. Third, in cats, whereas 0.7 mg/kg did not inhibit TBX B2 synthesis, 4.0 mg/kg reduced ex vivo synthesis of TBX B2 for up to 24 hours when administered subcutaneously [36]. In cats, carprofen has a similar potency and selectivity against COX-1 and COX-2 but is not metabolized as efficiently compared with dogs. The lower dose of 0.7 mg/kg likely resulted in blood levels below the COX-1 inhibitory concentration, whereas the 4.0-mg/kg dose likely exceeded the COX-1 inhibitory concentration for an extended period. Taken together, these data do not refute activity against COX-2 but rather support it in light of the fact that ex vivo prostaglandin E2 (PGE2) levels were not determined.

The effectiveness of carprofen for the treatment of osteoarthritis was established in a multicenter study in dogs diagnosed with osteoarthritis [37]. Safety
studies in healthy, laboratory dogs have demonstrated that carprofen has a high safety margin according to the US prescribing information label. When administered at 1, 3, and 5 times the recommended total daily dose for 6 weeks, no significant adverse reactions were reported. When 10 times the recommended total daily dose was administered for 14 days, hypoalbuminemia was reported in two of eight dogs, but there was no GI ulceration. In separate safety studies lasting approximately 2 weeks and 1 year, dogs were administered orally up to 5.7 times the recommended total daily dose. No gross or histologic changes were reported in any of the treated animals, with the primary finding being an increase in serum alanine aminotransferase (ALT) of approximately 20 IU in dogs receiving the highest doses.

In field studies, anorexia, vomiting, and diarrhea are the most commonly reported adverse reactions, affecting 8.9 cases per 10,000 treated dogs [38]. In contrast to the apparent high safety margin described in laboratory and field studies, however, idiosyncratic hepatic toxicity has also been reported [39]. Pharmacovigilance information from the manufacturer has further described liver involvement into two categories: elevated enzymes without hepatic dysfunction affecting 4.2 cases per 10,000 treated dogs and liver insufficiency or failure affecting 1.7 cases per 10,000 dogs treated [38]. As a result, it is recommended that pretreatment blood samples be obtained to establish a baseline. Posttreatment blood samples should be obtained at regular intervals or if an adverse reaction is suspected. Anorexia seems to be associated with hepatopathy as well as with elevation of ALT and aspartate aminotransferase (AST) within the first few days. If encountered, carprofen should be discontinued and supportive care initiated. It should be noted that with the addition of other approved NSAIDs, pharmacovigilance has shown that hepatic toxicity is not limited to carprofen.

There have been limited head-to-head comparisons with other drugs. In one study, carprofen was compared with meloxicam in dogs presented with osteoarthritis [40]. A total of 16 dogs were each treated with meloxicam (0.2 mg/kg once and then 0.1 mg/kg daily thereafter) or carprofen (1 mg/lb twice daily) for 60 days. Subjective improvement was not noted by the owners of carprofen-treated dogs but was noted in dogs treated with meloxicam, which contradicted the previously reported findings [36]. Orthopedic surgeons noted subjective improvement in both groups, and objective ground reaction force improvements via a force plate were documented in both groups. The inability of the owners to identify an improvement in carprofen-treated dogs may be the result of large variability in subjective assessments in untrained observers and of the small number of animals participating in the study.

In another study [41], 575 dogs diagnosed with osteoarthritis were treated with firocoxib (5 mg/kg/d), carprofen (4 mg/kg/d), or etodolac (10–15 mg/kg/d) for 30 days. There were 292 dogs treated with firocoxib, 132 with carprofen, and 151 with etodolac. There was no report of comparative effectiveness; however, fewer dogs experienced diarrhea with firocoxib (3.1%) than with carprofen (6.8%). In addition, the incidence of at least one health-related event was
less with firocoxib (1.0%) compared with carprofen (6.1%). There was no difference in the number of dogs that dropped out of the study. To assign greater safety, data from larger numbers of dogs are needed via pharmacovigilance.

The effectiveness of carprofen to control postoperative pain was established in a study in which it was compared with the opioid pethidine [42]. Forty dogs undergoing a variety of orthopedic surgical procedures were randomly assigned to pethidine (2 mg/kg administered before surgery and 3 mg/kg after surgery) or carprofen (4 mg/kg administered before surgery). Carprofen provided slightly better pain relief than pethidine, produced less sedation, and provided good analgesia during the 18 hours the dogs were in the hospital. Subsequently, it was demonstrated that better analgesia was provided when carprofen was given before surgery compared with postoperative administration [31,43,44].

The safety of carprofen in association with anesthesia and surgery has been extensively examined in healthy dogs. A safety summary was reported in 628 dogs that were randomly allocated to administration of placebo (312 dogs) or carprofen (316 dogs) orally or subcutaneously at a dose of 2 mg/lb (4.4 mg/kg) approximately 2 hours before surgery and then daily after surgery as needed [45]. Study subjects were client-owned dogs presented to veterinary practices for one of the following surgery types: ovariohysterectomy (262 dogs), aural surgery (192 dogs), or cruciate repair (174 dogs). There were no clinically significant differences in mean clinical pathologic variables evaluated, including hematology, clinical chemistries, coagulation profile, urinalysis, urinary GGT/creatinine ratio, and fecal occult blood. In addition, instances of abnormal health were mild and infrequent, with similar distributions for the placebo- and carprofen-treated dogs. Carprofen has also been shown to have no effect on bleeding time in conscious dogs [46] and dogs undergoing orthopedic surgery [47]. In addition, when administered to normal dogs undergoing anesthesia, carprofen did not cause clinically important alterations in renal function [48–51]. Finally, carprofen has no effect on the minimum alveolar concentration of halothane when administered to dogs [52].

Carprofen is not approved for use in cats in the United States or Canada, but the injectable solution has been approved in Europe at a dose of 4 mg/kg administered intravenously or subcutaneously. In addition, several independent publications have supported its safe use in cats primarily for soft tissue and orthopedic postoperative pain. In a double-blind, randomized, placebo-controlled study, carprofen administered after surgery was compared with pethidine in 60 cats undergoing ovariohysterectomy [53]. Cats administered carprofen were in less pain after surgery overall, with 4.0 mg/kg being the most effective dose and superior to pethidine from 2 to 20 hours after extubation. In addition, none of the analgesic regimens seemed to affect renal function adversely, as measured by urea and creatinine levels. A subsequent study in which carprofen was administered in a preemptive manner confirmed the previous findings [54]. In addition, carprofen seems to provide analgesia superior to butorphanol [55] and equivalent to other NSAIDs [56] when examined on the day of surgery.
For orthopedic pain, an additional dosage regimen has been evaluated over a 5-day period [57]. In a placebo-controlled, randomized, blind study, carprofen was administered on extubation at an initial dose of 4 mg/kg of body weight, followed by one third of that dose three times daily on days 2 to 5. This was compared with buprenorphine (0.01 mg/kg administered on extubation and subsequently every 8 hours) and levomethadone (0.3 mg/kg administered on extubation and subsequently every 8 hours). Carprofen was found to have better antinociceptive efficacy when compared with the two opioid analgesics but showed greater pain variability on the first postoperative day. Nevertheless, it was noted that none of the tested analgesics produced sufficient analgesia in the postoperative phase. From a safety perspective, there were no clinically relevant adverse reactions or any undesired renal, GI, or hepatic effects.

Whereas clinical data may support the safe use of carprofen for postoperative pain in cats, caution must be exercised. There are no published reports of chronic use; therefore, the true safety profile and margin of safety are unknown. In addition, compared with dogs, the pharmacokinetics in cats are markedly different [58]. The mean half-life in cats is approximately 20 hours, whereas carprofen has a mean half-life of approximately 8 hours in dogs [59]. Given the lack of a clear pharmacokinetic-pharmacodynamic relation for carprofen, additional dose titration work in cats is necessary to understand its safe use in that species. Such caution is exemplified in a 1-year-old, female, domestic short-hair cat that developed septic peritonitis secondary to a perforated duodenum after a routine ovariohysterectomy and subsequent oral administration of carprofen [60].

**Etodolac**

Etodolac is approved in dogs for the management of pain and inflammation associated with osteoarthritis (NADA 141-108). It should be noted that etodolac has not been evaluated in cats for any clinical use. It is available in scored tablets and is approved at the flexible dose of 10 to 15 mg/kg administered once daily based on the responsiveness of the disease condition and individual tolerance to the drug. Etodolac has been reported to inhibit COX-2 preferentially as evaluated in a canine whole-blood assay [61]. This seems to be corroborated based on its reported GI safety. In healthy laboratory dogs administered etodolac at the approved dose over a 1-month period, gastric lesions were minor when observed endoscopically and were equivalent to those caused by carprofen and placebo [62,63]. Nevertheless, there are opposing data suggesting that etodolac may not selectively inhibit COX-2. For example, in dogs with osteoarthritis administered etodolac at the approved dose for 10 days, PGE2 concentrations in blood at days 3 and 10 were not suppressed compared with baseline [33]. In contrast, carprofen and deracoxib significantly suppressed PGE2 concentrations in blood. In this same study, none of the drugs suppressed TBX B2 in blood or gastric prostaglandin E1 (PGE1) synthesis, whereas all three drugs significantly decreased gastric and synovial synthesis of PGE2. This differential effect on prostaglandin synthesis suggests
that etodolac may be COX-1 sparing but also has variable effects on COX-2, depending on the tissue. Moreover, in a different in vitro assay, etodolac was reported to be COX-1 selective [64].

The effectiveness of etodolac for the treatment of osteoarthritis was established in a multicenter study in client-owned dogs diagnosed with osteoarthritis [65]. According to the US prescribing information label, etodolac was well tolerated when given at the approved dose for periods as long as 1 year. In a study of healthy laboratory dogs, oral administration at the approved dose for up to 12 months resulted in some dogs showing a mild weight loss; loose, mucoid, mucosanguineous feces or diarrhea; and hypoproteinemia. Erosions in the small intestine were observed in one of eight dogs receiving 15 mg/kg after 6 months of daily dosing. At elevated doses of 40 mg/kg/d or greater (2.7 times the maximum daily dose), etodolac caused GI ulceration, emesis, fecal occult blood, and weight loss. At a dose of 80 mg/kg/d or greater (5.3 times the maximum daily dose), six of eight treated dogs died or became moribund as a result of GI ulceration. One dog died within 3 weeks of treatment initiation, whereas the other five died after 3 to 9 months of daily treatment. Death was preceded by clinical signs of emesis, fecal abnormalities, decreased food intake, weight loss, and pale mucous membranes. Renal tubular nephrosis was also found in one dog treated with 80 mg/kg for 12 months. Taken together, it seems that etodolac has a comparatively narrower margin of safety, as demonstrated by severe adverse events and death at doses greater than the approved dose.

When evaluating thyroid function tests in dogs administered etodolac, caution should be exercised when interpreting the results [66]. In client-owned dogs with orthopedic disorders that received etodolac at the approved dose, there was a significant decrease in thyroxine (T4) values, with 21% of values falling below the reference range. In conjunction, a significant increase in canine thyroid-stimulating hormone (cTSH) was reported, but none of the values was above the reference range. There was no significant change in the mean free thyroxine (fT4) values; however, 10% of the values fell below the reference range. These results were not observed when etodolac was administered for 1 month to random-source mixed-breed dogs, although significant decreases in plasma total protein, albumin, and globulin concentrations were detected on days 14 and 28 of administration [67].

Keratoconjunctivitis sicca (KCS) has been reported in dogs receiving etodolac. According to the adverse drug event reports by the FDA CVM, complaints of KCS comprised 78 of 1169 total etodolac-associated adverse event reports during a 28-month period from 1999 to 2001 [68]. The mean age of dogs was 10.2 years, and the range of onset times after first drug administration was from 6 days to 18 months, with most incidents occurring between 3 months and 1 year after first administration. Although the exact mechanism is not defined, anecdotal evidence suggests that when KCS attributable to etodolac administration develops, it is severe and usually irreversible [69]. This may be because dogs continue to receive etodolac after KCS develops. Accordingly, signs of KCS, such as blepharospasm, conjunctival hyperemia, and mucoid ocular discharge, should be monitored.
Should clinical signs of KCS be observed, tear production should be evaluated before continuing therapy.

Etodolac has also been evaluated for the control of postoperative pain associated with ovariohysterectomy in dogs [70]. In laboratory 1-year-old, healthy, mixed-breed, hound-type dogs, etodolac administered at 12 to 14 mg/kg 1 hour before surgery resulted in reduced measures of pain alone or in combination with butorphanol (0.4 mg/kg administered intravenously). Isoflurane concentration over time (area under the curve), buccal mucosal bleeding time, and indices of renal function were not significantly different among the treatment groups.

Meloxicam

Dogs

Meloxicam is approved in dogs for the control of pain and inflammation associated with osteoarthritis (NADA 141-213). It is available as a 1.5-mg/mL flavored suspension intended for oral administration. On the first day of dosing, a 0.2 mg/kg loading dose should be administered once, followed by 0.1 mg/kg given once daily on all subsequent days. A 5-mg/mL injectable solution that is indicated for the control of pain and inflammation associated with osteoarthritis (NADA 141-219) is also approved for dogs. It should be noted that it is not approved for postoperative pain. The injectable form should be administered initially as a single dose at 0.2 mg/kg intravenously or subcutaneously, followed by the oral suspension, if needed, beginning 24 hours after the injection.

Preferentially, inhibition of COX-2 by meloxicam has been established through in vitro assays [61,71,72]. This observation has been further confirmed in vivo by demonstrated GI safety in healthy dogs [73,74] and dogs with osteoarthritis [75]. In addition, decreased GI safety was demonstrated when meloxicam was coadministered with dexamethasone over 3 days (0.25 mg/kg given subcutaneously every 12 hours), and like all NSAIDs, caution should be exercised when it is used in conjunction with glucocorticoids.

The effectiveness of the meloxicam oral suspension formulation for the control of pain and inflammation associated with osteoarthritis was demonstrated in an induced synovitis model in dogs [76,77] and in multicenter trials in client-owned dogs [40,78,79]. Interestingly, in acute synovitis induced by intra-articular injection of monosodium urate, meloxicam was less effective than carprofen and etodolac, as measured by ground reaction forces applied on a force plate [77]. This result needs confirmation in large, randomized, head-to-head studies, which are currently lacking in the veterinary literature. The more recently introduced injectable solution has also been evaluated in dogs with osteoarthritis in a randomized, controlled, multicenter clinical trial [80]. In this study, dogs were randomly assigned to meloxicam (n = 105, 0.2 mg/kg administered subcutaneously once on day 1 and then 0.1 mg/kg administered orally every 24 hours for 13 days) or placebo (n = 112). Dogs treated with meloxicam had significantly greater improvement in general clinical scores assigned by a veterinarian blinded to treatment, compared with baseline scores, on days 8 and 15 than did dogs treated with placebo.
Meloxicam demonstrates a wide margin of safety when evaluated in healthy laboratory dogs. As reported on the US prescribing information label, meloxicam was administered orally at one, three, and five times (8 dogs per group) the recommended dose with no clinically significant adverse reactions. Some treatment-related changes seen in hematology and chemistry were observed, including decreased red blood cell counts in 4 dogs given three times the recommended dose and 3 dogs given five times the recommended dose; decreased hematocrit in 18 of 24 dogs (including 3 control dogs); dose-related neutrophilia in 1 dog given one time the recommended dose, 2 dogs given three times the recommended dose, and 3 dogs given five times the recommended dose; evidence of regenerative anemia in 2 dogs given three times the recommended dose and 1 dog given five times the recommended dose; increased blood urea nitrogen (BUN) in 2 dogs given five times the recommended dose; and decreased albumin in 1 dog given five times the recommended dose. No macroscopic or microscopic renal changes were observed in any dogs receiving meloxicam. The primary adverse reactions observed in field studies as reported on the US prescribing information label are vomiting, diarrhea, and inappetence, which are similar to those of other NSAIDs. Additional adverse reactions reported in the literature include hepatotoxicity and death [81], perforating duodenal ulcer [82], and peritonitis secondary to ulceration [83]. As with other NSAIDs, appropriate laboratory testing to establish hematologic and serum biochemical baseline data is recommended before and periodically during administration.

Although not approved for use, there are numerous reports on the use of meloxicam for the control of pain associated with soft tissue surgery. In an assessment limited to the day of surgery, 15 dogs were each administered meloxicam (0.2 mg/kg subcutaneously) or butorphanol (0.2 mg/kg intramuscularly) 30 minutes before anesthetic induction, followed by ovariohysterectomy [84]. Over the first 12 hours after surgery, animals administered meloxicam were in significantly less pain than those administered butorphanol based on various pain assessment methods. In another study evaluating various soft tissue abdominal operations in healthy dogs, 12 dogs were each administered meloxicam (0.2 mg/kg intravenously), ketoprofen (2 mg/kg intravenously), or butorphanol (0.2 mg/kg intravenously) after anesthetic induction [85]. At the end of the operation, dogs in the butorphanol group were administered a second dose (0.2 mg/kg intravenously). Using subjective pain assessments, overall efficacy was rated as good or excellent in 9 of the 12 dogs that received meloxicam compared with 9 of the 12 dogs that received ketoprofen and only 1 of the 12 dogs that received butorphanol. It was concluded that the analgesic effects of meloxicam were comparable to those of ketoprofen and superior to those of butorphanol over the 20-hour observation period. In a final study evaluating postoperative soft tissue pain, treatment and observations were extended beyond the day of surgery [86]. Over 72 hours, 13 dogs were each administered meloxicam (0.2 mg/kg subcutaneously) or carprofen (4 mg/kg subcutaneously) 30 minutes before anesthetic induction, followed by ovariohysterectomy. Beginning the day after surgery, treatment was continued and
dogs were administered an oral meloxicam suspension (0.1 mg/kg once daily with food) or carprofen (2 mg/kg twice daily). Carprofen and meloxicam provided satisfactory analgesia for 72 hours, supporting the idea that therapy can be extended beyond the day of surgery.

The safety of administering meloxicam to control pain associated with soft tissue surgery is also supported. In a study to evaluate primary hemostasis, 10 healthy female dogs undergoing elective ovariohysterectomy were administered meloxicam (0.2 mg/kg intravenously) and control dogs received an equivalent volume of saline solution administered intravenously [87]. There was no measured effect on platelet aggregation, buccal mucosa bleeding time, platelet count, or hematologic indices when evaluated at 0, 1, 6, and 24 hours after the administration of meloxicam. Other studies have demonstrated that meloxicam given during surgery has no effect on bleeding time [84,85], packed cell volume (PCV), total solids, ALT, BUN, or creatinine [85]. Although not evaluated in animals undergoing surgery, the renal safety of meloxicam was evaluated in healthy dogs that were anesthetized and subjected to painful electrical stimulation [49]. Meloxicam (0.2 mg/kg intravenously) was administered to 12 female, healthy, young-adult Beagles 1 hour before anesthetic induction, and the dogs were then subjected to intermittent electrical stimulation for 30 minutes. There was no effect on glomerular filtration rate or serum concentrations of urea and creatinine compared with values for the saline treatment.

Again, although not approved for use, there are several reports on the use of meloxicam for the control of pain associated with orthopedic surgery on the day of surgery. In a double-blind, prospective, randomized clinical trial, 60 client-owned dogs with surgical orthopedic disorders were randomly assigned to meloxicam (0.2 mg/kg administered intravenously immediately before induction) or ketoprofen (2 mg/kg administered intravenously 30 minutes before the end of surgery) [88]. No significant differences in pain were observed, supporting the use of meloxicam for surgical orthopedic pain for 24 hours. Moreover, there was no effect on buccal bleeding time and whole-blood clotting. Alkaline phosphatase (ALP) and ALT were significantly elevated compared with baseline in both groups, but this was thought to be attributable to anesthesia. Vomiting and subcutaneous hematoma were the only adverse events reported in meloxicam-treated dogs. In a second study that corroborates the results of the first, 32 dogs undergoing orthopedic surgery were randomly assigned to carprofen (4 mg/kg subcutaneously) or meloxicam (0.2 mg/kg subcutaneously) administered 30 minutes before anesthetic induction [89]. As in the previous study, both drugs were effective in alleviating pain for up to 24 hours in all the dogs. Supporting safety, there were no significant changes in the concentrations of urea and creatinine, and no adverse effects were reported during the postoperative period.

Meloxicam has also been evaluated in conjunction with other analgesics. The analgesic efficacy of an epidural morphine-mepivacaine combination alone versus epidural morphine-mepivacaine in combination with meloxicam administered before the onset of anesthesia was assessed in 20 dogs undergoing
cranial cruciate ligament repair \[90\]. Pain scores tended to be lower in dogs receiving meloxicam, and no meloxicam-treated dogs required rescue analgesia compared with 3 of 10 dogs in the epidural-only group. Administration of meloxicam thus seems to provide improved analgesia as compared with epidural morphine-mepivacaine alone. In another study, the combination of meloxicam and butorphanol was compared with butorphanol alone for control of postoperative pain in dogs undergoing surgical repair of a cranial cruciate ligament rupture \[91\]. In this blind randomized study, 40 client-owned dogs were assigned to receive butorphanol (0.2 mg/kg administered intravenously) and meloxicam (0.2 mg/kg administered intravenously) just before surgery or butorphanol alone just before surgery (0.2 mg/kg administered intravenously) and at incision closure (0.1 mg/kg administered intravenously). Subjective pain assessments were improved in dogs that were treated with the meloxicam-butorphanol combination. In addition, the total serum cortisol concentration was significantly lower in meloxicam-butorphanol–treated dogs compared with dogs treated with butorphanol alone. Taken together, these data support the idea that a single dose of meloxicam-butorphanol is equivalent to or slightly better than the administration of two perioperative doses of butorphanol for the control of pain associated with orthopedic surgery.

**Cats**

Unique to currently available NSAIDs, meloxicam is approved for use in cats (NADA 141-219). A 5-mg/mL solution for injection is indicated in cats for the control of postoperative pain and inflammation associated with orthopedic surgery, ovariohysterectomy, and castration. For this use, a single subcutaneous dose of 0.3 mg/kg of body weight should be administered before surgery. Use of additional meloxicam or any other NSAIDs is contraindicated.

A recent in vitro method of testing the COX selectivity of NSAIDs in cats has been published that concluded that meloxicam is only slightly preferential for COX-2 \[92\]. This may be the reason why meloxicam is not approved for chronic use, in that chronic use or elevated doses are associated with unacceptable adverse events. According to the US prescribing information label, in a 3-day safety study, subcutaneous administration of up to 1.5 mg/kg (five times the recommended dose) resulted in vomiting, loose stools, and fecal occult blood. Clinically significant hematologic changes described included increased prothrombin time, increased activated partial thromboplastin time, and elevated white blood cell counts in cats having renal or GI tract lesions. Serum chemistry changes observed included decreased total protein and increased BUN and creatinine levels. Histologic examination revealed GI lesions ranging from inflammatory cell infiltration of the mucosa of the GI tract to erosions. Renal changes ranged from dilated medullary and cortical tubules and inflammation or fibrosis of the interstitium to necrosis of the tip of the papilla. These adverse events seemed to increase in severity when treatment was extended out to 9 days.

Again, according to the US prescribing information label, when meloxicam was given as a single subcutaneous injection of 0.3 or 0.6 mg/kg on day 0 and
Meloxicam oral suspension was then administered orally once daily at the same dose (0.3 or 0.6 mg/kg, respectively) for 8 consecutive days. Clinical adverse reactions included vomiting, diarrhea, lethargy, and decreased food consumption. Necropsy revealed reddened GI mucosa in three of four cats in the 0.3-mg/kg group and in one of four cats in the 0.6-mg/kg group. By day 9, one cat in the 0.3-mg/kg group and one cat in the 0.6-mg/kg group died, and another cat in the 0.3-mg/kg group was moribund. The cause of death for these cats could not be determined, although the pathologist reported pyloric or duodenal ulceration in the cats in the 0.6-mg/kg group. These safety studies demonstrate a narrow margin of safety; thus, repeat injections or follow-up with oral NSAIDs is contraindicated. One study contradicts this conclusion, where meloxicam suspension was administered at a dose of 0.3 mg/kg orally on day 1 followed by 0.1 mg/kg daily for 4 more consecutive days in cats with chronic locomotor disorders [93]. This treatment resulted in a significant improvement in demeanor, feed intake, and weight bearing as well as a significant reduction in lameness, pain on palpation, and inflammation and was associated with minimal observed side effects.

Evidence that meloxicam is effective for the control of postoperative pain in cats was provided in a study in which cats underwent onychectomy or onychectomy plus neutering (castration or ovariohysterectomy) [94]. In this study, cats were randomized to meloxicam (0.3 mg/kg administered subcutaneously) or butorphanol (0.4 mg/kg administered subcutaneously) 15 minutes after premedication and before anesthesia. Meloxicam-treated cats were less lame, had lower pain scores, and had better general impression scores compared with butorphanol-treated cats. As an objective measurement, cortisol concentrations were lower at 1, 5, and 12 hours in the meloxicam-treated cats and fewer meloxicam-treated cats required rescue analgesia compared with butorphanol-treated cats. Safety was supported by the fact that there was no treatment effect on buccal bleeding time; PCV and BUN concentrations decreased in both groups, and glucose concentration decreased in meloxicam-treated cats.

Additional work has concluded that meloxicam is equivalent to carprofen in controlling pain associated with ovariohysterectomy in cats [56,95]. Meloxicam has also been compared with buprenorphine for the control of postoperative pain associated with ovariohysterectomy in cats [96]. In a randomized controlled study of 51 cats, oral and subcutaneous meloxicam (0.3 mg/kg) was compared with oral and subcutaneous buprenorphine (0.01 mg/kg) administered at the time of anesthetic induction. Cats receiving meloxicam orally or subcutaneously had significantly lower pain scores compared with cats receiving buprenorphine orally. Moreover, rescue analgesia was not required by any of the cats receiving meloxicam compared with 3 of 10 cats receiving buprenorphine orally and 2 of 10 cats receiving buprenorphine subcutaneously. Taken together, cats receiving meloxicam orally or subcutaneously seemed to have less pain after surgery than those receiving oral buprenorphine but not less pain than those receiving subcutaneously administered buprenorphine.
Deracoxib
Deracoxib is approved in dogs for the control of pain and inflammation associated with osteoarthritis (NADA 141-203). It is commercially available as chewable tablets and should be administered at a dose of 1 to 2 mg/kg as a single daily dose as needed based on the responsiveness of the disease condition and individual tolerance to the drug. It is also approved for the control of postoperative pain and inflammation limited to orthopedic surgery. For this indication, 3 to 4 mg/kg/d should be administered before surgery and the same dose given on subsequent days as needed, not to exceed 7 days of administration.

Preferential inhibition of COX-2 by deracoxib has been established through in vitro and ex vivo assays in laboratory dogs with unilateral osteoarthritis treated with deracoxib for 10 days [33]. Like carprofen, deracoxib decreased synovial fluid and blood PGE2 concentrations but did not suppress blood TBX B2 concentrations or gastric PGE1 synthesis. GI safety is consistent with these results, as demonstrated by the administration of deracoxib to healthy dogs over 28 days [97]. Endoscopic lesion scores and days of vomiting were superior compared those in with dogs receiving aspirin and equivalent to those in dogs receiving placebo.

The use of deracoxib in dogs with osteoarthritis was demonstrated in two studies. In a dose titration study conducted in dogs with intra-articular urate crystal–induced synovitis, the minimum effective dose of deracoxib (1 mg/kg) was established to treat joint inflammation and was equivalent to carprofen (2.2 mg/kg) [98]. There are no published multicenter controlled studies on the effectiveness of deracoxib on the treatment of pain and inflammation associated with osteoarthritis. The US prescribing information label describes a placebo-controlled blind study in 209 client-owned dogs with clinical and radiographic signs of osteoarthritis, however. Deracoxib was administered by the owner at a dosage of approximately 1 to 2 mg/kg/d for 43 consecutive days. Although details are limited, an improvement in force plate parameters and owner evaluations was reported. As with other NSAIDs, vomiting and diarrhea were the most common adverse reactions reported in this study.

There are no published multicenter controlled studies on the effectiveness of deracoxib on the treatment of pain with orthopedic surgery. The US prescribing information label describes a placebo-controlled study in 207 dogs admitted to veterinary hospitals for repair of a cranial cruciate injury, however. Placebo or deracoxib was administered at a dose of 3 to 4 mg/kg beginning the evening before surgery and continued once daily for 6 days after surgery. Significant improvement was reported for lameness at the walk and trot as well as for pain on palpation values at all postsurgical time points compared with placebo. The most frequent adverse reactions were vomiting, diarrhea, hematochezia, and draining or oozing at the incision site. There are no published reports on the effectiveness of deracoxib for the control of pain associated with soft tissue surgery.

When administered chronically, deracoxib seems to have a wide safety margin, with some evidence of reduced renal safety with increasing doses. As described on the US prescribing information label, in a 6-month study, where
dogs were dosed at 0, 2, 4, 6, 8, and 10 mg/kg, there were no clinical abnormalities observed and buccal bleeding time was not altered. Urinalysis results showed hyposthenuria (specific gravity < 1.005) and polyuria in one male dog and one female dog in the 60-mg/kg group after 6 months of treatment, however. After 6 months of treatment, the mean BUN values for dogs treated with 6, 8, or 10 mg/kg/d were above normal and were 30.0, 35.3, and 48.2 mg/dL, respectively. Moreover, dose-dependent focal renal tubular degeneration or regeneration was seen in some dogs treated at a dose of 6, 8, or 10 mg/kg/d, and focal renal papillary necrosis was seen in dogs dosed at 8 or 10 mg/kg/d. In a second study at doses of 0, 4, 6, 8, and 10 mg/kg of body weight for 21 consecutive days, a dose-dependent trend toward increased levels was observed. Taken together, although no renal lesions were seen at the label doses of 2 and 4 mg/kg/d, appropriate precautions should be taken in dogs with preexisting renal disease and overdosing should be avoided.

As stated previously, it has been generally established that selective inhibition of COX-2 results in anti-inflammatory activity, whereas sparing COX-1 minimizes GI, renal, and other toxicities associated with NSAIDs. Recently reported GI tract perforation in dogs administered deracoxib may add a caveat to this notion [29]. Perforation and death seemed to be related to higher than approved doses of deracoxib or coadministration with other NSAIDs or glucocorticoids. It was concluded that deracoxib should only be used at approved dosages and that glucocorticoids and other less selective NSAIDs should not be coadministered in close temporal association with selective COX-2 inhibitors. Therefore, although COX-2–selective NSAIDs have demonstrated GI safety in normal laboratory dogs, in clinical cases, coadministration of other NSAIDs or glucocorticoids should be avoided, and when there are preexisting GI pathologic findings, caution should be exercised.

The safety and effectiveness of deracoxib in cats have not been evaluated at any dose or for any indication. The pharmacokinetics of deracoxib have been described in seven cats administered a single oral dose of 1 mg/kg using a compounded liquid formula, however [99]. The terminal half-life ($t_{1/2}$) was 7.9 hours, and the time to reach maximum plasma concentration ($T_{\text{max}}$) was 3.64 hours, which are slightly longer than those reported in dogs ($t_{1/2} = 3$ hours and $T_{\text{max}} = 2$ hours according to the US prescribing information label in dogs). Although no adverse effects were observed in this small study, treatment in cats should be avoided until margin-of-safety studies are completed and demonstrated effectiveness is achieved in clinical field studies.

**Firocoxib**

Firocoxib is the most recently approved COX-2–selective NSAID introduced in the United States. It is approved in dogs and is indicated for the control of pain and inflammation associated with osteoarthritis in dogs (NADA 141-230). It is available as a chewable tablet and should be administered at a dose of 5 mg/kg once daily. The selectivity of firocoxib to inhibit COX-2 was demonstrated using an in vitro assay [100]. The effectiveness of firocoxib
to treat joint inflammation was demonstrated in a dose titration study conducted in dogs with intra-articular urate crystal–induced synovitis [100]. Confirmation of this effect in a multicenter, active, controlled study in 249 client-owned dogs with osteoarthritis is described on the US prescribing information label. Dogs treated with firocoxib were reported to show a level of improvement in veterinarian-assessed lameness, pain on palpation, range of motion, and owner-assessed improvement that was comparable to the active control. In addition, the level of improvement in firocoxib-treated dogs in limb weight bearing on the force plate gait analysis assessment was comparable to the active control. The most frequent adverse reactions in this study were vomiting and decreased appetite.

In a target animal safety study, firocoxib was administered orally to healthy adult Beagle dogs (eight dogs per group) at 5, 15, and 25 mg/kg (one, three, and five times the recommended total daily dose) for 180 days. At the indicated dose of 5 mg/kg, there were no treatment-related adverse events. Decreased appetite, vomiting, and diarrhea were seen in dogs in all dose groups, including unmedicated controls, although vomiting and diarrhea were seen more often in dogs in the group given five times the recommended dose. One dog in the group given three times the recommended dose was diagnosed with juvenile polyarteritis of unknown etiology after exhibiting recurrent episodes of vomiting and diarrhea, lethargy, pain, anorexia, ataxia, proprioceptive deficits, decreased albumin levels, decreased and then elevated platelet counts, increased bleeding times, and elevated liver enzymes. On histopathologic examination, a mild ileal ulcer was found in one dog given five times the recommended dose. This dog also had decreased serum albumin, which returned to normal by study completion. One control and three dogs given five times the recommended dose had focal areas of inflammation in the pylorus or small intestine. Vacuolization without inflammatory cell infiltrates was noted in the thalamic region of the brain in three control dogs, one dog given three times the recommended dose, and three dogs given five times the recommended dose. Mean ALP was within the normal range for all groups but was greater in the groups given three times and five times the recommended dose than in the control group. Transient decreases in serum albumin were seen in multiple animals in the groups given three times and five times the recommended dose and in one control animal.

The margin of safety, as demonstrated in healthy laboratory dogs, seems to be narrow in young dogs. A specific warning is included on the US prescribing information label that states the use of this product at doses greater than the recommended 5.0 mg/kg in puppies less than 7 months of age has been associated with serious adverse reactions, including death. The results supporting this are as follows. In a separate safety study, firocoxib was administered orally to healthy juvenile (10–13 weeks of age) Beagle dogs at 5, 15, and 25 mg/kg (one, three, and five times the recommended total daily dose) for 180 days. At the indicated recommended dose of 5 mg/kg, on histopathologic examination, 3 of 6 dogs had minimal periportal hepatic fatty change. On
histopathologic examination, 1 control dog, 1 dog given the recommended
dose, and 2 dogs given five times the recommended dose had diffuse slight
hepatic fatty change. These animals showed no clinical signs and had no liver
enzyme elevations. In the group given three times the recommended dose, 1
dog was euthanized because of poor clinical condition (day 63). This dog
also had mildly decreased serum albumin. At study completion, of 5 surviving
and clinically normal dogs given three times the recommended dose, 3 had
minimal periportal hepatic fatty change. Of 12 dogs in the group given five
times the recommended dose, 1 died (day 82) and 3 moribund dogs were
euthanized (days 38, 78, and 79) because of anorexia, poor weight gain, depres-
sion, and, in 1 dog, vomiting. One of the euthanized dogs had ingested a rope
toy. Two of these dogs in the group given five times the recommended dose
had mildly elevated liver enzymes. At necropsy, all 5 of the dogs that died or
were euthanized had moderate periportal or severe panzonal hepatic fatty
change, 2 had duodenal ulceration, and 2 had pancreatic edema. Of 2 other
clinically normal dogs given five times the recommended dose (of 4 dogs eutha-
nized as comparators to the clinically affected dogs), 1 had slight and 1 had
moderate periportal hepatic fatty change. Drug treatment was discontinued
for 4 dogs in the group given five times the recommended dose. These dogs
survived during the remaining 14 weeks of the study. On average, the dogs
in the groups given three and five times the recommended dose did not gain
as much weight as control dogs. The rate of weight gain was measured (instead
of weight loss), because these were young growing dogs. Thalamic vacuolation
was seen in 3 of 6 dogs in the group given three times the recommended dose,
5 of 12 dogs in the group given five times the recommended dose, and to
a lesser degree in 2 unmedicated controls. Diarrhea was seen in all dose groups,
including unmedicated controls.

As stated previously, comparative field safety has been reported [41]. Five hun-
dred seventy-five dogs diagnosed with osteoarthritis were treated with firocoxib
(5 mg/kg/d), carprofen (4 mg/kg/d), or etodolac (10–15 mg/kg/d) for 30 days.
There were 292 dogs treated with firocoxib, 132 with carprofen, and 151 with
etodolac. There was no report of comparative effectiveness; however, fewer
dogs experienced diarrhea with firocoxib (3.1%) than with carprofen (6.8%). In
addition, the incidence of at least one health-related event was less with firocoxib
(1.0%) compared with carprofen (6.1%). There was no difference in the number
of dogs that dropped out of the study. To assign greater safety accurately, data
from larger numbers of dogs are needed via pharmacovigilance.

Although not approved for the control of postoperative pain, firocoxib has
been evaluated in dogs undergoing ovariohysterectomy [101]. In a negative-
control double-blind study of 20 client-owned female dogs, firocoxib was ad-
ministered orally approximately 3 hours before surgery at a dose of 5 mg/kg
and then once daily for 4 additional days. Pain scores were lower for the
firocoxib-treated group at 2 hours and 4 hours after surgery as well as on
day 1. On days 2, 3, and 4, pain scores were not statistically different between
treatments. Treatment of orthopedic pain has not been evaluated.
The safety and effectiveness of firocoxib in cats has not been evaluated at any dose or for any indication. The COX selectivity, pharmacokinetics, and effect on lipopolysaccharide (LPS)-induced fever have been accepted in laboratory cats, however [102]. In vitro evaluation confirmed that firocoxib is COX-2 selective in cats. In addition, pharmacokinetic properties were determined after intravenous (2 mg/kg) and oral (3 mg/kg) administration showed moderate to high oral bioavailability (54%–70%), low plasma clearance (4.7–5.8 mL/min/kg), and an elimination t1/2 of 8.7 to 12.2 hours. When administered 1 or 14 hours before LPS-induced pyrexia in female cats, firocoxib attenuated fever at doses ranging from 0.75 to 3 mg/kg. Although no adverse effects were observed in this small study, treatment in cats should be avoided until margin-of-safety studies are completed and demonstrated effectiveness is achieved in clinical field studies.

**DUAL INHIBITORS**
The alternative metabolic pathway of AA is the leukotriene pathway. The enzyme 5-lipoxygenase (5-LOX) converts AA into leukotrienes that are potent chemotactic agents involved in inflammation. Dual COX/5-LOX inhibitors constitute a valuable alternative to classic NSAIDs and selective COX-2 inhibitors for the treatment of pain and inflammation. It remains to be seen if balanced inhibition of COX and 5-LOX provides superior effectiveness and reduced adverse reactions compared with COX-2–selective NSAIDs. Presently, the recently introduced tepoxalin is the only dual inhibitor available in veterinary medicine.

**Tepoxalin**
Tepoxalin is approved in dogs for the control of pain and inflammation associated with osteoarthritis. The safety and effectiveness of tepoxalin have not been evaluated at any dose or for any indication in cats. It is available as a rapidly dissolving oral tablet and should be administered with food at an initial dose of 10 or 20 mg/kg on the first day of treatment, followed by 10 mg/kg once daily thereafter as needed based on the responsiveness of the disease condition and individual tolerance to the drug.

The dual action of tepoxalin has been established by an in vitro assay [103]. Selectivity against COX isoforms and 5-LOX has also been evaluated in vivo [104]. In mixed-breed adult dogs with chronic unilateral arthritis in a stifle joint, the dogs were administered placebo, meloxicam, or tepoxalin for 10 days at the approved doses. Consistent with dual inhibition, tepoxalin decreased leukotriene B4 concentrations in the blood and gastric mucosa and PGE2 in the synovial fluid. Interestingly, tepoxalin also inhibited TBX B2 in blood, which is supportive of COX-1 inhibition, an effect not observed in meloxicam- or placebo-treated dogs. Therefore, although tepoxalin may be a dual inhibitor, it may also inhibit COX-1 in a tissue-dependent manner.

Effectiveness in the control of pain and inflammation associated with osteoarthritis has been demonstrated in dogs. There are no published reports;
however, as described on the US prescribing information label, 62 dogs were evaluated in a 7-day, controlled, blind field study. On the seventh day of treatment, improvements in ambulation, weight bearing, pain, forced movement, general improvement, and overall improvement were reported. In a separate uncontrolled field safety study of 107 client-owned dogs, the most frequent adverse reactions included diarrhea, vomiting, and inappetence. Laboratory safety evaluation supports a wide margin of safety. When administered for 1 year at doses of 0, 10, 30, and 100 mg/kg/d, the primary findings were increased emesis and gastric ulceration in 2 of 8 dogs in the highest dose group.

Although not approved for use in postoperative pain, tepoxalin has been evaluated in an experimental pain model [105]. Twelve laboratory dogs were randomized to placebo or tepoxalin (10 mg/kg) administered 2 hours before anesthetic induction, followed by a full-thickness thoracic skin incision. Tepoxalin had no effect on buccal mucosal bleeding when assessed out to 24 hours. In addition, when measured out to 48 hours, tepoxalin had no effect on hematology, renal parameters (BUN, creatinine, creatinine clearance, and GGT/creatinine ratio) and hepatic parameters (ALT, AST, and GGT). Although this pilot study supports its safe use in soft tissue surgery, larger multicenter studies in client-owned dogs should more closely gauge true safety and effectiveness.

SUMMARY

The discovery of COX isoforms as the target for NSAIDs led to a greater understanding of the mechanism and clinical use of NSAIDs. Later, COX-2 was targeted in drug discovery efforts, resulting in the introduction of highly selective COX-2 inhibitors. As a result, over the past decade, there have been several NSAIDs introduced in veterinary medicine with an increased GI safety profile consistent with a COX-1–sparing effect. More recently, an NSAID with additional 5-LOX activity has also been approved for use. Although it is tempting to equate in vitro COX-2/COX-1 and 5-LOX inhibition to overall in vivo safety, the data do not support this approach. The true overall safety for any individual compound is based on its evaluation in laboratory margin-of-safety studies, reproductive safety studies, and blind multicenter field studies in client-owned animals. Therefore, when choosing a COX-2–selective or dual-inhibitor NSAID for clinical use, all in vivo data must be taken into account to understand comparative safety, and continued use must be based on the drug’s performance in the individual being treated. Until head-to-head trials in multicenter blind studies are published, comments on comparative safety and effectiveness must be reserved.

References


