

REVIEW

Clinical pharmacology of nonsteroidal anti-inflammatory drugs in dogs

Butch KuKanich*, Tara Bidgood† & Oliver Knesl†

*Kansas State University College of Veterinary Medicine, Manhattan, KS, USA

†Pfizer Animal Health, 5 Giralda Farms, Madison, NJ, USA

Correspondence: Oliver Knesl, Pfizer Animal Health, 5 Giralda Farms, Madison, NJ 07940, USA. E-mail: oliver.knesl@pfizer.com

Abstract

Objectives To discuss the clinical pharmacology of currently licensed veterinary NSAIDs and to review gastrointestinal and renal adverse effects as well as drug-drug interactions that have been reported with these drugs. To review the use of NSAIDs in the peri-operative setting and their use in patients with osteoarthritis. To further review the reported effects of NSAIDs on canine articular cartilage and liver as well as the clinical relevance of a washout period.

Databases used PubMed, CAB abstracts and Google Scholar using dog, dogs, nonsteroidal anti-inflammatory drugs and NSAID(s) as keywords.

Conclusions A good understanding of the mechanisms by which NSAIDs elicit their analgesic effect is essential in order to minimize adverse effects and drug-drug interactions. Cyclooxygenase (COX) is present in at least two active isoforms in the body and is the primary pharmacologic target of NSAIDs. Inhibition of COX is associated with the analgesic effects of NSAIDs. COX is present in the gastrointestinal tract and kidneys, along with other areas of the body, and is also the likely reason for many adverse effects including gastrointestinal and renal adverse effects. The newer veterinary approved NSAIDs have a lower frequency of gastrointestinal adverse effects in dogs compared to drugs such as aspirin, ketoprofen and flunixin, which may be due to differential effects on the COX isoforms. There are currently no published reports demonstrating that

the newer NSAIDs are associated with fewer renal or hepatic adverse effects in dogs. NSAIDs remain the cornerstone of oral therapy for osteoarthritis unless contraindicated by intolerance, concurrent therapies or underlying medical conditions. NSAIDs are also effective and frequently used for the management of post-operative pain.

Keywords adverse effects, drug-drug interactions, gastrointestinal, non steroidal antiinflammatory drugs, pharmacology, renal.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are effective for managing acute and chronic orthopedic pain as well as post-surgical pain (Doig et al. 2000; Hanson et al. 2006; Pollmeier et al. 2006; Ryan et al. 2006; Autefage & Gosselin 2007; Mansa et al. 2007; Deramaxx FOI; Previcox FOI; Rimadyl FOI). It is, however, important to understand the mechanisms by which NSAIDs elicit their analgesic effects, and any potential drug-related adverse effects, in order to minimize the risk for these adverse effects as well as any possible drug-drug interactions. The freedom of information summaries (FOIs) for the various Food and Drug Administration (FDA) approved canine NSAIDs and European Medicines Agency, European Public Assessment Reports (EMA EPARs) as well as independent studies note the most common adverse effects are associated with the gastrointestinal (GI) tract (Doig et al. 2000; Hanson et al. 2006; Pollmeier et al. 2006;

Raekallio et al. 2006; Ryan et al. 2006; Autefage & Gossellin 2007; Luna et al. 2007; Mansa et al. 2007; Deramaxx FOI; Etogesic FOI; Metacam FOI; Onsiar EMA EPAR; Previcox FOI; Rimadyl FOI; Trocoxil EMA EPAR; Zubrin FOI). Renal and hepatic adverse effects have been reported at a lower frequency while inhibition of coagulation, lethargy, and polydipsia are infrequently reported in clinical studies (Doig et al. 2000; Hanson et al. 2006; Pollmeier et al. 2006; Raekallio et al. 2006; Ryan et al. 2006; Autefage & Gossellin 2007; Luna et al. 2007; Mansa et al. 2007; Deramaxx FOI; Etogesic FOI; Metacam FOI; Onsiar EMA EPAR; Previcox FOI; Rimadyl FOI; Trocoxil EMA EPAR; Zubrin FOI). If failure to respond to treatment were to be considered an adverse effect, it would have the second highest frequency behind gastrointestinal adverse effects with a reported range of 1–12% in dogs with osteoarthritis (Hanson et al. 2006; Pollmeier et al. 2006; Autefage & Gossellin 2007; Mansa et al. 2007).

The recently licensed veterinary NSAIDs appear to have decreased frequencies of gastrointestinal adverse effects in dogs compared to drugs such as aspirin, ketoprofen, phenylbutazone, tolfenamic acid, and flunixin (Varro et al. 1959; Bhatia et al. 1965; Reimer et al. 1999; Nishihara et al. 2001; Luna et al. 2007; Tolfedine package insert). However, extensive studies have not directly evaluated the available NSAIDs in dogs. The gastrointestinal adverse effects such as vomiting, anorexia, and diarrhea can occur independently of gastrointestinal ulcerations and therefore GI adverse effects are not pathognomonic and are poorly correlated to GI damage or ulceration (Dow et al. 1990). However some animals with vomiting, anorexia, and diarrhea may progress to GI ulceration. It is also important to note that GI erosion, ulceration or perforation can occur without previous signs of GI adverse effects in dogs (Stanton & Bright 1989; Wooten et al. 2010).

In contrast to gastrointestinal adverse effects, there are no published reports which demonstrate that the newer NSAIDs are associated with fewer renal (hyposthenuria, azotemia, renal failure) or hepatic adverse effects (hepatocellular toxicosis, hepatic failure) in companion animals. The purpose of this paper is to provide a review of the clinical pharmacology of NSAIDs, their clinical use, and a comprehensive overview of the GI and renal adverse effects as well as drug-drug interactions that have been reported with the newer NSAIDs.

Pharmacokinetics

The pharmacokinetic properties of veterinary approved NSAIDs are available on their respective labels, FOIs and EMA EPARs, as well as some independent reports in the literature (Zech et al. 1993; McKellar et al. 1994; Busch et al. 1998; Homer et al. 2005; Jung et al. 2009; Cox et al. 2010). NSAIDs tend to be well absorbed after oral administration with the exception of tepoxalin which is better absorbed with food and the licensed formulation of firocoxib which has a low oral bioavailability (Homer et al. 2005; Lees 2009; Previcox FOI). Deracoxib is better absorbed with food, but efficacy also occurs when administered to fasted dogs (Deramaxx FOI). Most NSAIDs are highly bound to plasma proteins, but the clinical implications of high protein binding are limited (see drug-drug interactions/contraindications). Hepatic elimination is the primary route of elimination for NSAIDs via biliary secretion, conjugation reactions, and metabolic reactions such as cytochrome P450 metabolism (Lees 2009). Hepatic disease may decrease the rate of elimination, subsequently increasing the terminal half-life and total drug exposure (area under the curve) which could increase GI and renal adverse effects (see the effects of NSAIDs on the liver). Some renal elimination of NSAIDs occurs, which may be increased by urinary alkalinization (due to ion trapping of the weak acids), but this is a secondary route of elimination. A thorough review of the pharmacokinetics is available elsewhere for further reading (Lees 2009).

Mechanisms of action

Despite the large structural diversity of NSAIDs they all have a similar mechanism of action, namely, the inhibition of cyclooxygenase (COX) (Simmons et al. 2004). Cyclooxygenase is present in most tissues within the body and can become up-regulated with a variety of stimuli (Lascelles et al. 2009). Two primary forms of COX have been identified, COX-1 and COX-2 (Simmons et al. 2004). Initially, COX-1 was identified as a constitutive isoform whereas COX-2 was identified as an inducible isoform, but further studies have shown that both isoforms are constitutive and inducible (Wooten et al. 2008, 2010; Lascelles et al. 2009). COX-3 has been identified primarily in the canine cerebral cortex with minimal amounts found peripherally (Chandrasekharan et al. 2002). The activity and

physiological effects of COX-3 in the dog have been questioned due to some methodological controversy, low concentrations and low activity (Kis et al. 2005; Lucas et al. 2005).

COX-1 produces many different eicosanoids, but prostaglandin (PG) E₂ and thromboxane A₂ produce many clinically important effects and will be focused on in this review (Simmons et al. 2004). PGE₂ produces numerous physiologic responses including vasodilation, sensitization of nociceptors enhancing both peripheral and central sensitization, and a number of effects in the GI tract including increased mucus production, decreased gastric acid secretion, increased secretion of bicarbonate in the duodenum, and increased turnover of mucosal cells. Thromboxane A₂ is primarily associated with platelets and results in increased platelet aggregation and vasoconstriction enhancing coagulation and blood clot formation with the result that exclusive inhibition of COX-1 produces an anticoagulant effect. COX-1 is also constitutively expressed in the cerebral cortex where its inhibition may contribute to the central analgesic and antipyretic effects of NSAIDs (Braga 1990).

COX-2 also produces a variety of eicosanoids with PGE₂, prostacyclin (PGI₂) and 15-epi-lipoxinA₄, also known as aspirin triggered lipoxin (ATL), resulting in many clinical effects and will be focused on in this review (Simmons et al. 2004). PGE₂ produced by COX-2 results in the same physiologic effects as PGE₂ produced by COX-1. PGI₂ is produced in endothelial cells and results in vasodilation and inhibition of platelet aggregation, producing an antagonistic effect to thromboxane A₂ (Simmons et al. 2004). Therefore exclusive inhibition of COX-2 produces a pro-coagulant effect. PGI₂ has also been identified in inflamed tissues and in the GI tract where it produces similar gastroprotective effects as PGE₂ (Simmons et al. 2004). PGE₂ and PGI₂ also alter renal physiology by increasing sodium excretion, inhibiting sodium reabsorption, and altering chloride transport (Simmons et al. 2004). PGE₂ and PGI₂ also stimulate renin release and profoundly alter total renal blood flow and regional blood flow within the kidneys of dogs (Osborn et al. 1984; Simmons et al. 2004).

COX-2 is constitutively expressed in the dorsal horn of the spinal cord and contributes to the propagation of nociceptive (pain) stimuli with the result that inhibition of COX-2 can also produce central analgesic effects (Malmberg & Yaksh 1992; Nishiyama 2006). COX-2 expression is increased in

injured tissue, producing PGE₂ and PGI₂ resulting in sensitization of peripheral nociceptors coupled with enhanced pain transmission as with COX-1 (Simmons et al. 2004). Recent studies have indicated both COX-1 and COX-2 are up-regulated in the synovium of dogs with naturally occurring hip osteoarthritis (Lascelles et al. 2009). COX-2 is also up-regulated in the endothelial cells within the hippocampus during fevers, which may explain the antipyretic effect of some NSAIDs.

Lipoxins are eicosanoids that produce anti-inflammatory effects and are thought to be produced to modulate the inflammatory response (Parkinson 2006). At least three metabolic pathways associated with lipoxin production have been identified including 15-lipoxygenase and 5-lipoxygenase, producing lipoxin A₄ and lipoxin B₄ and COX-2 producing 15-epi-lipoxin A₄ and B₄ also known as Aspirin Triggered Lipoxins (ATLs). The latter are potent anti-inflammatory and gastroprotective products of COX-2. ATLs have antagonistic effects on leukotriene C₄ induced bronchoconstriction and vasoconstriction and they also antagonize the effect of leukotriene D₄ mediated decreases in glomerular filtration rate (Parkinson 2006). ATL production is up-regulated in aspirin treated patients via the COX-2 pathway and may provide an adaptive gastrointestinal protective response (Fiorucci et al. 2002). As such, the inhibition of COX-2 in animals that have or will receive aspirin has been hypothesized to block the adaptive protective response increasing the potential for gastrointestinal adverse effects (Papich 2008).

The 5-lipoxygenase (LOX) pathway of the arachidonic acid cascade also produces a variety of leukotrienes (Bertolini et al. 2001). Leukotrienes have been associated with vasoconstriction, increased vascular permeability, bronchoconstriction, and attraction of inflammatory cells such as neutrophils, lymphocytes, and eosinophils. Leukotriene production in the GI tract may be increased when nonselective COX inhibitors are administered due to a shunting of the arachidonic acid pathway through LOX (Rainsford 1993). Inhibition of LOX and subsequent leukotriene formation in the GI tract during nonselective inhibition of COX results in significantly reduced GI adverse effects compared with nonselective COX inhibition (Rainsford 1999). However leukotriene production in the GI tract of dogs administered a preferential COX-2 inhibitor (COX-1 sparing) remained similar to placebo treated dogs (Agnello et al. 2005).

Tepoxalin is unique among the veterinary approved NSAIDs in that it inhibits LOX in addition to COX-1 and COX-2, therefore it is considered a dual inhibitor (Argentieri et al. 1994; Agnello et al. 2005). Administration of a single dose of tepoxalin inhibits the *ex vivo* production of LTB₄ (A LOX product) by 50% or greater for approximately 6 hours, whereas PGF_{2α} (a COX product) was inhibited for 24 hours, corresponding to the persistence of tepoxalin plasma concentrations ($T_{1/2} = 2$ hours) inhibiting both LOX and COX and its metabolite plasma concentrations ($T_{1/2} = 13$ hours) inhibiting COX only (Argentieri et al. 1994; Zubrin FOI). A study administering multiple doses of tepoxalin to dogs reported the *in vivo* COX inhibitory effects were observed at the first measured time point (day 3), but the LOX inhibitory effects were not observed until day 10 (Agnello et al. 2005). The differential effects on COX and LOX are probably due to differential COX and LOX inhibitory profiles and elimination of tepoxalin and the active metabolite.

Other mechanisms of action

The more NSAIDs are studied, the more apparent it becomes that they may affect physiologic processes other than the COX enzymes. However, the extent of these effects at clinical doses is unclear. Some NSAIDs, flurbiprofen, carprofen, and tepoxalin for example, have been documented to inhibit the activation of Nuclear Factor kappa-B (NFκ-B), which regulates proinflammatory enzymes, cytokines, chemotactic factors, and cellular adhesion molecules (Kazmi et al. 1995; Tegeder et al. 2001; Bryant et al. 2003). Additionally, flurbiprofen and some other NSAIDs have been shown to inhibit activator protein 1 (AP-1), which is involved with a variety of processes including inflammation, immune function, and tumor formation and progression (Tegeder et al. 2001). Studies have also found that certain NSAIDs may alter the function or expression of a variety of ion channels including: sodium (Park, et al. 2007), voltage-gated potassium (Freeman et al. 2007; Brueggemann et al. 2009), and L-type calcium (Brueggemann et al. 2009) channels. However, the extent of these non-cyclooxygenase NSAID effects is yet to be fully elucidated. An extensive review of these potential pathways is beyond the scope of this article, but has been reviewed elsewhere (Tegeder et al. 2001).

The usefulness and limitations of COX selectivity

The COX-1/COX-2 inhibitory ratio, also known as the IC₅₀ ratio (the ratio of 50% inhibition of COX-1 and COX-2), is often referenced as a measure of NSAID safety. Such statements must be interpreted cautiously due to numerous limitations. The COX selectivity or COX sparing concept only applies to the potential decrease in the frequency of GI adverse effects in healthy GI tissues, and has no association with renal or hepatic adverse effects, effects on diseased or injured gastrointestinal tracts, nor to efficacy (Mattia & Coluzzi 2005). The renal adverse effects of NSAIDs may be more related to COX-2 inhibition and all commercially available NSAIDs inhibit COX-2 (see the effects of NSAIDs on the kidneys). Hepatic adverse effects may be related to production of reactive metabolites and be independent of COX inhibition as idiosyncratic toxicity has been observed with all licenced NSAIDs in the USA. (MacPhail et al. 1998).

Numerous inconsistencies exist in the literature with regards to COX selectivity, for example the reported COX-1/COX-2 inhibitory ratio for phenylbutazone ranges from 9.7, (COX-2 preferential), (Streppa et al. 2002) to 0.6, COX-1 preferential. (Brideau et al. 2001) due to variations in the assay employed, species differences, and laboratory to laboratory variability. The variability within a single type of assay is also wide. As another example the IC₅₀ COX-1/COX-2 for meloxicam using canine whole blood assays varied from 2.72 (Streppa et al. 2002) to 10 (Brideau et al. 2001) and from 6.5 (Brideau et al. 2001) to 16.8 (Streppa et al. 2002) for carprofen. The ratios are often determined *in vitro*, with purified enzymes or whole blood, which may or may not predict *in vivo* effects produced when the NSAID is administered to an animal. Additionally, *in vitro* models do not account for fluctuating plasma concentrations that occur when the NSAID is actually administered to an animal. The most clinically relevant (but also the most difficult) evaluation requires using pharmacokinetic-pharmacodynamic modeling *in vivo* (Lees et al. 2004a). A comparison of deracoxib, carprofen, and etodolac administered to dogs at the label doses for 10 days resulted in no significant suppression of thromboxane, a COX-1 product, at days 3 and 10 during administration for any compound despite the wide variability in COX inhibitory ratios (Sessions et al. 2005). All three compounds resulted

in decreased gastric PGE₂ concentrations on the third day of administration, the authors hypothesized that this was due to inhibition of constitutive COX-2 activity in the gastric mucosa, but the gastric PGE₂ concentrations returned to normal for all treatments on day 10.

As mentioned above, while the IC₅₀ ratio is often referenced as a measure of NSAID safety, the clinical applicability of this ratio is questionable. *In vivo*, 80% inhibition of COX-2 is typically required to elicit a clinical analgesic effect, whereas 20% inhibition of COX-1 or less is targeted to minimize the gastrointestinal adverse effects (Lees et al. 2004a). For example the COX1/COX2 IC₅₀ of racemic carprofen in dogs is 16.8, but the IC₈₀ is 101.2 (Streppa et al. 2002) based on an *in vitro* model. Therefore the apparent COX selectivity determined *in vitro* by IC₅₀ ratios may not correspond to effective doses or minimize adverse effects. The COX inhibitory ratios may be helpful in screening potential compounds for future drug development, but the magnitudes of *in vitro* COX inhibitory ratios (COX-2 selective versus COX-1 sparing) are not predictive of the magnitude of differences in GI or other adverse effects (Mattia & Coluzzi 2005; Wooten et al. 2008). The most valuable data evaluating the safety of any drug are collected from pharmacovigilance data and controlled clinical trials, when the drug is actually administered to clinical patients and adverse effects are monitored and reported.

Comparison of IC₅₀ or IC₈₀ ratios is also dependent on parallel inhibitory curves for COX-1 and COX-2 inhibition which do not always occur. The lack of parallel COX inhibitory curves may result in inappropriate conclusions as to COX selectivity as the COX inhibitory ratios will change with increasing concentrations or doses (Lees et al. 2004b). A lack of parallel COX inhibitory curves has been identified for robenacoxib (Giraudel et al. 2009).

Species specific differences in the COX inhibitory concentrations have also been documented for some NSAIDs (Lees et al. 2004b). For example, the COX1:COX2 inhibitory ratio (IC₅₀) of carprofen has been reported to be 0.020 (COX-1 preferential) in humans to 16.8 (COX-2 preferential) in dogs (Warner et al. 1999; Streppa et al. 2002). Therefore extrapolations of COX inhibitory ratios between species may not be accurate and should be avoided.

The pharmacokinetics of the drug are also important to consider when assessing the safety

and efficacy of NSAIDs (Lees et al. 2004b). The bioavailability of tepoxalin was decreased when administered orally to fasted animals resulting in a 50% lower maximum plasma drug concentration and 50 and 62% decreases in the AUC of tepoxalin and the active metabolite respectively (Homer et al. 2005). Therefore the efficacy of tepoxalin is also dependent on its pharmacokinetics and administering the drug with food to achieve the desired plasma concentration and subsequently desired analgesic effect.

The COX selectivity of an NSAID has no association with efficacy. There have been no studies indicating one specific NSAID to be consistently more effective than another. It is important to remember that an individual patient may, however, have a better response to one NSAID than to another. Similarly, a specific patient may develop adverse effects to one NSAID but not to another, and some patients may not tolerate any NSAID. It is also important to realize that COX selectivity is dependent on dose and all NSAIDs become nonselective COX inhibitors at high concentrations (Lees et al. 2004a). However, studies have demonstrated that drugs which maintain some activity of COX-1 (i.e. COX-2 selective or COX-2 preferential inhibitors) have decreased frequencies of gastrointestinal adverse effects and subsequently a better GI adverse effect profile than NSAIDs which inhibit both COX isoforms when assessed *in vivo* (Reimer et al. 1999; Nishihara et al. 2001; Luna et al. 2007). The one exception is tepoxalin, which inhibits both COX isoforms, and LOX which may mitigate the deleterious effects of nonselective COX inhibition (see the effects of NSAIDs on the GI tract).

NSAIDs approved for chronic use in dogs

The currently licensed NSAIDs for chronic use in dogs include: carprofen, deracoxib, etodolac, firocoxib, mavacoxib, meloxicam, phenylbutazone, robenacoxib, and tepoxalin (Table 2). Historically, aspirin has also been used in some cases, but aspirin is not licensed for use in dogs. Table 2 provides the approved indications for NSAID usage in dogs.

The best indicators of NSAID safety are controlled clinical trials and comprehensive adverse event reporting. During clinical trials drugs are administered to clinical patients with the patients evaluated in a systematic manner and the evaluator blinded to the treatment administered. Controlled clinical trials require large numbers of animals, should involve multiple locations to avoid a regional bias, and

should include a wide variety of breeds, ages, and clinical conditions. Currently approved veterinary NSAIDs for dogs, with the exception of phenylbutazone, have exhibited similar adverse effect profiles during the clinical trials associated with drug approval, regardless of the magnitude of differences in their respective COX selectivity (Deramaxx FOI; Etogesic FOI; Metacam FOI; Onsior EMA EPAR; Previcox FOI; Rimadyl FOI; Trocoxil EMA EPAR; Zubrin FOI). Similarly, studies independent of the drug approval process have confirmed similar NSAID adverse effects profiles as those reported in the FOI/EPAR summaries (Doig et al. 2000; Hanson et al. 2006; Pollmeier et al. 2006; Raekallio et al. 2006; Ryan et al. 2006; Autefage & Gosselin 2007; Luna et al. 2007; Mansa et al. 2007; Roberts et al. 2009). No study has comprehensively compared the adverse effect profiles or efficacy of the currently approved veterinary NSAIDs in head to head trials. Similarly, none of the studies have produced consistent results to indicate any one of the current veterinary-approved NSAIDs as being associated with more or less adverse effects in clinical patients.

Once a product is approved, owners and veterinarians voluntarily report adverse events to the manufacturer, or appropriate regulatory agency within their respective country (i.e. the FDA in the USA). The manufacturer is obligated to report all adverse events received to the regulatory agency. Cumulative post-licensing adverse event data are useful in providing an assessment of product safety under conditions of mass usage over time, although the precise number of animals treated and the duration of treatment of individual animals is usually not known. Despite likely underreporting of adverse events by veterinarians, these data remain one of the best indicators of product safety, with validity increasing in proportion to the integrity of the reporting methods.

Reporting of adverse events associated with NSAIDs by veterinarians is extremely important as it contributes to the development of a comprehensive adverse events database for these drugs. Receipt of reports of known or suspected adverse events is the only way manufacturers can obtain the data necessary to evaluate the safety and efficacy of their products in the clinical setting. Suspected or known adverse events should be reported to the appropriate regulatory agency as well as the manufacturer of the product. Specific adverse event forms and contact numbers are available from the FDA

(<http://www.fda.gov/AnimalVeterinary/SafetyHealth/ReportaProblem/ucm055305.htm>) and manufacturers for this purpose.

Carprofen was the first of the newer NSAIDs to be approved for canine use in the USA, in 1997, and, as such, has the most comprehensive safety record of the canine NSAIDs currently registered in the US. Subsequent NSAIDs that were approved for use in dogs include: etodolac (1998), deracoxib (2002), meloxicam (2003), tepoxalin (2003), firocoxib (2004), mavacoxib (2008), and robenacoxib (2008).

Adverse class-effects of NSAIDs

The effects of NSAIDs on the gastrointestinal tract

NSAIDs can cause GI adverse events indirectly through the inhibition of PGE₂ and directly by irritating the GI mucosa. Other mechanisms potentially resulting in GI adverse effects include increased production of leukotrienes, alteration of ion channel conductance, inhibition of PGI₂, and inhibition of aspirin triggered lipoxin. Many NSAIDs are weak acids and, as such, can directly irritate the GI mucosa when administered orally or following secretion in bile regardless of the route of administration. The high concentrations of NSAIDs in the gastrointestinal tract after oral administration or due to biliary secretion within the duodenum is also hypothesized to contribute to the direct irritant effects of NSAIDs to the GI tract (Carter et al. 1980). Prostaglandin E₂ and PGI₂, have important gastro-protective effects including increased mucosal blood flow, increased mucus production, increased bicarbonate production, decreased acid secretion and increased turnover of gastrointestinal epithelial cells (Simmons et al. 2004). Given the important role of PG in the GI tract, it is expected that NSAID induced inhibition of PGE₂ and PGI₂ can be associated with GI toxicity (Wolfe et al. 1999; Whittle 2004).

Both COX-1 and COX-2 are constitutively expressed in the canine GI tract and the inhibition of these enzymes can lead to GI adverse effects including gastritis, enteritis, ulceration, and perforation (Wallace et al. 2000; Simmons et al. 2004; Wooten et al. 2008). Inhibition of COX-1 or COX-2, exclusively, results in minimal GI adverse effects (Wallace et al. 2000). The lower frequency of GI adverse effects when only one isoform of COX is inhibited is thought to be due to up-regulation of the other isoform since both COX-1 and COX-2 produce

PGE₂. For example, 3 days of aspirin administration to dogs, which inhibits COX-1 to a greater extent than COX-2, results in a significant induction of COX-2 in the canine duodenum, whereas the amount of COX-1 remains unchanged in the stomach and intestines (Wooten et al. 2008).

The recently licensed veterinary NSAIDs appear to have decreased frequency of gastrointestinal adverse effects in dogs compared to drugs such as aspirin, ketoprofen, phenylbutazone, tolfenamic acid, and flunixin (Varro et al. 1959; Bhatia et al. 1965; Reimer et al. 1999; Nishihara et al. 2001; Luna et al. 2007; Tolfedine package insert). The decreased adverse effects may be due to less than complete inhibition of COX-1, resulting in continued PGE₂ production in the GI tract by COX-1. However, extensive studies comparing the effects of the available NSAIDs on the GI tract of clinical dogs in a randomized crossover study design are not available. The available studies have primarily included research animals and have not included all of the available NSAIDs in dogs, so it is difficult to make direct comparisons, but they are suggestive that the COX-1 sparing NSAIDs produce a lower frequency of GI lesions. For example, the frequency of phenylbutazone induced ulceration in experimental dogs receiving 75 mg kg⁻¹ day⁻¹, approximately twice the recommended daily dose of 44 mg kg⁻¹ day⁻¹ was 30/46 animals, but no study has directly compared phenylbutazone to a COX-1 sparing NSAID in dogs (Varro et al. 1959). In contrast, ketoprofen, flunixin, and etodolac produced greater gastric lesion scores than the placebo (lactose), carprofen, and meloxicam treated research dogs after 90 days of treatment (Luna et al. 2007). A separate study resulted in greater GI lesions after aspirin administration compared to carprofen and etodolac in healthy experimental dogs (Reimer et al. 1999). Further studies concurrently evaluating aspirin, phenylbutazone and the approved NSAIDs in clinical dogs would provide beneficial information.

COX-2 is up-regulated in damaged and healing tissues within the GI tract, (Mizuno et al. 1997; Wooten et al. 2010) increasing angiogenesis at the edge of gastric ulcers by inhibiting cellular kinase activity and increasing production of PGE₂ and vascular endothelial growth factor (VEGF). It is through these mechanisms that COX-2 is thought to promote ulcer healing (Jones et al. 1999; Hirose et al. 2002). Inhibition of COX-2 in an animal with preexisting GI damage, regardless of COX-1 inhibi-

tion, can result in delayed or inhibited healing of the GI tissues which, in turn, can lead to severe adverse effects including perforation and death (Goodman et al. 2009). NSAID-associated GI ulcers are most commonly reported in the proximal duodenum and pylorus of dogs (Stanton & Bright 1989; Dow et al. 1990; Lascelles et al. 2005b). A recent study examined the effects of the COX-2 selective NSAID, firocoxib, and tepoxalin, a COX/LOX inhibitor, on the healing rates of endoscopic biopsy sites in the stomach (pylorus and gastric body) in dogs (Goodman et al. 2009). Dogs had significantly larger lesions at the biopsy sites when treated with the approved dose of firocoxib compared to tepoxalin or placebo suggesting COX-2 selective inhibitors may actually produce more adverse effects when underlying gastric damage is present. The lack of inhibition of healing by tepoxalin may be in part due to its activity on LOX, inhibiting leukotriene formation. Previous studies have demonstrated that administration of leukotriene antagonists to rats ameliorates the GI adverse effects of NSAIDs (Dengiz et al. 2007). It is important to state that these data do not support the use of tepoxalin in animals with gastric lesions, but support the notion that COX-2 selective NSAIDs decrease gastric healing despite maintaining normal COX-1 activity.

Due to their effects on healing gastric lesions, NSAIDs should be avoided or used cautiously in animals that have pre-existing GI damage such as ulceration, surgical intervention, or are concurrently receiving glucocorticoids, such as prednisone or dexamethasone, as they are at an increased risk for severe GI adverse effects from NSAIDs (Dow et al. 1990; Boston et al. 2003; Lascelles et al. 2005b; Narita et al. 2007). Examination of the GI tract of 27 clinically healthy dogs, not receiving any drugs, showed GI erosions in 4/27 (15%) dogs despite the lack of any clinical signs of gastrointestinal injury (Wooten et al. 2010). Therefore the lack of a previously reported GI disease should not be equated to a healthy GI tract, and intensive monitoring of GI adverse effects by the owners and veterinarians should occur even in healthy animals.

Gastrointestinal adverse effects can range from vomiting, anorexia and diarrhea to mild gastritis and severe gastrointestinal ulceration, bleeding and death. One of the most common reasons for a dog to be taken off a particular NSAID is the occurrence of vomiting and/or diarrhea. The most conservative action would be to discontinue NSAID administration until clinical signs resolve. Once the clinical

signs have resolved treatment options include: concurrently administering a gastroprotectant such as omeprazole, famotidine, or misoprostol with the NSAID; starting another analgesic that is not an NSAID; or starting a different NSAID. There are no data currently available describing which strategy, if any, is the safest.

Animals with vomiting, diarrhea, and anorexia may not have GI erosions or ulcers as clinical signs are poorly correlated with GI tract injury (Dow et al. 1990). It is also important to note that clinically observed GI adverse effects are not always present when erosions and ulcerations are present (Stanton & Bright 1989; Wooten et al. 2010). As discussed above, when considering the most recently approved canine NSAIDs (carprofen, etodolac, meloxicam, deracoxib, tepoxalin, firocoxib, mavacoxib, and robenacoxib), there is no specific evidence in the published literature, using controlled clinical trials, demonstrating that one drug produces a lower frequency of GI adverse effect than another. Wooten et al. (2009) assessed the *in vivo* effects of the short-term administration (3 days) of three NSAIDs (deracoxib, firocoxib and meloxicam) with varying COX-2 selectivity on the normal pyloric and duodenal mucosa of dogs and, under the experimental conditions of their study, found no apparent differences between the preferential and selective COX-2 inhibitors with regards to adverse effects on the gastric and duodenal portions of the GI tract of dogs.

The accepted belief for the safety of these drugs is that they have a preferential COX-2 inhibitory action (or COX-1 sparing effect) (Peterson & Cryer 1999). That being said, some of these drugs may lose this COX-1 sparing effect at high doses (Wolfe et al. 1999). This dose dependence is seen with etodolac where higher doses caused GI lesions (2.7× label dose) or death (5.3× label dose) (Etogesic FOI). Similarly, meloxicam has also been associated with GI toxicity (including GI perforation) at higher doses (Reed 2002; Enberg et al. 2006). Forsyth et al. (1998) reported that the sponsors of meloxicam in Europe recommended reducing the original approved dose from 0.2 to 0.1 mg kg⁻¹ given the potential for GIT problems. Animal safety studies required for FDA licensure of firocoxib identified adverse reactions associated with the administration of above-label doses of the drug in puppies (Previcox FOI) suggesting that immature animals may be more likely to experience GI associated adverse events when administered firocoxib (Bergh

& Budsberg 2005). Deracoxib has also been associated with gastrointestinal ulceration, particularly at higher than recommended doses, in dogs which had received another NSAID, or in dogs that received a glucocorticoid (Lascelles et al. 2005b). In a study evaluating the adverse effects of long term (90 days) administration of carprofen, etodolac, flunixin, ketoprofen and meloxicam in dogs, Luna et al. (2007) found that carprofen induced the lowest frequency and severity of gastrointestinal adverse effects but, as previously mentioned no study has comprehensively compared all of the FDA approved veterinary NSAIDs.

Given that GI adverse effects are considered to be the most common adverse class-effect associated with NSAIDs, clinicians need to be particularly heedful of any evidence of GI toxicity. Clinical signs that may be suggestive of GI ulceration include depression, anorexia, reduced appetite, vomiting, diarrhea, and hematochezia or melena. However, as previously noted, GI ulceration can occur in dogs without overt clinical signs (Stanton & Bright 1989; Wooten et al. 2010). Appropriate patient selection is very important when prescribing NSAIDs and every effort should be made to advise all clients of potential adverse events and to avoid using these drugs in at-risk cases. Similarly it is important to adhere to the recommended label doses and wash-out periods (see below) to reduce adverse effects if switching between NSAIDs.

Various gastroprotectant strategies can be considered when NSAIDs are prescribed for chronic use and a number of anti-ulcer drugs may be used to treat cases of GI ulceration based on extrapolations from human data (Budsberg 2009a,b). Drugs such as misoprostol, famotidine, and omeprazole have been recommended for decreasing GI adverse effects, but have not been comprehensively studied in dogs. Omeprazole (0.7 mg kg⁻¹ PO every 24 hours), misoprostol (2 µg kg⁻¹ PO every 8 hours), or placebo were administered to dogs treated with glucocorticoids for intervertebral disc disease and were not significantly different in decreasing endoscopic gastric mucosal scores (Neiger et al. 2000). Omeprazole (1.0–2.5 mg kg⁻¹ PO every 24 hours) increased gastric pH significantly more than famotidine (1.0–1.3 mg kg⁻¹ PO every 24 hours) and placebo in laboratory dogs (Tolbert et al. 2011). Omeprazole (~1.0 mg kg⁻¹ PO every 24 hours) significantly decreased exercise induced gastritis in sled dogs compared to famotidine (~2 mg kg⁻¹ PO every 24 hours) and placebo (Williamson et al.

2010). However, it is unclear as to the direct applicability of these results to NSAID induced GI adverse effects including vomiting, diarrhea, gastritis, erosions or ulcerations in dogs.

The effects of NSAIDs on the kidneys

Cyclooxygenase is constitutively expressed in the kidneys and is up-regulated in ischemic and hypotensive states. PGE₂ and prostacyclin (PGI₂) alter renal physiology by increasing sodium excretion, inhibiting sodium reabsorption, and altering chloride transport (Simmons et al. 2004). PGE₂ and PGI₂ also stimulate renin release and profoundly alter total renal blood flow and regional blood flow within the kidneys of dogs (Osborn et al. 1984; Simmons et al. 2004).

In dogs, COX-1 and COX-2 are both constitutively expressed and COX-2 is up-regulated in renal ischemia and hypotension (Khan et al. 1998; Sellers et al. 2004). Species specific differences in the anatomic distribution of constitutive COX isoforms occur in animals and humans (Khan et al. 1998). Species differences in the up-regulation of COX isoforms during volume depletion has been also documented (Khan et al. 1998). Therefore interspecies extrapolations may not be appropriate.

In response to volume depletion, hypotension, or hyponatremia, PGE₂ production is increased by COX-2 in dogs, resulting in alteration of renal blood flow by decreasing vascular resistance (Opgenorth et al. 1987; Khan et al. 1998; Rodriguez et al. 2000). Prostaglandin E₂ plays an important role in maintaining renal perfusion in hypovolemic situations during which renal injury secondary to NSAID administration may occur as a result of the inhibition of prostaglandin synthesis (Feigen et al. 1976; Budberg 2009a,b). The effects of label doses of veterinary approved NSAIDs on renal blood flow and the distribution of blood flow within the renal cortex have not been investigated extensively. Reported cases of NSAID-induced nephropathy in dogs are most commonly associated with high doses of NSAIDs or other complicating factors (e.g. dehydration, poorly managed anesthesia, shock and pre-existing renal disease).

COX-1 and COX-2 are involved in renal blood flow regulation and tubular function, therefore it cannot be assumed that COX-1-sparing NSAIDs infer greater safety in the kidney (Sellers et al. 2004; Frendin et al. 2006; Rodriguez et al. 2009). Experimental studies in rats have demonstrated that

the COX selectivity of NSAIDs was not associated with renal adverse effects, with the selective inhibition of COX-2 and nonselective inhibition of both COX isoforms producing renal adverse effects (Harirforoosh & Jamali 2005). Further studies in rats have suggested that accumulation of NSAIDs within the kidney was most associated with renal adverse effects, not COX selectivity (Harirforoosh et al. 2006). It is, however, unclear if there are species specific differences in the degree of renal accumulation of individual NSAIDs. Luna et al. (2007) found that long term (90 days) administration of carprofen, etodolac, flunixin, ketoprofen and meloxicam in healthy dogs did not induce any evidence of renal injury as measured by urinalysis and serum biochemistry. These data, in addition to the safety and efficacy studies included with the FOIs, EPARs and independent studies suggest long-term administration of appropriate dosages of FDA approved NSAIDs in otherwise healthy, normovolemic, and normotensive dogs with normal sodium status result in minimal renal effects (Doig et al. 2000; Hanson et al. 2006; Pollmeier et al. 2006; Raekallio et al. 2006; Ryan et al. 2006; Autefage & Gosselin 2007; Mansa et al. 2007).

A study examining the impact of high doses (6× dose) of aspirin on renal blood flow by Data et al. (1976), found that the predominant acute effects of aspirin on the kidneys were a decrease in total renal blood flow and altered distribution of renal blood flow within the renal cortex (Table 1). Hypovolemic dogs without aspirin treatment only had a slightly decreased total renal blood flow, but distribution of

Table 1 The effects of aspirin, 100 mg kg⁻¹, on renal blood flow and the distribution of renal blood flow within different zones in the renal cortex in hypovolemic dogs subjected to controlled hemorrhage. Zone 1 is the outermost zone and zone 4 is juxtamedullary. Adapted from Data et al. 1976.

Total Renal Blood Flow (rbf)	Renal Cortex Zone 1
Untreated: 2% decreased blood flow	Untreated: 20% decreased blood flow
Aspirin: 45% decreased blood flow	Aspirin: 50% decreased blood flow
	Renal cortex zone 2
	Untreated: 10% increased blood flow
	Aspirin: 45% decreased blood flow
	Renal cortex zone 3
	Untreated: 20% increase blood flow
	Aspirin: 45% decreased blood flow
	Renal cortex zone 4
	Untreated: 35% increased blood flow
	Aspirin: 65% decreased blood flow

blood flow was markedly altered with increased blood flow to the regions of the cortex closest to the medulla. In contrast, hypovolemic dogs treated with high doses of aspirin (100 mg kg^{-1}) had a significantly decreased total renal blood flow and the distribution of blood flow in the cortex was decreased in all areas. It is important to reiterate that the dose of aspirin in the study (100 mg kg^{-1}) was markedly above the suggested doses ($10\text{--}25 \text{ mg kg}^{-1}$) in dogs (Papich 2007).

Other studies have examined the effects of indomethacin (a nonselective COX inhibitor), meclofenamate (a nonselective COX inhibitor), and nimesulide (a COX-1 sparing NSAID) on the renal physiology of dogs. Meclofenamate significantly decreased renal blood flow and altered redistribution of renal blood flow within the renal cortex during renal hypotension similar to high doses of aspirin in hypovolemic dogs (Oppenorth et al. 1987). A separate study with meclofenamate demonstrated decreased renal blood flow without alteration of glomerular filtration rate in dogs (Rodríguez et al. 2000) suggesting that glomerular filtration rate is not an appropriate indicator of acute NSAID induced renal effects. Nimesulide had minimal effects on renal blood flow in normal dogs, but dogs that were sodium depleted experienced a significant decrease in renal blood flow, again without significant effects on the glomerular filtration rate (Rodríguez et al. 2000). Indomethacin, administered to anesthetized dogs significantly decreased renal blood flow and decreased sodium excretion, and the glomerular filtration rate was again unaffected (Feigen et al. 1976).

The renal effects of carprofen (a COX-1 sparing NSAID), 4 mg kg^{-1} SC, ketorolac (a presumptive nonselective COX inhibitor in dogs) 0.5 mg kg^{-1} SC, and ketoprofen (a nonselective COX inhibitor) 1 mg kg^{-1} SC, were compared to morphine, 0.1 mg kg^{-1} SC, in 40 dogs undergoing ovariohysterectomy (Lobetti et al. 2000). Renal blood flow was not measured in the study, but the NSAID treated dogs experienced significant effects manifested by decreased renal sodium excretion compared to baseline values. In contrast, the morphine treated dogs did not have any significant renal effects compared to baseline values.

Freundin et al. (2006) studied the effects of carprofen on renal blood flow in anesthetized animals. Control animals were those treated with medetomidine, propofol, and isoflurane whereas the NSAID group was additionally treated with the label

dose of carprofen. Both treatment groups showed significant decreases in renal blood flow during anesthesia (about 50% compared to pretreatment values). There was not, however, a significant difference between the control group and the NSAID treated group, although the distribution of renal blood flow within the kidneys was not measured.

Numerous other studies have been published assessing the effects of carprofen, meloxicam, and tepoxalin on renal function given their use in the perioperative context, but due to study design the information provided by these studies is somewhat limited as detailed below (Ko et al. 2000; Bostrom et al. 2002; Crandell et al. 2004; Kay-Mugford et al. 2004; Bergmann et al. 2005; Freundin et al. 2006). These studies have evaluated the administration of these NSAIDs to healthy, anesthetized dogs. Various renal parameters (glomerular filtration rate, urine specific gravity, creatinine, and blood urea nitrogen) were minimally affected acutely after label doses of veterinary approved NSAIDs. However, these parameters are not sensitive indicators of the acute effects of NSAIDs on renal physiology, as previously discussed, and were not expected to be altered. These studies did not assess the sensitive indicators of the acute renal effects of NSAIDs: decreased renal blood flow, altered distribution of renal blood flow within the renal cortex and decreased urine sodium excretion (Data et al. 1976; Feigen et al. 1976; Oppenorth et al. 1987; Lobetti et al. 2000; Rodríguez et al. 2000).

High doses of NSAIDs, sodium depletion, hypotension, hypovolemia, and anesthesia appear to increase the risks of renal adverse effects of NSAIDs (Data et al. 1976; Oppenorth et al. 1987; Lobetti et al. 2000; Rodríguez et al. 2000; Surdyk et al. 2011). Anesthesia and hypotension are not unexpected risks for NSAID renal toxicity as isoflurane, halothane, and sevoflurane cause a dose-dependent decrease in renal blood flow in dogs (Hartman et al. 1992; Takeda et al. 2002). It should be expected that any animal undergoing inhalant anesthesia has the potential for decreased renal perfusion which may increase the risk of NSAID induced renal toxicity. Therefore the recommendation for animals administered NSAIDs undergoing anesthesia is to carefully monitor the cardiovascular status of the animals and concurrently administer intravenous fluids so as to ensure adequate perfusion of all vital organs, including the kidneys, is maintained, thereby minimizing the risk for renal

toxicity. Likewise, animals with decreased serum sodium concentrations or decreased renal perfusion of any cause, such as shock, dehydration, or hemorrhage, may be more susceptible to NSAID induced renal adverse effects and NSAIDs should only be administered once the cardiovascular status of these animal has been stabilized.

As stated previously, healthy dogs administered approved doses of NSAIDs are at a low risk for renal adverse events. Additionally it is important to reiterate that anesthesia is not a contraindication to NSAID administration, with numerous studies indicating appropriate anesthetic management results in a low risk for clinically detectable renal adverse effects (Ko et al. 2000; Lobetti & Joubert 2000; Bostrom et al. 2002; Crandell et al. 2004; Bergmann et al. 2005; Frendin et al. 2006). These studies have not, however, ruled out the possibility of subclinical renal adverse effects. Carprofen, deracoxib, firocoxib, and robenacoxib are licensed for perioperative use and as such have undergone the most extensive safety and efficacy testing and are therefore recommended for use perioperatively in dogs.

The effects of NSAIDs on the renal function of dogs with underlying renal disease have not been reported. It is hypothesized that dogs with underlying renal disease have increased COX-2 expression in the renal vasculature as a compensatory mechanism and NSAID administration could lead to acute decompensation resulting in exacerbation of renal disease (Simmons et al. 2004; Lascelles et al. 2005a). Definitive studies are, however lacking. Due to the lack of available data, NSAIDs should be used cautiously in patients with underlying renal disease and the owners should be well informed of the potential adverse effects.

The effects of NSAIDs on the liver

Adverse effects of NSAIDs on the liver can be divided into an intrinsic, dose-dependent toxicity and an idiosyncratic, dose-independent toxicity (Mensching & Volmer 2009). The intrinsic, dose-dependent toxicity is typically due to massive overdosing of NSAIDs which can occur when animals ingest large portions of medications, for example a dog eating a month's supply of an NSAID. Idiosyncratic hepatic toxicity is a dose-independent toxicity that typically occurs when a dog is administered the label dose of an NSAID. A published report has described acute, idiosyncratic hepatotoxicosis in dogs treated with carprofen with the onset of clinical signs varying

from within a few days to several weeks (MacPhail et al. 1998). The FDA adverse drug event reports for veterinary approved NSAIDs suggest that hepatic toxicity can occur with any veterinary NSAID, and there have been no reports identifying a particular NSAID as having an increased risk of idiosyncratic hepatic toxicity in dogs. There are also no reports evaluating the prevalence or severity of adverse effects (hepatic or otherwise) relative to the number of animals treated or number of doses dispensed. Additionally, there has been no breed identified as having an increased risk of idiosyncratic hepatic toxicity. Labrador Retrievers were the most common breed affect in the MacPhail (1998) report, but Labrador Retrievers are the most popular breed in the US and are often affected by musculoskeletal disorders such as osteoarthritis, hip dysplasia, and rupture of the cranial cruciate ligament. Therefore the increased numbers of Labrador Retrievers in this study is probably proportional to the breed popularity as well as frequency of NSAID administration to that breed.

Firocoxib has been associated with fatty liver changes in young dogs when administered at high doses (Previcox FOI) and a case report described heptatotoxicity in a single dog administered a sequential combination of carprofen per os and subcutaneous meloxicam (Nakagawa et al. 2005). In a study investigating adverse effects of long term administration of several different NSAIDs (carprofen, etodolac, flunixin, ketoprofen and meloxicam) in dogs Luna et al. (2007) found only minor and clinically insignificant changes in serum biochemical variables. In a recent study, Mansa et al. (2007) evaluated the long term (84 days) treatment of osteoarthritis with carprofen in 805 client owned dogs of different breeds, ages and body weights. In this study 3.2% of the dogs left the study because of adverse effects of any kind, with a majority of these leaving within the first 3 weeks of treatment. Ryan et al. (2006) also reported that long-term administration of firocoxib to 1002 dogs with osteoarthritis was well tolerated with only 5% of dogs leaving the study due to adverse effects of any kind. These studies suggest long-term administration of NSAIDs is not associated with hepatocellular toxicity and are the basis for recommendations for more intensive monitoring in the early stages of NSAID treatment (Lascelles et al. 2005a).

MacPhail et al. (1998) suggested that most NSAID-associated hepatopathies occur within the first 3 weeks of treatment and Lascelles et al.

(2005a) propose that clinicians should favor more intensive monitoring during the early stages of NSAID treatment, extending the intervals for later re-testing depending on a dog's response. Despite the lack of data in this area, it can be considered prudent to determine baseline renal and hepatic panels by clinical chemistries prior to initiating chronic NSAID therapy. This can be followed up with repeat testing within the first 2 weeks and periodically thereafter. Periodic testing allows the veterinarian to assess trends as well as absolute values and any unexplained increase in hepatic enzymes or bilirubin after initiating NSAID administration warrants investigation. It is also important that the owners are informed to continuously monitor their patients for adverse effects such as vomiting, diarrhea, anorexia, lethargy, depression, and icterus and to immediately inform their veterinarian if any of these adverse effects are observed.

There are very few data describing the use of NSAIDs in animals with underlying hepatic disease and no data indicating that animals with hepatic disease are at an increased risk of NSAID hepatic toxicity. However, the elimination of NSAIDs in these animals may be decreased since NSAIDs are primarily eliminated by hepatic mechanisms, but this may be drug and disease specific. In humans, the elimination of carprofen and etodolac were not altered in patients with liver dysfunction due to hepatic cirrhosis compared to healthy individuals (Holazo et al. 1985; Brater & Lasseter 1989). However, it is unclear if similar pharmacokinetics of carprofen or etodolac occur in dogs with and without liver disease. As such, it is unclear if the dose of an NSAID needs to be decreased for an animal with pre-existing hepatic disease. The precise dose adjustments in animals with hepatic disease have not been determined and, therefore, any use in animals with hepatic disease should be done with caution and owner consent. Patients with liver disease may be more prone to GI ulceration (Stanton & Bright 1989), independent of NSAID administration, and it is possible that the administration of NSAIDs to these cases may increase the risk of this complication. Therefore analgesics from other drug classes should be considered in animals with hepatic dysfunction.

The effect of NSAIDs on articular cartilage

NSAIDs are the most frequently recommended pharmaceutical treatment for canine osteoarthritis

(OA), this popularity is attributable to their effectiveness as anti-inflammatory and analgesic agents as well as to their relative ease of administration (Johnston et al. 2008). Given the popularity of NSAIDs for the treatment of OA and the fact that both primary and secondary degenerative joint disease/osteoarthritis are characterized by the breakdown of articular cartilage, and bone remodeling (Piermattei et al. 2006), it is important to understand the potential impact NSAIDs may have on articular cartilage.

Dassler et al. (2003) compared chronic osteoarthritic cartilage from canine stifles for differences in cartilage structure between dogs that had not received NSAIDs and those receiving clinical doses of carprofen. Utilizing a histologically based Mankin grading scale for cartilage they were not able to demonstrate a difference between treatment groups, suggesting that carprofen did not adversely affect cartilage in these patients. A number of other studies (Benton et al. 1997; Pelletier et al. 2000; Schneider & Budsberg 2001) also suggest that carprofen does not negatively impact canine arthritic cartilage and Pelletier et al. (2000) suggested carprofen actually resulted in a protective response in an experimental arthritis model. Similar studies with the other veterinary approved NSAIDs are needed.

The effect of NSAIDs on bone healing

Currently, no data in clinical patients including dogs and humans, demonstrate NSAIDs adversely affect bone healing in orthopedic patients. Studies evaluating the effects of NSAIDs on experimental models using rabbits and rodents have resulted in decreased bone healing following experimental fractures and have been reviewed extensively elsewhere (Barry 2010). Similarly, carprofen administered to experimental Beagle dogs for 120 days following tibial osteotomy resulted in decreased bone healing (Ochi et al. 2011). In contrast, phenylbutazone and indomethacin did not result in delayed healing in metacarpal transection in experimental mongrel dogs (Mbugua et al. 1989). The contradictory results in experimental dogs has not been extensively evaluated using multiple NSAIDs within a study, therefore it is difficult to assess if other contributing factors were present in either of these studies.

In contrast, no reports have documented impaired fracture healing in clinical cases of fractures in dogs.

Deracoxib ($n = 105$), carprofen ($n = 76$), and firocoxib ($n = 118$) are approved for perioperative use in orthopedic surgery in dogs with the specific number of animals receiving the NSAID for each approval given in parentheses according to their respective FOIs. A total of 299 dogs received one of these NSAIDs and no animals were reported to have delayed fracture healing or nonunion fractures. Additionally, a recent meta-analysis did not report a negative effect of NSAIDs on fracture healing in human patients (Dodwell et al. 2010). Therefore the experimental models in rabbits and rodents have not been predictive of the clinical effects of NSAIDs on fracture healing in humans and dogs. The lack of correlation between experimental models may be due to, but not limited to differences in inflammation, fracture edges (i.e. cut bone versus fractured bone), hematoma formation, timing of NSAID administration relative to the fracture occurrence, systemic inflammation or other factors. As a result, it appears that NSAIDs can be administered to clinical orthopedic patients as they do not appear to affect bone healing in clinical cases.

Drug-drug interactions/contraindications

NSAIDs are one of the most common classes of drugs used in veterinary medicine and are frequently used in combination with other classes of analgesic drugs for pain management, or given concurrently with other drugs used to manage underlying conditions. Therapeutic regimens involving such combinations should be assessed for drug-drug interactions and the potential for increased organ toxicity. Prior to instituting any chronic drug therapy a complete examination (physical examination, blood work, urinalysis, etc.) should be performed and regularly reevaluated during therapy. In addition, information on recent medications, previous drug adverse reactions, and any medical conditions should be evaluated.

Both COX-1 and COX-2 produce prostaglandins that play a significant role in maintaining renal function (Ferguson et al. 1999; Khan et al. 2002). As discussed above, NSAIDs can cause renal injury through inhibition of prostaglandins important in maintaining renal hemodynamics, although, the exact mechanisms have yet to be fully defined. Risk factors include concurrent disease (liver disease, renal disease, heart failure) volume depletion, hypotension, sodium depletion, high doses, and concurrent administration with drugs that

adversely affect renal function (e.g. aminoglycosides) (Perazella & Tray 2001, Scott et al. 2001; Knights et al. 2005). Prostaglandins also directly affect renal function by increasing sodium excretion, inhibiting sodium reabsorption, and altering chloride transport (Simmons et al. 2004). Prostaglandins and prostacyclin also stimulate renin release in dogs (Osborn et al. 1984; Simmons et al. 2004). As discussed above, comparing veterinary approved NSAIDs, there is a lack of evidence to support a reduction in renal adverse effects for those NSAIDs reported to have the highest COX-2 selectivity, but more research is needed before definitive clinical recommendations can be made.

NSAIDs may impact the management of hypertension through their effects on prostaglandin synthesis and have been shown to decrease the blood pressure lowering effect of ACE inhibitors and beta-blockers in humans (Webster 1985; Morgan & Anderson 2003). Lobo & Shenfield (2005) suggested that the co-administration of ACE inhibitors and NSAIDs may increase the risk of renal injury in patients with impaired renal function. There is only one published study (Fusellier et al. 2005) which looked at the effect of an NSAID on renal function in healthy dogs receiving an ACE inhibitor and although they did not find any interaction it was a limited study with only 12 animals. However, this combination of drugs has not been adequately studied in a larger population under clinical conditions to be able to draw meaningful conclusions. In another study, aspirin was shown to reduce the diuretic effect of furosemide in dogs (Berg & Loew 1977). The natriuretic effects of furosemide may result in sodium depletion which may increase the risk for renal adverse effects of NSAIDs (see the effects of NSAIDs on the kidney section), but case reports documenting this drug interaction are lacking (Oppenorth et al. 1987; Khan et al. 1998; Rodriguez et al. 2009). However, a study with experimental dogs resulted in significant effects of the combination of furosemide and an NSAID (carprofen or ibuprofen) compared to the NSAID or furosemide alone on the glomerular filtration rate in healthy dogs (Surdyk et al. 2011). It is important to note that NSAIDs differ in their potential to alter the pharmacologic effects of antihypertensive agents (Pavlicević et al. 2008) and these interactions have not been extensively studied in dogs with the approved NSAIDs.

Administration of NSAIDs with corticosteroids can significantly increase the risk of gastrointestinal

toxicity. The combination of prednisolone with either ketoprofen or meloxicam resulted in considerable adverse effects on the kidney, gastrointestinal mucosa and platelet function in dogs (Narita et al. 2007). In a report of gastrointestinal perforations in 29 dogs administered deracoxib, three dogs had received corticosteroids around the time of treatment with deracoxib (Lascelles et al. 2005b). In a short-term study with meloxicam administered to healthy dogs, co-administration with dexamethasone resulted in more gastric erosions than meloxicam alone (Boston et al. 2003). The administration of flunixin with prednisone to dogs resulted in earlier and more severe GI lesions than administration of flunixin alone (Dow et al. 1990). Based on the information available on NSAIDs and corticosteroids, concurrent use is not recommended.

The concurrent administration of different NSAIDs may increase the risk for gastrointestinal adverse effects. Reed (2002) describes a case of duodenal ulceration and perforation in a Rottweiler following the concurrent administration of meloxicam and aspirin. The dog had received 10 days of meloxicam followed by a single dose of aspirin. Histopathological examination of the ulcer suggested that the initial injury to the duodenal mucosa occurred prior to the perforation. Meloxicam may have been responsible for the initial lesion with the concurrently administered single-dose of aspirin causing further damage leading to the GI perforation. Lascelles et al. (2005b) identified concurrent administration of another NSAID with deracoxib as a risk factor for gastrointestinal perforation in 7/29 dogs with NSAID induced GI perforation. The reason for anecdotal recommendations for a washout period between administering different NSAIDs is to minimize GI adverse effects (see recommendations for washout period).

Aspirin inhibits COX-1 to a greater extent than COX-2 enzymes (i.e. COX-2 sparing) and causes an irreversible inhibition of platelet aggregation (Chandrasekharan et al. 2002). Aspirin Triggered Lipoxins are produced by COX-2 and have a protective effect on the gastric mucosa (Fiorucci et al. 2002). The protective effect of ATLs during aspirin treatment is eliminated with the administration of a COX-2 selective inhibitor (Fiorucci et al. 2002). Therefore, administration of aspirin with a COX-2 inhibitor may lead to an increased risk of GI injury. For these reasons co-administration of aspirin and any COX-2 inhibitor is not recommended (Reed 2002).

NSAIDs are highly protein bound and drug displacement from the proteins can occur, although, the clinical significance of these interactions is likely to be low (Benet & Hoener 2002). The free (unbound) drug is active and responsible for eliciting a pharmacological response and displacement of a drug from a protein binding site can result in an increase in the free fraction of drug. However, redistribution and elimination of the displaced drug is predicted not to change the free drug concentrations in most cases (Toutain & Bousquet-Melou 2002). Documented cases of altered clinical effects from interactions involving drug displacement from protein are uncommon. The characteristics of drugs that are more likely to be involved in clinically significant protein displacement drug interactions include: high protein binding (>85%), low therapeutic index, high clearance, and parenteral administration (Benet & Hoener 2002). There are few drugs that meet all of these requirements. Clinically significant protein binding displacement interactions involving NSAIDs used for chronic management of osteoarthritis are unlikely to cause adverse effects in patients.

Recommendations for washout period

All approved veterinary NSAIDs have been shown to be efficacious during field studies at label doses for their approved indications as documented in their respective freedom of information summaries and by independent reports (Innes et al. 2010). Individual responses in efficacy and safety may vary between NSAIDs. A lack of response to drug therapy used to control pain may be due to fluctuations in disease, individual variation in response to the drug, progression of disease, or inadequate dosing regimens. There is no evidence to suggest administering more than one NSAID concurrently will increase efficacy. There are, however, reports demonstrating increased frequency of adverse effects when multiple NSAIDs or when NSAIDs and corticosteroids are concurrently administered (Dow et al. 1990; Boston et al. 2003; Lascelles et al. 2005b; Narita et al. 2007). Therefore sequential or concurrent administration of different NSAIDs or NSAIDs and corticosteroids is not recommended.

If a patient has an inadequate response or adverse reaction to an NSAID after initiating therapy, switching to a different NSAID may be indicated. When switching, it may be appropriate to substitute an NSAID from a different chemical subclass, although

this recommendation has not been evaluated by clinical research studies (Table 2). If a patient has a favorable response to an NSAID during chronic pain management but experiences an increase in pain due to progression of the underlying condition, adding another analgesic from a different class of drugs may be more appropriate than switching NSAIDs.

An injectable NSAID is often used to provide perioperative pain management. Following the surgical procedure, oral NSAIDs, which may be different from the injectable NSAID, have been dispensed for a short treatment period. Although an appropriate washout period has not been evaluated in the perioperative clinical setting, an experimental study with healthy laboratory dogs administered an injectable NSAID (carprofen) followed by 4 days of an oral NSAID (carprofen or deracoxib) and did not find clinically important gastroduodenal ulceration (Dowers et al. 2006). However, it is important to note that this study only included six dogs, these dogs were healthy laboratory animals, they did not undergo the stress of anesthesia or surgery, and had a 2-week acclimation period prior to enrolling in the study (Dowers et al. 2006). Therefore this study does not represent a typical clinical situation. Until more data are available, the authors do not recommend combining different NSAIDs.

Most experts recommend using a washout period between switching oral NSAIDs for chronic pain management to avoid the potential for adverse effects. However, an appropriate washout period has never been determined in a prospective study. Washout periods have been arbitrarily based on the half-life of the product and the prediction that the majority of a drug dose will be eliminated from the body after 4–5 half lives. The plasma half-lives of NSAIDs in dogs range from 1 to 24 hours with mavacoxib extending up to 39 days (Cox et al. 2010). The plasma concentrations and half-life of NSAIDs do not, however, directly correlate with clinical efficacy (Toutain et al. 2001; Lees et al. 2004a) as all veterinary approved NSAIDs have been shown to have some efficacy with once a day dosing despite the variable half-lives of the different products. The exception is mavacoxib which is dosed less frequently due to its prolonged half-life. Considering the half-life of the drug and the duration of clinical effect, conservative washout periods for NSAIDs, other than aspirin and mavacoxib, have been 5–7 days, assuming the change is not due to adverse effects (Lascelles et al. 2005a; Ryan et al. 2007). The washout period for mavac-

oxib would be 195 days utilizing the same principle. Due to aspirin's irreversible effect on platelets the washout period for aspirin is recommended to be no less than 7 days (time for platelet regeneration). If the animal is in need of analgesic treatment in the interim other drugs such as transdermal fentanyl (Kyles et al. 1996), codeine (KuKanich 2010), hydrocodone (KuKanich & Paul 2010), tramadol (Kukanich & Papich 2011), gabapentin (KuKanich & Cohen 2011), amantadine (Lascelles et al. 2008), and clomipramine could be considered, however no controlled clinical trials have demonstrated efficacy of these drugs in canine osteoarthritis as sole agents. It is important to reiterate that these recommendations are not made from controlled clinical trials and may change as new information becomes available.

If a patient experiences adverse effects from an NSAID, additional precautions should be considered before initiating treatment with another NSAID. If gastrointestinal toxicity occurs after NSAID administration then, if appropriate, another NSAID should not be administered until all clinical signs have resolved. In this scenario, it may be appropriate to administer a gastroprotectant agent (examples: H2 antagonist such as famotidine, proton pump inhibitor such as omeprazole, sucralfate, or misoprostol). In humans, proton pump inhibitors (PPIs) such as omeprazole are at least as effective as misoprostol in decreasing NSAID GI adverse effects and PPIs have less adverse effects and are more effective than double dose H2 antagonists (Hawkey et al. 1998; Ray et al. 2007).

The role of NSAIDs in the medical management of OA

Osteoarthritis (OA) is a progressive joint disease and a common cause of pain and dysfunction in dogs with current estimates of the prevalence of the disease in senior and geriatric dogs ranging from 20% to 25% or 1 in 5 adult dogs (Johnston 1997). There is no cure for osteoarthritis and, as such, it is important to initiate and optimize strategies to control symptoms and potentially slow the progression of the disease. Key goals in the management of OA are to control pain, achieve weight loss in overweight animals, maintain muscle strength and joint mobility, and improve the quality of life of the patient. Management of pain may best be achieved with multimodal therapy using a combination of nonpharmaceutical and pharmaceutical therapies. Surgical options can also be considered in

Table 2 Non-steroidal anti-inflammatory drugs approved for chronic use in dogs

Drug	Subclass	Dose form	Approved indication(s)	Dose	Comments*
Carprofen Rimadyl (Pfizer)	Propionic acid	Caplets Chewable tablets Injectable	Pain and inflammation associated with osteoarthritis Pain associated with soft-tissue or orthopedic surgery	4.4 mg kg ⁻¹ PO, once daily 2.2 mg kg ⁻¹ PO, twice daily 4.4 mg kg ⁻¹ SC	Safety not evaluated in dogs <6 weeks of age
Deracoxib Deramaxx (Novartis)	Coxib	Chewable tablets	Pain and inflammation associated with osteoarthritis Postoperative pain and inflammation associated with orthopedic surgery	Osteoarthritis: 1–2 mg kg ⁻¹ PO once daily Postoperative: 3–4 mg kg ⁻¹ PO once daily (7 day limit)	Safety not evaluated in dogs <4 months of age
Etodolac Etoogesic (Fort Dodge)	Pyranocarboxylic acid	Tablets	Pain and inflammation associated with osteoarthritis	10–15 mg kg ⁻¹ PO once daily	Safety not evaluated in dogs <12 months of age
Firocoxib Previcox (Merial)	Coxib	Chewable tablets	Pain and inflammation associated with osteoarthritis Pain associated with soft-tissue surgery and orthopedic surgery	5 mg kg ⁻¹ PO, once daily	Use of this product at doses above the recommended 5 mg kg ⁻¹ in puppies <7 months of age has been associated with serious adverse reactions including death
Mavacoxib Trococil (Pfizer Animal Health) Non-USA	Coxib	Chewable tablets	Pain and inflammation associated with degenerative joint disease in cases where continuous treatment exceeding one month is indicated	2 mg kg ⁻¹ PO Days 1, 14, 30 days then once monthly	Do not exceed 6.5 months duration of continuous therapy
Meloxicam Metacam (Boehringer Ingelheim)	Oxicam	Oral suspension Injectable	Pain and inflammation associated with osteoarthritis	0.2 mg kg ⁻¹ PO (Injectable SC/IV) on day 1, then 0.1 mg kg ⁻¹ PO once daily	Safety not evaluated in dogs <6 months of age
Phenylbutazone various manufacturers	Pyrazolone derivative	Tablets	Relief of inflammatory conditions associated with the musculoskeletal system	3 mg kg ⁻¹ (max 800 mg per 24 hours) PO every 8 hours. Maintain the lowest dose capable of producing the desired clinical response	No age related safety information reported
Robenacoxib Onsior (Novartis Animal Health) – non-USA	Coxib	Tablets	Treatment of pain and inflammation associated with acute musculoskeletal disorders Treatment of pain and inflammation associated with orthopedic or soft tissue surgery	1 mg kg ⁻¹ PO once daily	Do not administer with food. The safety has not been evaluated in dogs <2.5 kg (5.5 lbs.) or, < 3 months of age
Tepoxalin Zubrin™ (Schering-Plough)	Hydroxamic acid derivative	Tablets	Pain and inflammation associated with osteoarthritis	10 or 20 mg kg ⁻¹ on day 1, then 10 mg kg ⁻¹ once daily	Safety not evaluated in dogs <6 months of age

Tabulated data is derived from US and EMA label package inserts.

*General precautions for NSAIDs: Do not use in patients with GI or renal disease; discontinue use in case of vomiting or diarrhea; not recommended in hypovolemic or dehydrated patients or those with bleeding disorders; not for concurrent use with other NSAIDs or corticosteroids.

certain cases of OA, including techniques like joint replacement, excision arthroplasty, and arthrodesis.

The primary pharmaceutical therapy used for pain management of OA in dogs and humans is NSAIDs. This class of drugs has been shown to be clinically effective in reducing pain and lameness in dogs (Mansa et al. 2007; Innes et al. 2010). NSAIDs represent the cornerstone of oral OA therapy unless contraindicated by concurrent therapy or underlying medical conditions. In OA, disease progression, peripheral and central sensitization can all contribute to chronic pain.

Conclusions

NSAIDs are an effective class of analgesics and widely used for the management of soft tissue surgical orthopedic surgical, and osteoarthritic pain in dogs. Compared to the original NSAIDs that were used in veterinary medicine, such as aspirin, recently approved veterinary NSAIDs have decreased frequencies of gastrointestinal adverse effects. A good understanding of the mechanisms by which NSAIDs elicit their analgesic effect is essential in order to minimize adverse effects and drug-drug interactions. Osteoarthritis is a common, painful, and progressive joint disease of dogs often requiring multimodal therapy. NSAIDs represent the cornerstone of oral OA therapy unless contraindicated by concurrent therapy or underlying medical conditions.

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