An Update on Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) in Small Animals

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KEYWORDS

• NSAIDs • Anti-inflammatory drugs • Analgesic drugs
• Dogs • Cats • Pain • Arthritis • COX-1

There are several nonsteroidal anti-inflammatory drugs (NSAIDs) to choose from (**Box 1**). The pharmacologic activity of the NSAIDs has been reviewed in other articles, textbooks, popular journals, and promotional material distributed by drug sponsors. It is not necessary to review in-depth information on chemistry, mechanism of action, history, discovery, or pharmacokinetics of these drugs, because that information has been described previously. The clinical use and dosages of these drugs are provided in a recent book by the author,[1] and this topic was last reviewed by this author in 2000.[1,2] A description of the chemistry, mechanism of action, and clinical use of the cyclooxygenase-2 inhibiting (COXIB) class of NSAIDs was provided in a thorough review.[3] Pharmacokinetics and pharmacodynamics of NSAIDs were reviewed extensively by Lees and colleagues.[4] Guidelines for clinical use in dogs[5] and cats[6] was recently provided in excellent reviews. This article primarily reviews developments that were not available at the time of this author's previous review in 2000 and discusses issues for which updates are necessary.

MECHANISM OF ACTION

The review articles by experts in this area are sufficient to describe the basic pharmacology and mechanism of action of these drugs.[7,8] The most significant development in our understanding of NSAIDs occurred in the early 1990s with a revision in the understanding of the targets of these drugs. At that time, it was discovered that there are two isoenzymes (isoforms) of cyclooxygenase (prostaglandin synthase) that are responsible for synthesis of prostaglandins. Prostaglandin synthase-1 (COX-1) is

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Box 1
Currently available nonsteroidal anti-inflammatory drugs for dogs

Aspirin[a]

Phenylbutazone[b]

Carprofen (Rimadyl, and generic)[f]

Etodolac (EtoGesic)

Meloxicam (Metacam)[c,f,1]

Ketoprofen (Anafen)[d,4]

Deracoxib (Deramaxx)

Firocoxib (Previcox)

Meclofenamic acid (Arquel)[e,11]

Tepoxalin (Zubrin)

Tolfenamic acid (Tolfedine)[d,f]

[a] Aspirin is not US Food and Drug Administration (FDA)–registered for dogs, but some forms are marketed for dogs as if there were FDA approval. There is an approved combination with methylprednisolone (Cortaba tablets, 0.5 mg of methylprednisolone and 300 mg of aspirin).
[b] Registered for dogs but not actively marketed.
[c] Registered for cats also as a single dose.
[d] Registered in Canada only.
[e] Registered but not marketed.
[f] Also available as an injectable and oral; the others are all available in oral forms.

usually a constitutive enzyme expressed in tissues.[9] Prostaglandins, prostacyclin, and thromboxane synthesized by this enzyme are responsible for normal physiologic functions. Prostaglandin synthase-2 (COX-2), on the other hand, is inducible and synthesized by macrophages and inflammatory cells after stimulation by cytokines and other mediators of inflammation. In some tissues, COX-2 may be constitutive. For example, COX-2 production of prostaglandins was found to be constitutive in canine pyloric and duodenal mucosa,[10] even though it previously was believed to be induced only in the presence of injury or inflammation. COX-2 may be up-regulated in these tissues, responding to inflammatory stimuli to produce a protective and healing role.[11] There is evidence, confirmed in two independent studies,[10,12] that prostaglandin synthesis is inherently higher in gastric mucosa than duodenal mucosa. This suggests that, in the duodenum, there may be a greater requirement for induction of COX-2, and that there is a protective mechanism to emerge in the duodenum rather than in the stomach. The perception that COX-2 is a bad enzyme and COX-1 is a good enzyme is probably overly simplistic because we now understand that there is some overlap in the functions of these isoforms.[13] Nevertheless, the target of most of the most recently developed NSAIDs has been COX-2—or to spare COX-1 as much as possible—with the goal of producing analgesia and suppressing inflammation without inhibiting physiologically important prostanoids.

Selectivity of COX-2 versus COX-1 is often expressed as the COX-1/COX-2 inhibitory ratio. This ratio is derived from an in vivo study in which the inhibitory effect, usually expressed as the inhibitory concentration to inhibit 50% of activity (IC_{50}), is measured from stimulating cells that are capable of expressing products of these enzymes. In the whole blood assay, the source for COX-1 products (thromboxane or TXA_2) is platelets, and the source of COX-2 products (PGE_2) is leukocytes. The ratio is expressed as COX-1 [IC_{50}]/COX-2 [IC_{50}], or simply COX-1/COX-2. The higher the

value above 1.0, the more specific the drug is for COX-2 compared with COX-1. There is subjective value placed on the magnitude of the ratio to consider the drug as "COX-1 sparing," "COX-2 specific," "COX-2 preferential," or "COX-2 selective." These terms have been used by many authors without any true definition of the magnitude of the ratio used to determine the criteria for each term.

Is there a COX-3?

After the discovery of COX-1 and -2, interest emerged of the presence of yet another isozyme, the COX-3 enzyme. Interest in COX-3 began after a discovery, in dog tissues, that there was a central cyclooxygenase that was inhibited by acetaminophen.[14] This substance was called COX-3. It is believed now that COX-3 is a variant of COX-1, rather than a distinct isomer.[15,16] The term "COX-3" has even been rejected by some authors.[17] This variant of the COX enzyme was selectively inhibited by acetaminophen in dogs[15] and this inhibition may represent a target for a central mechanism for some NSAIDs, including acetaminophen and dipyrone. As proposed by Chandrasekharan and colleagues,[15] other NSAIDs that produce analgesia, but are not selective for COX-2, perhaps have a central mechanism of action targeting COX-3. Despite the initial interest in COX-3, this enzyme may be more prominent in dogs than in people or laboratory rodents.[17] Subsequently, there has been little focus on inhibition of this enzyme in the human literature and some of the initial enthusiasm about COX-3 has waned. (See the review by Kis and colleagues[18] for a more in-depth treatment of this topic.) Nevertheless, there is evidence to suggest that an enzyme exists centrally in dogs, at levels that are distinct from humans and laboratory animals, that may be a central target for some NSAIDs. It may be worthwhile to consider this method of treatment in dogs for some types of pain (see later discussion).

Inconsistencies Among the Studies

When one examines the drugs registered for veterinary medicine, there is disagreement in the literature with respect to the selectivity for the COX-1 versus COX-2 enzyme (**Table 1**). For example, deracoxib is considered a highly selective COX-2

Table 1
COX-1/COX-2 inhibitory ratios based on IC_{50} values in dogs

Drug	Streppa et al 2002[a]	Ricketts et al 1998[21,a]	Kay-Mugford et al 2000[22,a]	Cryer et al 1998[b]	Brideau et al 2001[b]	Wilson et al 2004[23,b]	Gierse et al 2002[19,c]
Ketoprofen	0.17	0.23	0.36	0.125	0.6	0.5	—
Aspirin	0.39	<0.3	—	0.32	—	0.37	—
Etodolac	0.53	0.52	—	7.92	—	6.3	3.4
Ibuprofen	0.74	—	—	0.6	—	—	—
Piroxicam	2	—	—	1.27	—	1.75	—
Meloxicam	2.72	2.9	12.3	—	10	—	—
Meclofenamic acid	5	15.4	—	12.1	—	5	—
Phenylbutazone	9.7	>2.6	—	—	0.6	—	—
Carprofen	16.8	129	1.75	—	6.5	5.3	65
Deracoxib	—	—	—	—	—	—	1275

[a] Assay with canine cell lines.
[b] Assay with human cell lines.
[c] Assay with purified enzymes.

inhibitor based on an assay performed in purified enzymes.[19] In this study, the COX-1/COX-2 ratio was 1275, much higher than other drugs tested. But when tested in canine whole blood and compared with other NSAIDs, deracoxib had a ratio of only 12. In this study, carprofen had a ratio of 6 to 7, and firocoxib (the newest NSAID for dogs) had a ratio of 384 to 427.[20]

Some of the confusion regarding understanding the action of the veterinary NSAIDs is that in vitro studies to examine their relative effects on COX-1 versus COX-2 have varied in their techniques and the cell system used. For example, in a study using canine enzyme systems, carprofen had a COX-1/COX-2 ratio of 129.[21] In another study, using cell lines of another species (sheep and rodent) the ratio was 1.0,[7] and in a study using canine macrophages, the ratio was 1.75.[22] Yet another study on carprofen showed a ratio of 5.3 and that it was 1000 times less potent in whole blood than in cell culture.[23] This emphasizes the effect of protein binding on in vitro assays (see later discussion). An in vivo study with carprofen in dogs did not demonstrate that it was capable of inhibiting prostaglandins systemically in dogs.[24]

Carprofen is not the only drug for which conflicting results have been reported. The ratios for etodolac, another NSAID approved for dogs, has a COX-1/COX-2 ratio of 8.1 in humans, but 0.52 to 0.53 in dogs. Another study with etodolac showed that the selectivity for COX-2 was 10 times greater in people than dogs.[19,25] Dr. Vane, a preeminent expert on COX inhibition, concludes that the inhibitory activity of a drug for COX-1 to its inhibitory activity for COX-2 can vary according to whether tests are done on pure enzymes, cell homogenates, or intact cells, or with the types of cells used.[7] According to Dr. Lees, one of the leading investigators of NSAIDs in veterinary medicine, there are several unexplored questions to be answered for veterinary drugs.[26]

What is the Best Assay?

In view of the discrepancies among studies and techniques, it is now generally accepted that the whole-blood assay should be the gold standard for determining COX-1/COX-2 specificity. The first evidence of this technique was published in 1992[27] and it is now used in most of the veterinary drug studies. The advantage of the whole-blood assay is that it incorporates the components into the assay that normally occur in circulating blood: proteins, cells, platelets, and circulating enzymes. These components are not present in isolated cells or enzyme systems used for some earlier assays.

Because the NSAIDs are highly protein bound, this is particularly important because only a small fraction—the unbound fraction—is biologically active in the blood. The whole-blood assay measures COX-2 products (PGE_2) from stimulated leukocytes, and COX-1 products (TXA_2) from stimulated platelets.

Taking the whole-blood assay one step further is to perform an ex vivo assay in which blood samples are collected after administration of the NSAID. This assay is perhaps more clinically relevant than the in vitro assay because it accounts for differences in metabolism among the drugs, pharmacokinetic variations, and the potential presence of active metabolites.[28,29] The ex vivo assay allows the investigator to study the time course of prostaglandin inhibition (duration of effect) and may be more relevant to predict clinical and adverse effects of NSAIDs.[29]

Pharmacokinetic-pharmacodynamic modeling

There has been tremendous interest in combining the pharmacodynamic studies that measure COX-1 and COX-2 inhibitory concentrations with the pharmacokinetics of the drug to derive the clinically optimal and safe doses for animals. Pharmacokinetics

and pharmacodynamics (PK-PD) can be useful for preclinical evaluation to select the most appropriate dose to use in further studies. These approaches were described in an excellent review by Lees and colleagues,[4,30] and demonstrated for specific drugs in studies by Giraudel and colleagues.[31,32] The approach by these investigators is to use a blood concentration corresponding to 80% inhibition of COX-2 (IC_{80}) to produce a therapeutic effect, and only 20% inhibition of COX-1 (IC_{20}) to avoid adverse effects. As reviewed by Hinz and Brune[29] 80% COX-2 inhibition to predict clinical effects also has been supported by other studies. A drug concentration producing 50% inhibition may not be enough to produce a therapeutic effect and an inhibitory concentration of 80% may be more realistic.

Using these inhibitory concentration values as targets, PK-PD mathematical modeling can be performed by taking into consideration the corresponding pharmacokinetics of the drug (plasma clearance). Safe and effective doses can be derived to attain these blood concentration targets. The calculations and descriptions of the model are beyond this article but are well described in the citations above. In a PK-PD modeling approach using these techniques, the investigators determined a dose of meloxicam of 0.17 mg/kg every 24 hours in cats.[32] At this dose inhibition of COX-1 actually exceeded 20%.[32] This dose is below the US Food and Drug Administration (FDA)–registered single dose for cats, but higher than the chronic dose registered in Europe (doses of meloxicam are discussed later in the section on cats). The PK-PD approach suggested that meloxicam is safe for a single dose of 0.3 mg/kg, despite high COX-1 inhibition, but for chronic treatment lower doses are necessary to minimally inhibit COX-1. This agrees with the clinical experience with meloxicam in cats.

Rather than using an in vitro assay, such as the whole-blood assay, to measure cyclooxygenase inhibition as the pharmacodynamic surrogate marker for efficacy, another approach is to use an in vivo measure. An in vivo measure is more likely to reflect physiologic and pathologic conditions and predict clinical outcome. Several in vivo models have been used to test NSAIDs in animals. These are described in more detail by Lees and colleagues.[30] An in vivo model may involve inducing inflammation in a tissue cage and measuring the inhibition of inflammation in response to the drug concentration. It may use an injection of an irritant in a joint and observing the response by measuring the degree of lameness produced, heat, and pain. Injections of an irritant (kaolin) have been administered to cats to measure inflammatory pain and heat. Values such as 50% inhibitory concentration (IC_{50}) can be calculated from the in vivo model, as for the in vitro model.

Using this approach, induced inflammation in cats was used for PK-PD modeling of meloxicam.[31] These investigators calculated a single dose of 0.25 to 0.3 mg/kg of meloxicam to produce optimum analgesic, anti-inflammatory, and antipyretic effects. This dose agrees with the dose derived from clinical trials that led to the current FDA-registered dose for cats.

Do in vitro Tests Predict in vivo Performance?

Whether or not in vitro measurements of COX-1 versus COX-2 inhibition predict in vivo response and safety has been debated. PK-PD approaches to dose determination may not always agree with results from clinical trials. Deviations from clinically-derived doses are attributed to effects of NSAIDs that may not directly correlate with blood concentrations. As the authors of the studies cited above explained,[4,30–32] participation of other mechanisms of action in the anti-inflammatory effects of NSAIDs may explain deviations from these models, along with the accumulation of the active compound in the target cells or biotransformation leading to active metabolites. These effects cannot be measured with in vitro whole-blood assays alone. For example,

although carprofen etodolac and meloxicam all have been shown to inhibit COX-2 with different magnitudes of COX-1/COX-2 ratios and meloxicam generally being more selective, carprofen and etodolac were equally effective for reducing pain scores in experimentally treated dogs[33] but were more effective than meloxicam. Likewise, according to safety studies available from the drug sponsor, firocoxib, carprofen, and etodolac all were similar with respect to incidence of gastrointestinal adverse effects in dogs, even though they vary widely in the COX1/COX-2 ratios, with deracoxib being the most COX-2 specific.

Many in vitro studies have agreed qualitatively with results from in vivo assays. When effects of meloxicam were compared with aspirin in dogs, meloxicam, which is a somewhat selective COX-2 inhibitor using a whole-blood assay, also had a sparing effect on gastrointestinal prostaglandins (COX-1 mediated) compared with aspirin.[34] Meloxicam also was a potent inhibitor of lipopolysaccharide-induced prostaglandin synthesis (COX-2 mediated). These findings are consistent with COX-2 inhibition and COX-1–sparing effects of meloxicam, but demonstrate the lack of such specificity for aspirin. In a follow-up study by the same laboratory they compared carprofen, deracoxib, and etodolac.[35] All three drugs failed to inhibit prostaglandins in the stomach mucosa, and thromboxane in platelets, consistent with a COX-1–sparing effect. All three drugs produced the same degree of COX-1 sparing, despite a wide range in COX-1/COX-2 inhibitory ratios among these drugs. In the same study, etodolac did not suppress the COX-2–mediated product, PGE_2, in a blood assay compared with carprofen and deracoxib on days 3 and 10 of treatment. Carprofen and deracoxib did not differ in their in vivo effects on either COX-1 or COX-2 inhibition, despite large differences for in vitro COX-1/COX-2 ratios. In a more recent study, the same laboratory showed that firocoxib and meloxicam, both of which have a preference for COX-2 but have widely different COX-1/COX-2 ratios, were similar in their ability to suppress COX-2–mediated prostaglandins in whole blood and sparing COX-1–mediated prostaglandins in gastric mucosa.[12] These results suggest that the in vitro assays may be helpful for demonstrating qualitative differences among the NSAIDs, but do not provide a quantitative measure of difference in efficacy or safety.

Is Prostaglandin Inhibition all there is?

Although we assume that prostaglandin inhibition is the most important mechanism of action for most NSAIDs, there may be other mechanisms, some not fully understood, that also may explain the actions of these drugs. For example, some NSAIDs, including salicylates, may inhibit nuclear factor kappa-B (NF-κB). NF-κB is an important promoter for inflammatory mediators.

Carprofen seems to be a COX-1–sparing drug,[25] but there is not agreement among investigators on whether it also inhibits COX-2 in vivo. Although there is evidence for inhibitory effects on the enzyme cyclooxygenase in some models, carprofen did not show an in vivo anti-prostaglandin effect in dogs,[24] which may explain the low rate of gastrointestinal adverse effects at approved doses. In one study, the investigators were unable to show that carprofen inhibited either COX-1 or COX-2,[36] suggesting either a central mechanism of action or activity on other pathways.

IS THERE REALLY AN ADVANTAGE FOR COX-2 INHIBITORS?

After the discovery of two isoenzymes, COX-1 and -2, there was a focus in drug development toward developing highly selective COX-2 inhibitors. Drugs that emerged from this work were celecoxib (Celebrex), valdecoxib (Bextra, now discontinued), and rofecoxib (Vioxx, now discontinued).[37] These are often referred to as the

COXIBs and they were among the top-selling prescription drugs of any category in human medicine. The removal of rofecoxib and valdecoxib from the human market has been well chronicled in the human literature and is discussed later. The background and pharmacology of the COXIBs was reviewed thoroughly by Bergh and Budsberg.[3]

Deracoxib was the first veterinary drug in this group; the next one approved was firocoxib (Previcox). Both are licensed for dogs to treat pain associated with osteoarthritis. Other COX-2–specific drugs may follow in veterinary medicine. Based on in vitro tests in one study, firocoxib is more specific for COX-2 than deracoxib, with a COX-1/COX-2 ratio of 384 to 427 compared with deracoxib with a ratio of 12.[38] In efficacy studies, firocoxib was compared with etodolac and carprofen and was shown in some measurements to have better improvement in lameness scores. Although studies that have performed safety assessment comparisons among drugs have been scarce and of low statistical power, firocoxib, carprofen, and etodolac all were similar with respect to incidence of vomiting and anorexia in dogs. There was a lower incidence of diarrhea with firocoxib compared with carprofen and etodolac and less melena compared with etodolac (data available from drug sponsor).

Evaluations of the COXIBs in people have shown that they are not necessarily more effective than older drugs, but they may be safer for the gastrointestinal tract[39] during short-term evaluations. In veterinary studies, there is no convincing evidence that drugs with higher COX-1/COX-2 ratios produce fewer gastrointestinal or renal adverse effects than drugs with low ratios. One of the veterinary drugs with selective COX-2 inhibitory action, deracoxib, was shown to be safe in studies performed by the manufacturer.[3] In 2005, however, investigators from North Carolina State University reported on 29 cases of gastrointestinal perforation and bleeding in association with deracoxib use in dogs.[40] Most occurred in the duodenum near the pyloric junction. Some of these animals may have had predisposing factors that contributed to the gastrointestinal perforations (for example, high dose or concurrent corticosteroid administration).

The adverse reactions from the COXIBs in people have resulted in removal of some from the market. Thousands of lawsuits against the drug sponsor are still being settled in the courts. The studies that originally demonstrated safety and led to initial FDA approval in people have been criticized.[41–43] Some reviews have pointed out that these selective COX-2 inhibitors may have been no better for long-term therapy than older established drugs, many with mixed COX-1/COX-2 inhibition in gastrointestinal safety and efficacy.[44,45] Some skeptics have proposed that selective COX-2 inhibitors may not be appropriate for all patients because COX-2 enzyme products may be involved in actions other than inflammation. For example, COX-2 products may be biologically important for angiogenesis, renal function, regulation of bone resorption, reproductive function, and healing of gastroduodenal ulcers.[46]

The safety concern in people from COX-2 selective drugs is a higher risk for cardiovascular problems because they preserve COX-1, which may promote platelet aggregation and vasoconstriction.[47] This cardiovascular risk is why the popular drug rofecoxib (Vioxx) was voluntarily taken off the market, soon followed by valdecoxib (Bextra). Some experts believe that the high COX-2 selectivity of this drug led to this increased risk.[48,49] There have been serious concerns expressed about the events that led up this withdrawal and whether or not the public was aware of the safety concerns. Editorials in major journals[41,43] suggested that the drug review process was inadequate for these drugs and we anticipate closer scrutiny of highly selective COX-2 human drugs in the future.[50,51]

DUAL INHIBITORS

There have been older drugs promoted to be dual inhibitors of arachidonic acid metabolites, but none were commercially successful. Dual inhibitor drugs effectively inhibit both cyclooxygenase (COX) and lipoxygenase (LOX). Therefore, they inhibit synthesis of inflammatory prostaglandins (PG) and leukotrienes (LT). Interest in a dual inhibitor has focused on the potential benefits in inhibiting LOX, which may include higher gastrointestinal safety and greater analgesic efficacy.[52] Lipoxygenase metabolites are involved in hyperalgesia and inflammatory responses.[13] Older drugs believed to have dual inhibitor capability were benoxaprofen and ketoprofen. Benoxaprofen was taken off the market, and the evidence for ketoprofen acting as a dual inhibitor is weak. A new drug being evaluated in people and dogs is licofelone, which is a true dual inhibitor, but it is not yet on the market. Licofelone may have greater gastrointestinal safety than other NSAIDs.[53]

Corticosteroids have been shown to be dual inhibitors in some studies because they inhibit phospholipase A_2, the enzyme that forms arachidonic acid from cell membranes. Corticosteroid inhibition of both LT and PG by way of this mechanism may not be clinically relevant, however. There is evidence that corticosteroids block COX-2 gene expression resulting in inhibition of synthesis of COX-2, which may be responsible for some anti-inflammatory effects. By inhibition of COX-2 in the gastrointestinal tract during conditions in which COX-2 products are needed for healing and repair, corticosteroids may exacerbate or produce injury to the gastrointestinal mucosa.[11,54,55]

The only drug approved in Europe and the United States that acts as a dual inhibitor in animals is tepoxalin (Zubrin). The metabolite is active, but only acts as a COX inhibitor. The COX inhibitor functions are more specific for COX-1 than COX-2, although this was not a canine-specific assay (data from Schering-Plough). In vivo and in vitro studies in dogs administered tepoxalin showed that it inhibited COX-1– and COX-2–mediated prostaglandins in blood and gastroduodenal mucosa, but it also inhibited LOX activity, consistent with its proposed mechanism of action.[12,56]

Despite being a nonselective COX inhibitor (primarily COX-1 using in vitro assays), tepoxalin has a gastrointestinal safety profile that matches other more selective COX-2 inhibitors. Tepoxalin has been effective in dogs that have osteoarthritis and showed gastrointestinal safety at several times the label dose. A question remaining about tepoxalin is the duration of the LOX inhibitory effect. The half-life for the LOX inhibitor parent drug is much shorter than the metabolite, which has little LOX inhibition (**Table 2**). The other question remaining to be answered for tepoxalin is the contribution of anti-LOX action on the overall therapeutic effect. Studies in osteoarthritis in dogs (the registered indication for tepoxalin) have not revealed whether it is the COX or the LOX inhibition (or possibly some other mechanism) that is responsible for a favorable clinical effect. Whether the dual inhibition action of tepoxalin will be effective for other inflammatory diseases (eg, respiratory disease, dermatitis) has not been reported.

IS IT TIME TO RECONSIDER ACETAMINOPHEN?

Veterinarians have been reluctant to consider acetaminophen treatment in animals because of its well-known toxicity in cats.[57] It should not be prescribed to cats under any circumstances—but what about dogs? Acetaminophen has been safe in dogs, even when administered at high doses. Although it produces analgesic effects, it does not produce anti-inflammatory effects at clinically relevant doses.[58–60] A study in a canine surgery model that demonstrated anti-inflammatory effects used doses that are higher than recommended clinically.[59] Acetaminophen has not produced

Table 2
Pharmacokinetic data for nonsteroidal anti-inflammatory drugs at the dosages tested in dogs

Drug	Half-Life in Dogs	Test Dose
Aspirin	8 h	10–20 mg/kg q8–12 h, oral
Carprofen	8 h (range 4.5–10)	4.4 mg/kg q24 h, or 2.2 mg/kg q12 h, oral
Deracoxib	3 h at 2–3 mg/kg;19 h at 20 mg/kg	3–4 mg/kg q24 h, oral
Etodolac	7.7 h fasted; 12 h nonfasted	10–15 mg/kg q24 h, oral
Flunixin	3.7 h	1 g/kg, oral or IM, once
Meloxicam	12–36 h	0.2 mg/kg initial, then 0.1 mg/kg q24 h, oral
Naproxen	74 h	5 mg/kg initial, then 2 mg/kg q48 h, oral
Phenylbutazone	6 h	15–22 mg/kg q12 h, oral
Piroxicam	40 h	0.3 mg/kg, q24 h, or q48 h, oral
Tepoxalin	1.6 h parent drug; 13 h for active metabolite	20 mg/kg initial; then 10 mg/kg q24 h, oral
Firocoxib	7.8 h	5 mg/kg q24 h, oral

renal or gastric injury in dogs when prescribed at commonly recommended doses for dogs (15 mg/kg orally, every 8 to 12 hours). Evidence of toxicity was not observed in dogs until doses of 100 mg/kg were exceeded.[61] It has been administered to dogs anecdotally, when other alternatives either are contraindicated or have caused adverse effects. It has been administered to dogs in combination with codeine, oxycodone (Percocet), and hydrocodone (Vicodin), despite a lack of clinical studies on the effectiveness of these preparations. Clinical-effectiveness seems to be mostly anecdotal.

More recent investigations reveal that acetaminophen actually is a COX inhibitor, but acts in cells in which low concentrations of arachidonic acid are present.[17] There is evidence that the site of acetaminophen action is the peroxidase enzyme component of prostaglandin H_2 synthase.[17] (Prostaglandin H_2 synthase consists of the peroxidase and cyclooxygenase portions, but it has collectively been referred to as "COX" in most recent studies.) The target for traditional NSAIDs is the cyclooxygenase portion of prostaglandin H_2 synthase. As reviewed by Davies and colleagues,[16] the COX inhibition probably occurs at site-specific tissues, sparing the gastrointestinal mucosa, platelets, and kidneys, but acting centrally. There also is evidence that it is a selective COX-2 inhibitor in selected tissues.[62]

Other supporting evidence for acetaminophen is that it seems to inhibit the COX-1 variant that was referred to as COX-3 earlier in this article.[15] The action is more prominent in dogs than in any other species and acts centrally, without affecting prostaglandin synthesis at other sites in the body that could potentially lead to adverse effects (for example, kidney and gastrointestinal mucosa). Other selected NSAIDs (dipyrone, phenacetin) also seem to inhibit COX-3. Because COX-3 may have a centrally mediated effect to produce analgesia and pyrexia, particularly dogs in which it was first discovered, perhaps acetaminophen has a role in treatment of some types of pain when other traditional NSAIDs are not appropriate.

In review articles, other authors have not supported this mechanism for the action of acetaminophen.[18,19,29] Other proposed mechanisms of action for acetaminophen involve pathways that may also be affected by other drug categories. Descending

inhibitory pain pathways are mediated by serotonin (5-HT_3). Acetaminophen can stimulate the inhibitory pain pathway mediated by serotonin, and this can be blocked by serotonin antagonists.[63] This evidence suggests that acetaminophen may directly activate serotonin receptors. Other drugs that have been used to treat pain in animals—tricyclic antidepressants (eg, amitriptyline) and selective serotonin reuptake inhibitors (eg, fluoxetine)—modulate serotonin activity by inhibiting the reuptake of serotonin at the synapse. These drugs also have been used in some pain syndromes. One of the enantiomers of tramadol, a widely used analgesic in people and animals, also affects serotonin systems. Although it is appealing to consider studies in which acetaminophen could be combined with these agents to treat pain in animals, there are no such reports available in animals. Clearly, there is a risk of combining drugs that act on the serotonergic system without understanding the implications. Other drugs used in veterinary medicine that affect serotonin systems include serotonin-reuptake inhibitors, tricyclic antidepressants, and selegiline. On the other hand, some antiemetic drugs (eg, ondansetron) compete with serotonin receptors. The benefits and risks of adding another drug to a patient already receiving any of these other drugs would have to be weighed.

PHARMACOKINETIC FEATURES

For most of the NSAIDs there are adequate pharmacokinetic data for dogs, and some for cats, available in the reviews cited previously. Most of the traditional drugs in this group are weak acids that are highly protein bound and most of them have a small volume of distribution (some new drugs are an exception to this standard). These drugs are excreted at varying rates, depending on the metabolic pathway and extent of enterohepatic circulation. There are tremendous species differences in drug elimination among the NSAIDs. For some drugs the enterohepatic cycling may increase the risk for toxicosis because the local effects of the drug may be focused on the intestinal mucosa through repeated cycling in the biliary system.

Although the drug distribution, half-life, and clearance have been characterized for most NSAIDs used in animals, this information has not always been of use for predicting safe and effective dosage regimens. For example, NSAIDs such as ibuprofen and indomethacin easily cause toxicity in dogs even though they have short half-lives. On the other hand, naproxen and piroxicam have long half-lives of 74 hours and 40 hours, respectively, but have been used safely when dosed carefully. Among the small animal NSAIDs, half-lives do not correlate with the frequency of administration. Most currently used NSAIDs are given once a day, but half-lives vary widely (see **Table 2**).

As reviewed by Lees and colleagues,[4] an important feature of the NSAID pharmacokinetics is that anti-inflammatory and analgesic effects persist longer than the plasma half-lives would predict. In dogs, several NSAIDs have half-lives of 24 hours or less, (aspirin and carprofen, 8 hours; phenylbutazone, 6 hours; flunixin, 3.7 hours; meloxicam, 10–24 hours; etodolac, 8–12 hours), but have been administered once every 24 hours with effective results.[64] One explanation for the long duration of effect is the high protein binding. The tissue protein binding (for example the protein in an inflamed site) may serve as a reservoir for the drug after it has been eliminated from the plasma. The NSAID may thus persist in inflamed sites longer than the plasma.

IS A WASHOUT TIME NECESSARY?

As cited above, the pharmacologic effects may persist for longer than predicted by the half-life. Does this warrant a washout period between treatments? The washout time is the period between administrations of an NSAID when switching from one drug to

another. Some promotional material published by veterinary pharmaceutical companies has advocated such a washout period when switching from one NSAID to another in animals. That is, when switching from one NSAID to another—which may be necessary because it is recognized that animals may respond to individual drugs differently, despite a shared mechanism of action—some unsupported citations have advocated an unspecified time to wash out the effects of one NSAID before another is administered. In one of the studies investigating this effect it was stated that, "In general, veterinarians are advised to discontinue an NSAID for 24 hours to 7 days before initiating administration of a second NSAID."[65] The intended purpose of a washout is to allow any residual effect from previous administration to wane before introducing another drug. Despite the well-meaning intentions, there is little scientific support for this practice. We do not know how much residual effect remains after a dose, and how long the period should be. Most NSAIDs used chronically are administered once per day (see **Table 2**), even some that have long half-lives. Piroxicam, a human drug that has a half-life of 35 to 40 hours in dogs, has been safely administered once daily.[66–68] The concept of assigning a washout time has gained support primarily through discussions on Internet sites and NSAID promotions by sponsors without any convincing scientific evidence for support. A remaining question is: should the patient be without treatment for 2 to 7 days before another NSAID is administered while waiting for the washout? This is indeed an important consideration because it may be common to switch NSAIDs between immediate postoperative care (with an injectable NSAID) to be followed by at-home treatment with another drug administered orally.

The Role of Aspirin-Triggered Lipoxin

The FDA-approved labels for these drugs give no guidance on prescribing that indicates that a washout period is needed, or how long it should be. A case can be made for caution when switching between treatment with aspirin and a COX-2 inhibitor. Aspirin is a nonselective COX inhibitor, and at low doses is more COX-1 selective. (Aspirin is not an FDA-approved drug for dogs.) As reviewed by Brune,[69] and Wallace and Fiorucci,[70] during treatment with aspirin a pathway is induced to produce lipoxin (lipoxin A4), also known as aspirin-triggered lipoxin (ATL). ATL is generated by COX-2 and has a protective role, reducing inflammation. Over time, gastrointestinal adaptation occurs, which is believed to be mediated by ATL, and induces the gastrointestinal mucosa to become more tolerant of potential injury caused by NSAIDs.[71,72]

COX-2 inhibitors inhibit the synthesis of ATL. If aspirin is administered simultaneously with a COX-2 inhibitor, or if a COX-2 inhibitor is administered before aspirin, it may prevent the process of adaptation, making the gastrointestinal mucosa more vulnerable to injury from NSAIDs.

There is evidence that gastric adaptation also involves other factors. As discussed by Brzozowski and colleagues,[73] who showed attenuation of gastric mucosal injury after repeated exposure to aspirin, gastric adaptation may rely on enhanced production of growth factors, increased cell proliferation, and mucosal regeneration. In this article the authors also argued that gastric adaptation is a long-lasting effect that produces increased resistance of the adapted mucosa to subsequent damage by ulcerogenic agents.

What is the evidence that NSAID adaptation and ATL synthesis is important in our patients? Most of the studies and review papers deal primarily with laboratory rodent studies. But studies in dogs from many years ago (Hurley and Crandal, 1964; Phillips 1973)[74] demonstrated that adaptation to administration of aspirin is possible in dogs. These reports showed that lesions were observed initially after aspirin treatment. After 1 to 2 weeks of aspirin treatment, the lesions resolved in the face of continued

administration. The adaptation to aspirin in the dogs of this study was accompanied by an increase in gastric blood flow, reduction in inflammatory cell infiltration, and an increase in mucosal cell regeneration and mucosal content of epidermal growth factor. These observations are consistent with the role of ATL. There is reason to suspect that ATL is synthesized after aspirin treatment in dogs and this can potentially be inhibited by COX-2 inhibitors. Additional evidence for up-regulation of COX-2 after mucosal injury was demonstrated by Wooten and colleagues,[10] in which COX-2 was increased in the duodenum of dogs after administration of aspirin after 3 days. It is plausible that treatment with a COX-2 inhibitor would suppress this induction, and possibly the protection derived from COX-2. A washout time of several days between switching from a COX-2 inhibitor to aspirin therefore seems appropriate. Additionally, caution should be exercised when administering aspirin simultaneously with a COX-2 inhibitor. The phenomenon of adaptation from chronic administration is not without controversy, because other studies have failed to demonstrate gastric adaptation after aspirin administration to dogs. When dogs received aspirin at a high dose of 25 mg/kg every 8 hours, there was no evidence of adaptation; the lesions were as severe or worse on day 28 compared with earlier in the study.[75]

Does adaptation occur with other nonsteroidal anti-inflammatory drugs?

There are insufficient data to resolve this question and some conflicting evidence. The study cited earlier by Dowers and colleagues[65] suggests that some adaptation may occur after repeated administration of NSAIDs other than aspirin. In their study the observed gastrointestinal lesions from administration of deracoxib and carprofen were worse early in the course of treatment to day 2, but improving by day 5. There was also conflicting evidence in that study that indicated that residual effects of NSAID treatment to these experimental dogs may have occurred. On day 1 of the crossover study, lesions were observed, despite a 16-day washout time to allow recovery of the previous crossover in the preceding weeks of the study. The investigators of this study suggested that sequential NSAID administration may exert long-term effects and requires further study. On the other hand, evidence for long-term effects after 2 months of treatment was not observed by Raekallio and colleagues,[76] but there is evidence that adaptation occurred in these dogs. Dogs that had arthritis were treated every day for two months with carprofen. Plasma proteins were lower at 4 weeks, but recovered to pretreatment levels by 8 weeks. The protein loss may have been from changes in permeability of the gastrointestinal mucosa, but recovered by two months.

Is a Washout Period Needed Between Nonsteroidal Anti-Inflammatory Drugs Other than Aspirin?

A washout time when switching between NSAIDS other than aspirin is not supported by evidence. Although ATL can be synthesized independently of aspirin, there has not been conclusive evidence that ATL is induced by drugs other than aspirin, despite investigations to identify other potential candidates.[70,77] A precaution to avoid switching between NSAIDs without a washout period because it decreases ATL and increases risk for adverse reactions seems to apply only to aspirin treatment in combination with other drugs.

In a clinical trial the COX-2 inhibitor firocoxib was administered to dogs after a washout period ranging from 1 to 5 days. After analysis of 1000 patients, there was no increased risk from switching from another NSAID to firocoxib within 7 days compared with a longer washout period.[78] The washout time within the 7-day period varied from 0 days to 7 days. Most common washout time within the 7-day period was 2 days or longer. Furthermore, there was no observed risk when switching from one NSAID to

another within 1 week, compared with administration of an NSAID without any previous treatment. The study only examined administering firocoxib after another NSAID and the results cannot necessarily be extended to other drugs. Furthermore, the study did not include aspirin, which would have induced ATL.

When dogs were administered sequential NSAIDs (deracoxib and carprofen), there was no evidence that following one NSAID treatment (injectable carprofen) with another (oral deracoxib) in sequential treatment produced treatment-related lesions in the gastrointestinal tract.[65] A clinical report described gastrointestinal lesions in dogs associated with administration of deracoxib.[40] Many of the dogs in that report had severe ulceration and had received either a high dose, concurrent treatment with a corticosteroid, or another NSAID in close temporal association with deracoxib. It has already been established in other studies that concurrent treatment with an NSAID and a corticosteroid exacerbates the gastroduodenal lesions.[11,54,55] The NSAID therapy reported by Lascelles and colleagues[40] was variable and consisted of different drugs and doses, making it difficult to determine whether these dogs were predisposed to NSAID-induced injury or if the NSAID therapy compounded the toxicity from deracoxib. COX-2 is important for healing to occur when gastrointestinal injury has occurred. By administering a COX-2 inhibitor to the dogs described in the clinical report,[40] the ability for mucosal recovery, regeneration, and healing may have been compromised. This evidence supports a recommendation that if gastrointestinal injury or compromise is observed, or even suspected, administration of another NSAID, particularly a COX-2 inhibitor, before allowing for healing to occur could produce additional injury.

ADVERSE EFFECTS OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Gastrointestinal Toxicity

Among the adverse reactions caused by NSAIDs, gastrointestinal problems are the most frequent reason to discontinue NSAID therapy or consider alternative treatment. The FDA's Freedom of Information (FOI) Summary for all the approved veterinary drugs provides the documentation of safety tests conducted prior to a drug's registration. The FOI summaries also provide the adverse events reported from clinical trials that led to FDA approval. For all drugs, adverse events that can be attributed to the gastrointestinal tract (vomiting, anorexia, diarrhea), but not necessarily to ulceration, are the most common. In animals, gastrointestinal effects can potentially range from mild gastritis and vomiting to severe gastrointestinal ulceration, bleeding, and even death. Gastrointestinal adverse events also have been documented for the past 3 decades in the veterinary literature. Gastrointestinal toxicity is caused by two mechanisms: direct irritation of the drug on the gastrointestinal mucosa and prostaglandin inhibition.[11,46,79] Direct irritation occurs because the acidic NSAIDs become more lipophilic in the acid milieu of the stomach and diffuse into the gastric mucosa where they cause injury. Prostaglandins have a cytoprotective effect on the gastrointestinal mucosa and inhibition of these compounds results in decreased cytoprotection, diminished blood flow, decreased synthesis of protective mucus, and inhibition of mucosal cell turnover and repair. In the gastrointestinal tract of healthy dogs, COX-1 is the primary COX enzyme that produces prostaglandins (primarily PGE_2),[23] but COX-2 may also be present and up-regulated after exposure to an irritant.[10] Two independent reports have confirmed a higher level of prostaglandin synthesis in the canine stomach compared with the mucosa.[10,12] A pattern is emerging to suggest that in the stomach there is an endogenous high level of COX-1–synthesized prostaglandins because of the requirement to protect the stomach from high shear forces and gastric acid and

produce mucosal bicarbonate. Consistent with published studies, inhibition of COX-1 in the stomach increases the risk for gastric erosions and ulcers. In the duodenum the prostaglandin requirement is lower because there is less acid, less requirement for mucosal bicarbonate (bicarbonate is secreted by the pancreas), and less shear force because of the trituration of food that has already occurred in the stomach. Injury or insult to the duodenum induces COX-2 to produce protective and healing prostaglandins. If the COX-2–mediated prostaglandins are inhibited by NSAIDs, it may increase the risk for duodenal ulceration.

An examination of published reports of gastrointestinal toxicity from administration of NSAIDs in animals indicates that the most serious problems are caused from doses that are higher than recommended, but toxicity also has been observed from relatively mild doses in susceptible individuals. Some factors may increase the risk for gastrointestinal toxicosis, including concurrent corticosteroids and other gastrointestinal diseases. In people, there is now evidence that genetic variation may determine one's susceptibility to NSAIDs.[80]

The most recently-approved NSAIDs in the United States for dogs are carprofen, etodolac, meloxicam, deracoxib, firocoxib, and tepoxalin (see **Box 1**). A few other drugs are approved in Canada and Europe (eg, tolfenamic acid and ketoprofen). For the newer veterinary-registered NSAIDs, the gastrointestinal safety profile compared with older drugs has contributed to their popularity in veterinary medicine. There is no evidence in the published literature using controlled clinical trials to show that one is noticeably safer or more effective than another, however. For example, in a study in which carprofen, meloxicam, and ketoprofen were compared in dogs after endoscopic evaluation after 7 and 28 days of administration, there was no statistical difference among the drugs with respect to development of gastroduodenal lesions.[81] In another study that compared the gastrointestinal effects of recommended doses of carprofen, etodolac, and aspirin on the canine stomach and duodenum for 28 days, etodolac and carprofen produced significantly fewer lesions than aspirin, but lesion scores in the carprofen- and etodolac-treated groups were no different than administration of placebo.[82]

The putative explanation for the safety of carprofen, etodolac, deracoxib, firocoxib, and meloxicam is that these drugs have preferential inhibitory action for COX-2 over COX-1 (high COX-1/COX-2 ratio). Perhaps a more accurate description of these drugs is that they have a COX-1–sparing effect.[39] COX-1/COX-2 ratios many not necessarily correlate with gastrointestinal safety, however, and the calculated ratios may vary from study to study and from species to species. Some drugs may lose their COX-2 selectivity at high doses.[46] The dose dependence was shown for etodolac. At the label dose it was safe, but at higher doses (2.7 × dose) it produced gastrointestinal lesions, and at the high dose (5.3 × dose) it caused death. At high doses, meloxicam—a drug ordinarily associated with good gastrointestinal safety[34,83]—also has produced some gastrointestinal toxicity.[84] According to one report, the sponsors of this drug in Europe recommended reducing the original approved dose from 0.2 mg/kg to 0.1 mg/kg because of some initial gastrointestinal problems.[81]

Renal Injury from Nonsteroidal Anti-Inflammatory Drugs

In the kidney, prostaglandins play an important role in modulating the tone of blood vessels and regulating salt and water balance. Renal injury caused by NSAIDs has been described in people and horses, but has not been as well documented in small animals. Reported cases of toxicity occurred when high doses were used or when there were other complicating factors. Renal injury occurs as a result of inhibition of renal prostaglandin synthesis. In animals that have decreased renal perfusion caused

by dehydration, anesthesia, shock, or pre-existing renal disease, this leads to renal ischemia.[64,85]

Healthy animals are somewhat immune from adverse effects from NSAIDs,[86] but if there is renal compromise (eg, dehydration, tubular dysfunction, electrolyte depletion, or anesthesia), the kidney depends on COX-1 and COX-2 for prostaglandin synthesis to autoregulate water metabolism, tubular function, and renal blood flow.[87] Animals that have renal disease are more at risk for dehydration, which can increase the likelihood of NSAID-induced nephropathy.

Renal toxicity associated with NSAIDs is characterized by decreased renal perfusion, sodium and fluid retention, and decreased tubular function. In people, pain in the kidney area has been recorded. One should not assume that NSAIDs that are more specific for the COX-2 enzyme are safer for the kidneys. Both COX-1 and COX-2 enzymes are involved in renal blood flow regulation and tubular function. Some of the prostaglandins that play an important role in salt and water regulation and hemodynamics in the kidney are synthesized by COX-2 enzymes.[88] Constitutive COX-2 is found in various sections of the kidney and administration of drugs that are selective for COX-2 may adversely affect the kidney during conditions in which the kidney is stressed because of dehydration, decreased perfusion, or disease. Administration of a specific COX-2 inhibitor to salt-depleted people decreased renal blood flow, glomerular filtration rate, and electrolyte excretion.[88] Corticosteroids may also increase the risk for injury because it was shown that administration of prednisolone to dogs in combination with either meloxicam or ketoprofen has a potential for serious adverse effects on the kidneys and the gastrointestinal tract.[55]

Of the currently available NSAIDs, the effect of carprofen and meloxicam on renal function has been the most extensively studied. Because these drugs are used in perioperative situations in an injectable formulation, investigations were performed to determine if there was any evidence of renal toxicity, particularly during conditions of anesthesia. In one study, carprofen, ketorolac, and ketoprofen were examined in healthy dogs undergoing surgery, but without intravenous fluid administration. There were minor increases in renal tubular epithelial cells on urine sediment, but carprofen had no adverse effects on renal function.[86] Some ketorolac- and ketoprofen-treated dogs had transient azotemia. In other studies, administration of carprofen to anesthetized healthy dogs had no adverse effects on renal function (Bergmann and colleagues, 2005).[89–93]

Meloxicam did not produce adverse renal effects in healthy dogs after short-term administration, with and without pimobendan.[94] In healthy dogs anesthetized and treated with acepromazine to produce hypotension, preanesthetic administration of meloxicam did not produce any altered renal function.[95] Healthy dogs administered meloxicam before anesthesia and electrical nociceptive stimulus did not have decreased renal function associated with treatment.[90] Tepoxalin was evaluated in anesthetized, healthy, normotensive, normovolemic dogs at a dose of 10 mg/kg (currently registered dose) using renal scintigraphy.[96] There were no adverse effects on renal function detected. In another study with tepoxalin on renal function, there were no adverse effects when it was administered to dogs in combination with an angiotensin-converting enzyme (ACE) inhibitor.[96]

The common design in the studies cited above was that dogs were healthy, generally young, and NSAID doses were from a single dose and within the recommended range. Deviations from this design, use of higher doses, longer treatment, or administration to clinical patients with other problems could produce different results.

Renal effects following deracoxib administration to dogs were reported by the manufacturer. At high doses, there is a dose-dependent effect on renal tubules. It is well

tolerated in most dogs up to 10 mg/kg for 6 months, but there is a potential for a dose-dependent renal tubular degeneration/regeneration at doses of 6 mg/kg or higher. (Clinically approved dose for long-term treatment is 1–2 mg/kg per day.) Long-term administration of carprofen, etodolac, flunixin, ketoprofen, or meloxicam to dogs did not induce any evidence of renal injury as measured by urinalysis and serum biochemistry.[97]

There is another form of analgesic nephritis, usually caused by chronic use of acetaminophen (eg, Tylenol) in people.[98] This syndrome has not been described in domestic animals.

Are there increased effects with angiotensin-converting enzyme inhibitors and nonsteroidal anti-inflammatory drugs?

Because ACE inhibitors carry a risk for decreased renal perfusion, administration of ACE inhibitors and NSAIDs has been suggested to increase the risk.[99] The review by Lefebvre and Toutain[100] examines the role of ACE inhibitors on the kidney and the potential for complications from coadministration of NSAIDs. For example, in humans there is concern that in some patients the combination of an ACE inhibitor and an NSAID may increase the risk for renal injury.[99] Only one study examining this combination has been published for dogs.[96] It was concluded in that study that tepoxalin did not alter renal function in healthy beagle dogs receiving an ACE inhibitor. Such an effect of other NSAID combinations has not been adequately studied in veterinary medicine to make adequate conclusions.

Sensitivity of Nonsteroidal Anti-Inflammatory Drugs in Cats

A complete and in-depth review of NSAIDs in cats was published by Lascelles and colleagues.[6] The toxic effects of salicylates in cats are well documented. Cats are susceptible because of slow clearance and dose-dependent elimination. Affected cats may have hyperthermia, respiratory alkalosis, metabolic acidosis, methemoglobinemia, hemorrhagic gastritis, and kidney and liver injury. Cats also are prone to acetaminophen toxicosis because of their deficiency in drug-metabolizing enzymes. Cases of acetaminophen toxicity in cats also have been well documented. Treatment of acetaminophen toxicity consists of measures to replenish compounds that can conjugate the metabolites of acetaminophen and increase clearance, such as acetylcysteine[57] or S-adenosyl methionine. Despite the sensitivity in cats to some of the NSAIDs, there are still drugs in this group have been used safely. Aspirin has been used at doses of 10 mg/kg every other day.[1] There are also reports of the safe use of ketoprofen (registered in Canada) at a dose of 1 mg/kg/day for 4 days and flunixin meglumine (1 mg/kg once) in cats for short-term treatment.

In the United States meloxicam is registered for single use at 0.3 mg/kg and also is used in Canada and Europe. The label instructions carefully warn not to administer more than one dose. When cats were administered high doses (5 × dose) vomiting and other gastrointestinal problems were reported. With repeated doses (9 days) of 0.3 mg/kg per day to cats, inflamed gastrointestinal mucosa and ulceration was observed. (Earlier in this article the PK-PD analysis of meloxicam indicated that this dose would be high for repeated doses.) On the other hand, many veterinarians have administered meloxicam to cats for multiple doses at lower doses. Some regimens recommend meloxicam in cats at 0.1 mg/kg initially, followed by decreased doses. If a favorable response is seen in the first few days, increase the dose interval to once every 48 to 72 hours, at a lower dose of 0.05 mg/kg and as low as 0.025 mg/kg. In Europe the approved dose for cats is 0.05 mg/kg per day for chronic use. There are safety data from the sponsor to support this claim. Long-term safety of meloxicam in cats was

published at a lower dose of 0.01 to 0.03 mg/kg, which is lower than the approved European dose.[101]

Use of carprofen in cats has been discouraged because of reports of gastroduodenal toxicosis when it was administered according to canine dose rates. Carprofen is approved for single-dose administration in Europe. Tepoxalin has not been tested clinically in cats, even though pharmacokinetic studies showed that both the parent drug and metabolite would allow for safe dosing at 10 mg/kg. At high doses, however, it has produced adverse effects and a safe dose for routine therapeutic use has not been identified. There is one report of use of firocoxib in cats.[102] In this report, cats were given doses of 0.75 to 3 mg/kg (single dose), which was effective for attenuating experimentally induced fever. Other selections of NSAIDs in cats should be guided by the review cited earlier.[6]

Hepatic Safety

As pointed out in a recent review, any NSAID has the potential for causing hepatic injury.[103] The author states that NSAIDs as a class have been associated with considerable hepatotoxicity. Hepatotoxicity caused by NSAIDs can be either idiosyncratic (unpredictable, non–dose related) or intrinsic (predictable and dose related).[104,105] Toxicity to acetaminophen and aspirin are intrinsic; reactions to other drugs tend to be idiosyncratic and unpredictable. Administration of NSAIDs to animals that have hepatic disease has been questioned because of the role of the liver in metabolizing these drugs, but there is no evidence that prior hepatic disease predisposes a patient to NSAID-induced liver injury. Drug enzyme systems are remarkably preserved in hepatic disease and pre-existing hepatic disease is not necessarily a contraindication for administration of an NSAID. Patients that have liver disease may be more prone to gastrointestinal ulceration, and there is concern that administration of NSAIDs could increase the risk for this complication.

Carprofen was approved by FDA in October 1996 for relief of pain and inflammation in dogs. Before this approval, it was registered for treatment of dogs in Europe (Zenecarp) and was evaluated in clinical trials. In studies in dogs that had arthritis, it was effective and had a low incidence of adverse effects.[106] In long-term studies in which carprofen was administered from 2 weeks to 5 years, the incidence of adverse reactions was only 1.3%. Vomiting, diarrhea, anorexia, and lethargy were the most common adverse reactions documented. Attention has focused on the hepatotoxicity caused by carprofen because of a report in the published literature.[107] Hepatic injury signs are also among the most common adverse events reported for carprofen to the FDA adverse events reporting site. In this report, 21 dogs were described in which carprofen was associated with acute, idiosyncratic hepatotoxicosis. Affected dogs had diminished appetites, vomited, and were icteric, with elevations in hepatic enzymes and bilirubin. Dogs received the usual recommended dose and developed signs an average of 19 days after therapy was initiated. No predisposing conditions were identified. Most dogs recovered without further consequences. Many of the dogs in that report were Labrador retrievers, but there is no follow-up evidence to show that this breed of dogs has increased risk for carprofen hepatotoxicity.[108] Among the other drugs, the newest drug, firocoxib, caused fatty liver changes in young dogs when administered at high doses (manufacturer's data). Other NSAIDs used in veterinary medicine also have potential for causing liver injury, but they are uncommon. In a study of long-term administration for 90 days, there were only minor and clinically unimportant changes in serum biochemical variables in dogs after administration of carprofen, etdolac, flunixin, ketoprofen, and meloxicam.[97] Idiosyncratic reactions are

rare (1/1000 to 1/10,000 patients). Any unexplained increase in hepatic enzymes or bilirubin 7 to 90 days after initiating NSAID administration should be investigated.

CLINICAL DRUG SELECTION

When selecting a drug for treatment in animals, there are several choices (see **Box 1**). Veterinarians should not allow unsubstantiated claims to affect the selection of one drug over another. Over the past several years we have learned some important information about these drugs that should guide treatment (**Box 2**), and one of the most significant of these is that we really do not know which NSAID drug is best. Each has advantages and disadvantages. There are different dosage forms that include injectable, oral liquid, rapidly dissolving tablets, regular tablets, and chewable tablets. The preference for each of these depends on the clinical situation and the pet owner. There are veterinary generic formulations of popular drugs and there are still some human-labeled drugs used off- label (eg, piroxicam).

For acute pain, such as perioperative use, there is good evidence of efficacy from oral and injectable formulations that has been published in previous reports and reviews. For these and other indications, NSAIDs have been used for short-term durations of 1 or 2 days to decrease fever and decrease pain from surgery or trauma. Preoperative injections of carprofen to dogs were shown to be beneficial to decrease postoperative pain in dogs after ovariohysterectomy.[109] Meloxicam effects for surgical pain have been reported and were shown to be superior to butorphanol in some of the pain assessments that were measured.[110–112]

Oral NSAIDs also may be used for acute treatment of myositis, arthritis, and postoperative pain, or they may be administered chronically for osteoarthritis. Drugs that have been administered in the United States to small animals are listed in **Box 1**, and some veterinarians also have used human-label drugs, such as aspirin, piroxicam, and naproxen. If these human-label drugs are considered, consult appropriate references for accurate dosing because it may differ from the human dose schedule. The most recently approved drugs are carprofen, etodolac, meloxicam, firocoxib, tepoxalin, and deracoxib. Doses are listed in **Table 2**. For long-term use there are no controlled studies that compare which is the most effective. When drugs are compared with one another it is difficult, using subjective measurements, to demonstrate differences between these drugs for reducing pain in animals. Without a very large number of patients, the statistical power to detect differences among drugs in clinical veterinary studies is difficult.

In summary, there are several choices of NSAIDs for treating dogs that have osteoarthritis. Like people, there may be greater differences among individuals in their

Box 2
What have we learned about nonsteroidal anti-inflammatory drugs?

All NSAIDs, regardless of COX-1/COX-2 specificity, are capable of producing gastrointestinal lesions, particularly at high doses.

All NSAIDs (selective or nonselective) can produce other gastrointestinal signs, including vomiting, diarrhea, and decreased appetite, without producing ulceration.

All NSAIDs have potential for producing hepatic injury. Susceptibility seems to be idiosyncratic and unpredictable.

All NSAIDs have the potential for producing renal injury. Previous renal disease, salt depletion, and dehydration increase the risk.

No NSAID is consistently more clinically effective than another.

response than there are differences among the drugs. In past practice, veterinarians often selected aspirin or phenylbutazone as an initial drug, and then progressed to off-label human drugs (eg, piroxicam) or other agents as an alternative. Now we have the advantage of several approved NSAIDs for which there are excellent published studies and FDA or foreign approval to guide clinical use and safe dosages. Among the drugs available (see **Box 1**) there may be variations among animals with respect to tolerance of adverse effects and clinical response. It is a rational approach to consider a rotating schedule of two or more drugs to identify which drug is better tolerated, more effective, and easier to administer in each patient. When considering a switch from one NSAID to another, the necessity of a washout period should be considered.

REFERENCES

1. Papich MG. Saunders handbook of veterinary drugs. 2nd edition. St. Louis (MO): Elsevier-Saunders Co.; 2007.
2. Papich MG. Pharmacologic considerations for opiate analgesic and nonsteroidal anti-inflammatory drugs. Vet Clin North Am Small Anim Pract 2000;30:815–37.
3. Bergh MS, Budsgerg SC. The COXIB NSAIDs: potential clinical and pharmacologic importance in veterinary medicine. J Vet Intern Med 2005;19:633–43.
4. Lees P, Landoni MF, Giraudel J, et al. Pharmacodynamics and pharmacokinetics of nonsteroidal anti-inflammatory drugs in species of veterinary interest. J Vet Pharmacol Ther 2004b;27(6):479–90.
5. Lascelles BDX, McFarland JM, Swann H. Guidelines for safe and effective use of NSAIDs in dogs. Vet Ther 2005;6(3):237–50.
6. Lascelles BDX, Court MH, Hardie EM, et al. Nonsteroidal anti-inflammatory drugs in cats: a review. Vet Anaesth Analg 2007;34:228–50.
7. Vane JR, Botting RM. New insights into the mode of action of anti-inflammatory drugs. Inflamm Res 1995;44:1–10.
8. Laneuville O, Breuer DK, DeWitt DL, et al. Differential inhibition of human prostaglandin endoperoxide synthases-1 and -2 by nonsteroidal anti-inflammatory drugs. J Pharmacol Exp Ther 1994;271:927–34.
9. Meade EA, Smith WL, DeWitt DL. Pharmacology of prostaglandin endoperoxide synthase isozymes-1 and -2. Ann N Y Acad Sci 1994;714:136–42.
10. Wooten JG, Blikslager AT, Ryan KA, et al. Cyclooxygenase expression and prostanoid production in pyloric and duodenal mucosae in dogs after administration of nonsteroidal anti-inflammatory drugs. Am J Vet Res 2008;69(4):457–64.
11. Konturek SJ, Konturek PC, Brzozowski T. Prostaglandins and ulcer healing. J Physiol Pharmacol 2005;56(Suppl 5):5–31.
12. Punke JP, Speas AL, Reynolds LR, et al. Effects of firocoxib, meloxicam, and tepoxalin on prostanoid and leukotriene production by duodenal mucosa and other tissues of osteoarthritic dogs. Am J Vet Res 2008;69(9):1203–9.
13. Bertolini A, Ottani A, Sandrini M. Dual acting anti-inflammatory drugs: a reappraisal. Pharmacol Res 2001;44:437–50.
14. Flower RJ, Vane JR. Inhibition of prostaglandin synthetase in brain explains the antipyretic activity of paracetamol (4-acetamidophenol). Nature 1972;240(5381):410–1.
15. Chandrasekharan NV, Dai H, Roos KL, et al. A cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: cloning, structure, and expression. Proc Natl Acad Sci U S A 2002;99(21):13926–31 (with commentary in Proc Natl Acad Sci U S A. 99(21):13371–13373, 2002).

16. Davies NM, Good RL, Roupe KA, et al. Cyclooxygenase-3: axiom, dogma, anomaly, enigma or splice error?—not as easy as 1, 2, 3. J Pharm Pharm Sci 2004;7(2):217–26.
17. Aronoff DM, Oates JA, Boutaud O. New insights into the mechanism of action of acetaminophen: its clinical pharmacologic characteristics reflect its inhibition of the two prostaglandin H2 synthases. Clin Pharmacol Ther 2005;79:9–19.
18. Kis B, Snipes JA, Busija DW. Acetaminophen and the cyclooxygenase-3 puzzle: sorting out facts, fictions, and uncertainties. J Pharmacol Exp Ther 2005;315(1): 1–7.
19. Gierse JK, Staten NR, Casperson GF, et al. Cloning, expression, and selective inhibition of canine cyclooxygenase-1 and cyclooxygenase-2. Vet Ther 2002;3: 270–80.
20. McCann ME, Andersen DR, Zhang D, et al. In vitro effects and in vivo efficacy of a novel cyclo-oxygenase-2 inhibitor in dogs with experimentally induced synovitis. Am J Vet Res 2004;65:503–12.
21. Ricketts AP, Lundy KM, Seibel SB. Evaluation of selective inhibition of canine cyclooxygenase 1 and 2 by carprofen and other nonsteroidal anti-inflammatory drugs. Am J Vet Res 1998;59:1441–6.
22. Kay-Mugford P, Benn SJ, LaMarre J, et al. In vitro effects of nonsteroidal anti-inflammatory drugs on cyclooxygenase activity in dogs. Am J Vet Res 2000; 61:802–10.
23. Wilson JE, Chandrasekharan NV, Westover KD, et al. Determination of expression of cyclooxygenase-1 and -2 isozymes in canine tissues and their differential sensitivity to nonsteroidal anti-inflammatory drugs. Am J Vet Res 2004;65:810–8.
24. McKellar QA, Delatour P, Lees P. Stereospecific pharmacodynamics and pharmacokinetics of carprofen in the dog. J Vet Pharmacol Ther 1994;17:447–54.
25. Glaser KB. Cyclooxygenase selectivity and NSAIDs: cyclooxygenase-2 selectivity of etodolac (lodine). Inflammopharmacology 1995;3:335–45.
26. Lees P. Pharmacology of drugs used to treat osteoarthritis in veterinary practice. Inflammopharmacology 2003;11:385–99.
27. Patrignani P, Panara MR, Greco A, et al. Biochemical and pharmacological characterization of the cyclooxygenase activity of human blood prostaglandin endoperoxide synthases. J Pharmacol Exp Ther 1994;271(3):1705–12.
28. Blain H, Boileau C, Lapicque F, et al. Limitation of the in vitro whole blood assay for predicting the COX selectivity of NSAIDs in clinical use. Br J Clin Pharmacol 2002;53(3):255–65.
29. Hinz B, Brune K. Can drug removals involving cyclooxygenase-2 inhibitors be avoided? A plea for human pharmacology. Trends Pharmacol Sci 2008;29(8): 391–7.
30. Lees P, Giraudel J, Landoni MF, et al. PK-PD integration and PK-PD modelling of nonsteroidal anti-inflammatory drugs: principles and applications in veterinary pharmacology. J Vet Pharmacol Ther 2004a;27(6):491–502.
31. Giraudel JM, Diquelou A, Laroute V, et al. Pharmacokinetic/pharmacodynamic modelling of NSAIDs in a model of reversible inflammation in the cat. Br J Pharmacol 2005a;146(5):642–53.
32. Giraudel JM, Diquelou A, Lees P, et al. Development and validation of a new model of inflammation in the cat and selection of surrogate endpoints for testing anti-inflammatory drugs. J Vet Pharmacol Ther 2005b;28(3):275–85.
33. Borer LR, Peel JE, Seewald W, et al. Effect of carprofen, etodolac, meloxicam, or butorphanol in dogs with induced acute synovitis. Am J Vet Res 2003;64: 1429–37.

34. Jones CJ, Streppa HK, Harmon BG, et al. In vivo effects of meloxicam and aspirin on blood, gastric mucosal, and synovial fluid prostanoid synthesis in dogs. Am J Vet Res 2002;63:1527–31.
35. Sessions JK, Reynolds LR, Budsberg SC. In vivo effects of carprofen, deracoxib, and etodolac on prostanoids production in blood, gastric mucosa, and synovial fluid in dogs with chronic osteoarthritis. Am J Vet Res 2005;66:812–7.
36. Bryant CE, Farnfield BA, Janicke HJ. Evaluation of the ability of carprofen and flunixin meglumine to inhibit activation of nuclear factor kappa B. Am J Vet Res 2003;64:211–5.
37. FitzGerald GA, Patrono C. The Coxibs, selective inhibitors of cyclooxygenase-2. N Engl J Med 2001;345:433–42.
38. McCann ME, Rickes EL, Hora DF, et al. In vitro effects and in vivo efficacy of a novel cyclooxygenase-2 inhibitor in cats with lipopolysaccharide-induced pyrexia. Am J Vet Res 2005;66:1278–84.
39. Peterson WL, Cryer B. COX-1-sparing NSAIDs—is the enthusiasm justified? J Am Med Assoc 1999;282:1961–3 [see also pages 1921 and 1929 of this issue.].
40. Lascelles BDX, Blikslager AT, Fox SM, et al. Gastrointestinal tract perforation in dogs treated with a selective cyclooxygenase-2 inhibitor: 29 cases (2002–2003). J Am Vet Med Assoc 2005;227:1112–7.
41. Drazen JM. COX-2 inhibitors – a lesson in unexpected problems. N Engl J Med 2005;352:1131–2.
42. Malhotra S, Shafiq N, Pandhi P. COX-2 inhibitors: a CLASS act, or just VIGORously promoted. MedGenMed 2004;6(1). Available at: www.medscape.com.
43. Psaty BM, Furberg CD. COX-2 inhibitors—lessons in drug safety. N Engl J Med 2005;352:1133–5.
44. Jüni P, Rutjes AWS, Dieppe PA. Are selective COX 2 inhibitors superior to traditional non steroidal anti-inflammatory drugs? Br Med J 2002;324:1287–8.
45. Rainsford KD. The ever-emerging anti-inflammatories. Have there been any real advances? J Physiol 2001;95:11–9.
46. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. N Engl J Med 1999;340:1888–99.
47. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. JAMA 2001;286:954–9.
48. FitzGerald GA. Coxibs and cardiovascular disease. N Engl J Med 2004;351:1709–11.
49. Topol EJ. Failing the public health—rofecoxib, Merck and the FDA. N Engl J Med 2004;351:1707–9.
50. Eisenberg RS. Learning the value of drugs—is rofecoxib a regulatory success story? N Engl J Med 2005;352:1285–7.
51. Okie S. Raising the safety bar—the FDA's Coxib meeting. N Engl J Med 2005;345:1283–5.
52. Trang T, McNaull B, Quirion R, et al. Involvement of spinal lipoxygenase metabolites in hyperalgesia and opiate tolerance. European Journal of Pharmacology 2004;491:21–30.
53. Moreau M, Daminet S, Martel-Pelletier J, et al. Superiority of the gastrointestinal safety profile of licofelone over rofecoxib, a COX-2 selective inhibitor in dogs. J Vet Pharmacol Ther 2005;28:81–6.
54. Boston SE, Moens NM, Kruth SA, et al. Endoscopic evaluation of the gastroduodenal mucosa to determine the safety of short-term concurrent administration of meloxicam and dexamethasone in healthy dogs. Am J Vet Res 2003;64(11):1369–75.

55. Narita T, Sato R, Motoishi K, et al. The interaction between orally administered non-steroidal anti-inflammatory drugs and prednisolone in healthy dogs. J Vet Med Sci 2007;69(4):353–63.
56. Agnello KA, Reynolds LR, Budsberg SC. In vivo effects of tepoxalin, an inhibitor of cyclooxygenase and lipoxygenase, on prostanoid and leukotriene production in dogs with chronic osteoarthritis. Am J Vet Res 2005;66(6):966–72.
57. Hjelle JJ, Grauer GF. Acetaminophen-induced toxicosis in dogs and cats. J Am Vet Med Assoc 1986;188:742–6.
58. Bradley JD, Brandt KD, Katz BP, et al. Comparison of an anti-inflammatory dose of ibuprofen, an analgesic dose of ibuprofen, and acetaminophen in the treatment of patients with osteoarthritis of the knee. N Engl J Med 1991;325:87–91.
59. Mburu DN, Mbugua LA, Skoglund LA, et al. Effects of paracetamol (acetaminophen) and acetylsalicylic acid on the post-operative course after experimental orthopaedic surgery in dogs. J Vet Pharmacol Ther 1988;11:163–71.
60. Mburu DN. Evaluation of the anti-inflammatory effects of a low-dose of acetaminophen following surgery in dogs. J Vet Pharmacol Ther 1991;14:109–11.
61. Savides MC, Oehme FW, Nash SL, et al. The toxicity and biotransformation of single doses of acetaminophen in dogs and cats. Toxicol Appl Pharmacol 1984;74:26–34.
62. Hinz B, Cheremina O, Brune K. Acetaminophen (paracetamol) is a selective cyclooxygenase-2 inhibitor in man. FASEB J 2007;22(2):383–90.
63. Pickering G, Esteve V, Loriot M-A, et al. Acetaminophen reinforces descending inhibitory pain pathways. Clin Pharmacol Ther 2008;84(1):47–51.
64. Mathews KA. Nonsteroidal anti-inflammatory analgesics in pain management in dogs and cats. Can Vet J 1996;37:539–45.
65. Dowers KL, Uhrig SR, Mama KR, et al. Effect of short-term sequential administration of nonsteroidal anti-inflammatory drugs on the stomach and proximal portion of the duodenum in healthy dogs. Am J Vet Res 2006;67(10):1794–801.
66. Galbraith EA, McKellar QA. Pharmacokinetics and pharmacodynamics of piroxicam in dogs. Vet Rec 1991;128:561–5.
67. Knapp DW, Richardson RC, Chan TCK, et al. Piroxicam therapy in 34 dogs with transitional cell carcinoma of the urinary bladder. J Vet Intern Med 1994;8(4):273–8.
68. Schmidt BR, Glickman NW, DeNicola DB, et al. Evaluation of piroxicam for the treatment of oral squamous cell carcinoma in dogs. J Am Vet Med Assoc 2001;218:1783–6.
69. Brune K. Safety of anti-inflammatory treatment—new ways of thinking. Rheumatology 2004;43(Suppl 1):i16–20.
70. Wallace JL, Fiorucci S. A magic bullet for mucosal protection.and aspirin is the trigger!. Trends Pharmacol Sci 2003;24(7):323–6.
71. Fiorucci S, de Lima OM Jr, Mencarelli A, et al. Cyclooxygenase-2-derived lipoxin A4 increases gastric resistance to aspirin-induced damage. Gastroenterology 2002;123(5):1598–606.
72. Souza MH, de Lima OM Jr, Zamuner SR, et al. Gastritis increases resistance to aspirin-induced mucosal injury via COX-2-mediated lipoxin synthesis. Am J Physiol Gastrointest Liver Physiol 2003;285(1):G54–61.
73. Brzozowski T, Konturek PC, Konturek SJ, et al. Role of prostaglandins in gastroprotection and gastric adaptation. J Physiol Pharmacol 2005;56(Suppl 5):33–55.
74. Taylor LA, Crawford LM. Aspirin-induced gastrointestinal lesions in dogs. J Am Vet Med Assoc 1968;152(6):617–9.
75. Sennello KA, Leib MS. Effects of deracoxib or buffered aspirin on the gastric mucosa of healthy dogs. J Vet Intern Med 2006;20:1291–6.

76. Raekallio MR, Hielm-Björkman AK, Kejonen J, et al. Evaluation of adverse effects of long-term orally administered carprofen in dogs. J Am Vet Med Assoc 2006; 228(6):876–80.
77. Wallace JL, Wallace JL, Zamuner SR, et al. Aspirin, but not NO-releasing aspirin (NCX-4016), interacts with selective COX-2 inhibitors to aggravate gastric damage and inflammation. Am J Physiol Gastrointest Liver Physiol 2004;286(1):G76–81.
78. Ryan WG, Moldave K, Carithers D. Switching NSAIDs in practice: insights from the Previcox (firocoxib) experience trial. Vet Ther 2007;8(4):263–71.
79. Whittle BJ. Mechanisms underlying intestinal injury induced by anti-inflammatory COX inhibitors. Eur J Pharmacol 2004;500(1–3):427–39.
80. Lee YS, Kim H, Wu TX, et al. Genetically mediated interindividual variation in analgesic responses to cyclooxygenase inhibitory drugs. Clin Pharmacol Ther 2006;79(5):407–18.
81. Forsyth SF, Guilford WG, Haslett SJ, et al. Endoscopy of the gastroduodenal mucosa after carprofen, meloxicam and ketoprofen administration in dogs. J Small Anim Pract 1998;39:421–4.
82. Reimer ME, Johnston SA, Leib MS, et al. The gastrointestinal effects of buffered aspirin, carprofen, and etodolac in healthy dogs. J Vet Intern Med 1999;13:472–7.
83. Doig PA, Purbrick KA, Hare JE, et al. Clinical efficacy and tolerance of meloxicam in dogs with chronic osteoarthritis. Can Vet J 2000;41(4):296–300.
84. Enberg TB, Braun LD, Kuzma AB. Gastrointestinal perforation in five dogs associated with the administration of meloxicam. Journal of Veterinary Emergency and Critical Care 2006;16:34–43.
85. Mathews KA, Doherty T, Dyson DH, et al. Nephrotoxicity in dogs associated with methoxyflurane anesthesia and flunixin meglumine analgesia. Can Vet J 1990; 31:766–71.
86. Lobetti RG, Joubert KE. Effect of administration of nonsteroidal anti-inflammatory drugs before surgery on renal function in clinically normal dogs. Am J Vet Res 2000;61:1501–6.
87. Gambaro G, Perazella MA. Adverse renal effects of anti-inflammatory agents: evaluation of selective and nonselective cyclo-oxygenase inhibitors. J Intern Med 2003;253:643–52.
88. Rossat J, Maillard M, Nussberger JU, et al. Renal effects of selective cyclooxygenase-2 inhibition in normotensive salt-depleted subjects. Clin Pharmacol Ther 1999;66:76–84.
89. Boström IM, Nyman GC, Lord PF, et al. Effects of carprofen on renal function and results of serum biochemical and hematologic analyses in anesthetized dogs that had low blood pressure during anesthesia. Am J Vet Res 2002;63:712–21.
90. Crandell DE, Mathews KA, Dyson DH. Effect of meloxicam and carprofen on renal function when administered to healthy dogs prior to anesthesia and painful stimulation. Am J Vet Res 2004;65(10):1384–90.
91. Frendin JH, Boström IM, Kampa N, et al. Effects of carprofen on renal function during medetomidine-propofol-isoflurane anesthesia in dogs. Am J Vet Res 2006;67(12):1967–73.
92. Ko JCH, Miyabiyashi T, Mandsager RE, et al. Renal effects of carprofen administered to healthy dogs anesthetized with propofol and isoflurane. J Am Vet Med Assoc 2000;217:346–9.
93. Bergmann HML, Nolte IJA, Kramer S. Effects of preoperative administration of carprofen on renal function and hemostasis in dogs undergoing surgery for fracture repair. Am J Vet Res 2005;66:1356–63.

94. Fusellier M, Desfontis J-C, LeRoux A, et al. Effect of short-term treatment with meloxicam and pimobendan on the renal function in healthy beagle dogs. Journal of Veterinary Pharmacology and Therapeutics 2008;31:150–5.
95. Boström IM, Nyman G, Hoppe A, et al. Effects of meloxicam on renal function in dogs with hypotension during anaesthesia. Vet Anaesth Analg 2006;33(1):62–9.
96. Kay-Mugford PA, Grimm KA, Weingarten AJ, et al. Effect of preoperative administration of tepoxalin on hemostasis and hepatic and renal function in dogs. Vet Ther 2004;5:120–7.
97. Luna SP, Basílio AC, Steagall PV, et al. Evaluation of adverse effects of long-term oral administration of carprofen, etodolac, flunixin meglumine, ketoprofen, and meloxicam in dogs. Am J Vet Res 2007;68(3):258–64.
98. de Broe ME, Elseviers MM. Analgesic nephropathy. N Engl J Med 1998;338: 446–52.
99. Loboz KK, Shenfield GM. Drug combinations and impaired renal function—the triple whammy. Br J Clin Pharmacol 2005;59:239–43.
100. Lefebvre HP, Toutain PL. Angiotensin-converting enzyme inhibitors in the therapy of renal diseases. J Vet Pharmacol Ther 2004;27(5):265–81.
101. Gunew MN, Menrath VH, Marshall RD. Long-term safety, efficacy and palatability of oral meloxicam at 0.01-0.03 mg/kg for treatment of osteoarthritic pain in cats. J Feline Med Surg 2008;10(3):235–41.
102. McCann ME, Rickes EL, Hora DF, et al. In vitro effects and in vivo efficacy of a novel cyclooxygenase-2 inhibitor in cats with lipopolysaccharide-induced pyrexia. Am J Vet Res 2005;66:01278–84.
103. Lee WM. Drug induced hepatotoxicity. N Engl J Med 2003;349:474–85.
104. Bjorkman D. Nonsteroidal anti-inflammatory drug-associated toxicity of the liver, lower gastrointestinal tract, and esophagus. Am J Med 1998;105(Suppl 5A): 17S–21S.
105. Tolman KG. Hepatotoxicity of non-narcotic analgesics. Am J Med 1998; 105(Suppl 1B). 13S–7S.
106. Vasseur PB, Johnson AL, Budsberg SC, et al. Randomized, controlled trial of the efficacy of carprofen, a nonsteroidal antiinflammatory drug, in the treatment of osteoarthritis in dogs. J Am Vet Med Assoc 1995;206:807–11.
107. MacPhail CM, Lappin MR, Meyer DJ, et al. Hepatocellular toxicosis associated with administration of carprofen in 21 dogs. J Am Vet Med Assoc 1998;212:1895–901.
108. Hickford FH, Barr SC, Erb HN. Effect of carprofen on hemostatic variables in dogs. Am J Vet Res 2001;62(10):1642–6.
109. Lascelles BDX, Cripps PJ, Jones A, et al. Efficacy and kinetics of carprofen, administered preoperatively or postoperatively, for the prevention of pain in dogs undergoing ovariohysterectomy. Vet Surg 1998;27:568–82.
110. Budsberg SC, Cross AR, Quandt JE, et al. Evaluation of intravenous administration of meloxicam for perioperative pain management following stifle joint surgery in dogs. Am J Vet Res 2002;63(11):1557–63.
111. Caulkett N, Read M, Fowler D, et al. A comparison of the analgesic effects of butorphanol with those of meloxicam after effective ovariohysterectomy in dogs. Can Vet J 2003;44(7):565–70.
112. Mathews KA, Pettifer G, Foster R, et al. Safety and efficacy of preoperative administration of meloxicam, compared with that of ketoprofen and butorphanol in dogs undergoing abdominal surgery. AM J Ver Res 2001;62(6):882–8.