Nonsteroidal Anti-inflammatory Drugs (NSAIDs) for Small Animals: Are There Any Differences?
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There are many nonsteroidal anti-inflammatory drugs (NSAIDs) available that have been used to treat osteoarthritis and pain. Many are registered for use in people (but we use them in animals also) and several are approved for use specifically for animals, particularly dogs. There has been a tremendous amount of information published on NSAIDs in the last 10 years (e.g., Lascelles 2005). A review of clinical trials for treating osteoarthritis may be found in the paper by Aragon et al. (2007). Comprehensive references on this topic were provided in the Veterinary Clinics of North America [July 2000, Vol. 30(4); and November 2008 Vol. 38, both edited by K.A. Mathews]. These issues contain several articles on drugs used for pain relief and control of inflammation. The last review by this author was in 2008 (Papich 2008) which was an update from an earlier manuscript (Papich 2000). A description of the chemistry, mechanism of action, and clinical use of the COXIB class of NSAIDs was provided in a thorough review (Bergh, Budsberg 2005). Pharmacokinetics and pharmacodynamics of NSAIDs were reviewed extensively by Lees et al. (2004b). A general summary (Lascelles 2005), guidelines for clinical use in dogs (Lascelles et al. 2005) and cats (Lascelles et al. 2007; Carroll, Simonson 2005; Taylor, Robertson (Part 1) 2004; Robertson, Taylor (Part 2) 2004; Sparkes et al. 2010) are available in excellent reviews. The paper by Sparkes et al. (2010) provides a current consensus of use in cats. A discussion of the physiologic characteristics of cyclooxygenase products can be found in the reference by Jones & Budsberg (2000). For a comparison on how osteoarthritis is treated in people, consult the review by Steinmeyer & Konttinen (2006).

CURRENT STATE OF UNDERSTANDING OF NSAID PHARMACOLOGY

It has been accepted since Dr. Vane’s work of the early 1970s that the most important mechanisms of action of NSAID are inhibition of the cyclooxygenase enzyme (Abramson et al. 1985, 1988) and the inhibition of prostaglandin synthesis. The NSAIDs are an important group of drugs for dogs. Older approved drugs include carprofen (Rimadyl) and etodolac (EtoGesic). We now have several new additions such as deracoxib (Deramaxx), firocoxib (Previcox, Equioxx), tepoxalin (Zubrin), meloxicam (Metacam), and perhaps in the future, robenacoxib (King et al. 2009). In other countries, additional drugs are available, such as mavacoxib, toltenamic acid (Tolfedine), nimesulide, and ketoprofen (Anafen).

The pharmacologic action of the NSAIDs has been reviewed (Vane, Botting 1995; Papich 2008). These drugs act to inhibit the isoenzymes of cyclooxygenase (COX). Cyclooxygenase 1 (COX 1) is a constitutive enzyme expressed in tissues (Meade et al. 1994). Prostaglandins, prostacyclin, and thromboxane synthesized by this enzyme are responsible for normal physiological functions. Cyclooxygenase 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, or may be
induced to maintain favorable conditions in healthy tissue. The target of recently developed NSAID has been COX-2, with the goal of producing analgesia and suppressing inflammation without inhibiting physiologically important prostanoids (Laneuville et al. 1994; Bergh, Budsberg 2005). Whether or not selective inhibition of COX-2 is the safest and most effective approach for animal treatment has yet to be established.

**ARE THE SELECTIVE COX-2 INHIBITORS BETTER?**

The evidence for superior efficacy for selective COX-2 inhibitors is lacking. They are not necessarily more effective than older drugs, but they may be safer for the gastrointestinal tract (Peterson, Cryer 1999). However, the studies demonstrating safety of COX-2 inhibitors in people have been criticized (Malhotra et al. 2004). 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 (Wolfe et al. 1999). There are high endogenous levels of COX-1 in the stomach, which is subject to high acid levels and shear forces. Inhibition of COX-1 in the stomach increases the risk of gastric ulceration. On the other hand, in the duodenum, COX-2 may be induced as a result of other treatments or injury to the duodenal mucosa (Wooten et al. 2008; Wooten et al. 2010). Injury and perforations that have been observed in the duodenum of dogs treated with COX-2 inhibitors (Lascelles et al. 2005; Case et al. 2010) may provide evidence that some patients have a requirement for upregulation of COX-2 in the duodenum. If the risk of mucosal injury to the duodenum is high, and the COX-2 inhibited by selective drugs, there is the possibility it may produce serious ulcers. COX-2 selective drugs also may cause a higher risk of cardiovascular problems in people because it preserves COX-1 which may promote platelet aggregation and vasoconstriction (Mukherjee et al. 2001). High COX-2 selectivity may increase risk of cardiovascular events (Topol 2004), which led to the removal of the popular drugs rofecoxib (Vioxx) and valdecoxib (Bextra) from human medicine in 2004. There is only one human COX-2 inhibitor left on the market.

**NSAIDs used in dogs**

- Aspirin a
- Phenylbutazone b
- Carprofen (Rimadyl, and generic) f
- Etodolac (EtoGesic) e
- Meloxicam (Metacam) c, f
- Ketoprofen (Anafen) d
- Deracoxib (Deramaxx)
- Firocoxib (Previcox)
- Meclofenamic acid (Arquel) e
- Robenacoxib (Onsior) ⁹
- Tepoxalin (Zubrin) ⁶
- Mavacoxib (Trocoxil) ⁹
- Tolfenamic acid (Tolfedine) ⁴,⁶

**NSAIDs used in cats**

- Aspirin
- Meloxicam ⁴,⁹
- Carprofen ⁹
- Robenacoxib ⁹
- Ketoprofen ⁴,⁹

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**ADVERSE EFFECTS OF NSAIDS**

**Gastrointestinal (GI) Toxicity**

The gastrointestinal effects of NSAIDs are by far the most common. These events can range from mild gastritis and vomiting, to severe gastrointestinal ulceration, bleeding, and even deaths. Vomiting, anorexia, nausea, and diarrhea are by far the most common events. There are two forms of GI injury that can occur as a result of NSAID administration (Wolfe et al. 1999): (a) a direct effect caused by exposure of the lining of the stomach and intestine to the drug, and (b) injury caused by prostaglandin inhibition.

NSAID can directly injure the lining of the stomach because of direct irritation of an oral medication. This is common from aspirin. It is usually not serious, but can cause stomach discomfort, dyspepsia, and nausea. The NSAIDs can directly injure the intestinal villi via exposure from the intestinal lumen. Drugs that enter the lumen via the bile perhaps have a higher risk for injury, which presents a greater problem for the NSAIDs that undergo enterohepatic recycling and produce high biliary concentrations. These effects may not result in a perforation, but can be an important cause for the nausea, vomiting, and diarrhea observed in animals following administration of NSAIDs.

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*a* Aspirin is not FDA-registered for dogs, cats or horses, but some forms are marketed for dogs as if there was FDA approval. There is an approved combination with methylprednisolone (Cortaba tablets, 0.5 milligram of methylprednisolone and 300 milligrams of aspirin).

*b* Registered for dogs, but not actively marketed.

*c* Registered for cats also as a single dose.

*d* Registered in Canada.

*e* Registered, but not marketed.

*f* Also available as an injectable as well as oral, the others are all available in oral forms.

*g* Registered in other countries, but not the U.S. (Robenacoxib approved in U.S. for cats).
A more serious form of GI injury occurs because prostaglandins are responsible for a healthy GI tract. When these prostaglandins are inhibited by NSAID, gastritis, GI ulcers, GI bleeding, perforations, diarrhea, and protein-losing enteropathy have all been described in animals. Gastrointestinal toxicity may be exacerbated by coadministration with corticosteroids in dogs. In horses, GI ulcers are an important problem as well, but most ulcers in horses occur from administering doses that are too high. The most severe ulcers in horses occur in the glandular mucosa because this is the region where prostaglandin inhibition plays the most important role.

**Kidney Injury**

COX-1 and COX-2 products play an important role in renal vascular tone (perfusion) and tubular function (natriuretic effect). Both COX-1 and COX-2 enzymes synthesize prostaglandins important for renal tubular function and blood perfusion during hypovolemia, hypotension, and salt depletion (Jones, Budsberg 2000). COX-2 may be inducible in the kidneys to prevent kidney injury. These effects of renal prostaglandins are particularly important during times of stress. In animals with decreased renal perfusion, NSAIDs may cause ischemic nephropathy.

**PHARMACOKINETIC FEATURES**

**Pharmacokinetic data for NSAIDs at the dosages tested in dogs**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half-life in dogs</th>
<th>Test dose</th>
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<tbody>
<tr>
<td>Aspirin</td>
<td>8 hours</td>
<td>10–20 mg/kg q 8–12 h, oral</td>
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<tr>
<td>Carprofen</td>
<td>8 hours (range 4.5–10)</td>
<td>4.4 mg/kg q 24 h, or 2.2 mg/kg q 12 h, oral</td>
</tr>
<tr>
<td>Deracoxib</td>
<td>3 h at 2–3 mg/kg</td>
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<tr>
<td></td>
<td>19 h @ 20 mg/kg</td>
<td>3–4 mg/kg q 24 h, oral</td>
</tr>
<tr>
<td>Etodolac</td>
<td>7.7 h fasted; 12 h non fasted</td>
<td>10–15 mg/kg q 24 h, oral</td>
</tr>
<tr>
<td>Flunixin</td>
<td>3.7 h</td>
<td>1 mg/kg, oral or IM, once</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>12–36 hours</td>
<td>0.2 mg/kg initial, then 0.1 mg/kg q 24 h, oral</td>
</tr>
<tr>
<td>Naproxen</td>
<td>74 h</td>
<td>5 mg/kg initial, then 2 mg/kg q 48 h, oral</td>
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<tr>
<td>Phenylbutazone</td>
<td>6 hours</td>
<td>15–22 mg/kg q 12 h, oral</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>40 hours</td>
<td>0.3 mg/kg, q 24 h, or q 48 h, oral</td>
</tr>
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</table>
Tepoxalin  | 1.6 h parent drug  | 20 mg/kg initial; then 10 mg/kg q 24 h, oral  
| | 13 h for active metabolite |

Firocoxib  | 7.8 hours  | 5 mg/kg q 24 h, oral |

For most of the NSAID there is adequate pharmacokinetic data for dogs and horses, some for cats and cattle, but more limited for other animals (e.g., exotic animals). 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 because they have higher volumes of distribution than expected.

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 (e.g., piroxicam at a low dose given once daily or once every other day to dogs). 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.

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, 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. Robenacoxib in cats has a very short half-life (1–2 hours) in plasma, but effective half-life in tissues is much longer. These drugs persist in tissues, and particularly inflamed tissues, longer than they persist in plasma.

**Drug Selection**

When selecting a drug for treatment in animals, there are several choices (see Table). Veterinarians should not allow unsubstantiated claims affect the decision of selecting one drug over another. When selecting an NSAID, **we really don’t know which NSAID is the best one**. Each has advantages and disadvantages. There are different dosage forms that include injectable, oral liquid, regular tablets, oral mucosal, and chewable tablets. The preference of each of these depends on the clinical situation and animal/owner preference. There are veterinary generic formulations of popular drugs and there are some human-labeled drugs used off-label (e.g., piroxicam).

**Consistent features of NSAIDs**

1. All NSAIDs, regardless of COX-1/COX-2 specificity are capable of producing gastrointestinal lesions, particularly at high doses.
2. All NSAIDs (selective or non-selective) can produce other gastrointestinal signs, including
vomiting, diarrhea, decreased appetite, without producing ulceration.

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

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

5. No NSAID is consistently more clinically effective than another.

**NSAIDs for Dogs**

For acute pain, such as perioperative use, there is evidence published showing that oral and injectable formulations are effective. NSAIDs have been used for this indication for short term of one or two days to decrease fever, pain, and discomfort from surgery or trauma. Preoperative injections of carprofen were shown to be beneficial to decrease postoperative pain in dogs after ovariohysterectomy (Lascelles et al. 1998). Meloxicam has been evaluated in two published studies for perioperative use and was shown to be superior to butorphanol in some of the pain assessments that were measured.

For chronic administration, such as treatment of myositis, arthritis, and osteoarthritis, drugs that have been administered in the U.S. to small animals were listed previously. Review papers have also summarized these choices (KuKanich et al. 2012). 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. For long-term use to treat osteoarthritis, there are no controlled studies to indicate which drug is the safest and most effective. When drugs are compared to one another, it is difficult, using subjective measurements, to demonstrate differences between the drugs when evaluating them for efficacy or safety. Without a very large number of patients, the statistical power to detect differences among drugs in clinical veterinary studies is difficult. It is a rational approach to consider a rotating schedule of two or more drugs to identify which drug is better tolerated, effective, and easier to administer in each patient.

**NSAIDs for Cats**

For a review of NSAID drug selection for cats, consult the references cited earlier (Lascelles et al. 2007; Sparkes et al. 2010; Carroll, Simonson 2005; Taylor, Robertson [Part 1] 2004; Robertson, Taylor [Part 2] 2004). Meloxicam is commonly used in cats because it can be injected for the initial use, and follow-up is possible with oral treatment. The oral solution has been palatable for cats, but the dose should be reduced compared to the canine dose. Robenacoxib also is approved for cats. In addition, ketoprofen, aspirin (at an extended interval), and occasionally other drugs listed for dogs have been used off-label. For short-term use, carprofen, deracoxib, and flunixin have been used.

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