NSAIDs: Comparative Toxicity and Drug Interactions

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With the availability of many prescription veterinary NSAID's, there are many choices for controlling acute and chronic pain and inflammation in dogs (but fewer for cats). Because patients with osteoarthritis may be older and have concurrent disease, the risk of toxicity and NSAID-associated drug interactions should always be considered when NSAIDs are prescribed.

I. NSAID mechanisms of action
  A. Cyclooxygenase 1 (COX-1)
    1. Constituitively expressed in many tissues
    2. Generates protective prostaglandins in stomach, intestine, and kidney
    3. Also generates thromboxane (TXA_2), which mediates platelet aggregation
  B. Cyclooxygenase 2 (COX-2)
    1. Induced by inflammation
    2. Generates pro-inflammatory prostaglandins
    3. Also generates protective renal prostaglandins
    4. Also important for healing of gastric ulcers once they occur
  C. NSAID inhibition of COX 1 and/or COX 2
    1. Anti-inflammatory, anti-pyretic, and analgesic (via COX-2 inhibition)
    2. Anti-platelet (via COX-1 inhibition)
      a. Non-selective agents
        1) Aspirin, Ketoprofen, Piroxicam
      b. COX-2 preferential
        1) Carprofen, Meloxicam, Etodolac
      c. COX-2 selective
        1) Deracoxib, Firocoxib
      d. Other agents
        1) Dual COX and lipoxygenase inhibitors
          a) Tepoxalin (Zubrin) – no longer marketed
        2) Acetaminophen

II. GI Toxicity of available NSAID's
  A. Vomiting, diarrhea
    1. Common early side effect; direct gastric irritation
  B. Gastric ulceration
    1. Inhibition of PGE2 generation
      a. PGE2 important for maintenance of gastric mucosa
        1) Epithelial turnover
        2) Mucus and bicarbonate secretion
      b. NSAID's also directly alter phospholipids in the mucus gel layer overlying the gastric mucosa
        1) Can damage this hydrophobic barrier
        2) Rationale for enteric coated aspirin
    2. Ulcer risk potentiated by glucocorticoids
      a. Inhibition of prostaglandin synthase
      b. Decreased peroxidase-mediated scavenging of free radical precursors
    3. All NSAID's have the *potential* to cause serious GI bleeding, but which NSAIDs are safest for the GI tract?
      a. Difficult to directly compare the relative GI toxicity of veterinary NSAID's
        1) Most published studies that use endoscopy (the gold standard) enroll relatively few dogs, and dogs are typically young and healthy.
      b. Lower risk with COX-2 preferential compared to non-selective agents
        1) Carprofen and etodolac lead to less GI ulceration than aspirin in dogs (Reimer 1999)
        2) Carprofen associated with fewer and milder gastric lesions compared to ketoprofen in dogs (Forsyth 1998)
      c. Coxibs (COX-2 selective) have a better safety profile than classical NSAID's in humans
        1) May carry a lower risk of GI bleeding in dogs, but have not been compared directly within the same study to COX-2 preferential NSAIDs

2) However, gastrointestinal ulceration and perforation have been reported in dogs with deracoxib
a) COX-2 is important for *healing* of gastric ulcers experimentally, and coxibs may impair healing of pre-existing ulcers

4. The ulcerogenic effects of NSAID's are potentiated by multiple NSAID use and by concurrent glucocorticoids, which are contraindicated

C. Monitoring for GI bleeding from NSAIDs
1. Clinical monitoring:
a. Vomiting and diarrhea
b. Lethargy, inappetance
c. Darkened stools – late finding
d. Biochemical monitoring:
1) PCV/TP
2) CBC
a) Polychromasia with drop in PCV and TP (acute)
b) Microcytosis (chronic)
3) Albumin, globulin, and BUN
a) Low albumin, low globulin, and increased BUN with no change in creatinine, suggest GI bleeding
e. Fecal occult blood
1) Can detect GI bleeding before overt melena, but available fecal occult blood tests lack high sensitivity and specificity in dogs and cat
2) Not recommended
2. Drugs that protect against NSAID ulcers
a. Note: gastric acid is necessary for the development of gastric ulcers with NSAID's
b. Omeprazole
1) Blocks HCl pump
2) Drug of choice for preventing NSAID ulcers in humans
c. Misoprostol
1) Synthetic PGE2 analog
2) Effective in preventing aspirin-induced ulcers in dogs
3) Drawback is diarrhea and cramping

III. Renal decompensation
A. Any NSAID can adversely affect renal perfusion
1. Prostaglandins are critical for renal perfusion in patients with low renal blood flow
a. Prostaglandins increase renal arterial blood flow in response to a drop in renal perfusion
b. Prostaglandins also stimulate renin release
2. Both COX-1 and COX-2 generate protective renal prostaglandins
a. Even COX-2 selective agents can decrease glomerular filtration to the same extent as classical NSAID's.
3. The risk of renal decompensation from NSAID's is greatest with:
a. Pre-existing renal disease
b. Hypovolemia or dehydration
c. Congestive heart failure
d. Sodium-restricted diets
e. Cirrhosis

B. Most studies on NSAID effect on renal function have been done in healthy animals undergoing elective procedures
1. Carprofen at the label dose showed no adverse effect on glomerular filtration rate (GFR) in one study
a. However, in another study, carprofen and ketoprofen both led to a decrease in GFR in healthy dogs undergoing castration (Forsyth 2000).
b. In addition, ketoprofen has been associated with transient azotemia, even in healthy dogs being spayed (Lobetti 2000).
2. Meloxicam in cats
a. Clearance in cats is <u>not</u> slower than in dogs
1) Does not rely on glucuronidation
b. No adverse effect on GFR in healthy euvolemic cats (Goodman 2009)
c. However, meloxicam has led to acute renal failure and death in client-owned cats given SC label dose (0.3 mg/kg) chronically

1) Chronic meloxicam dosing is label-prohibited in cats in the U.S.
2) Lower daily dosages (0.01-0.03 mg/kg daily) were clinically well tolerated in 46 geriatric cats with osteoarthritis, but renal function was not consistently monitored (Gunew 2008)
3) 21 older cats with IRIS stage 1-2 renal disease, treated with meloxicam at a median dose of 0.02 mg/kg/day, did not show clinical evidence of renal decompensation when followed for at least 6 months (Gowan 2011
    a) However, this chronic use of meloxicam is specifically contraindicated in the U.S.

C. Use of NSAIDS with pre-existing azotemia
1. Consider alternative agents for analgesia
    a. Fentanyl CRI
    b. Tramadol
    c. Gabapentin
    d. Buprenorphine
    e. Acetaminophen
2. If NSAIDs are necessary in azotemic animals:
    a. Always use with fluid support
    b. Use conservative doses and titrate to effect

IV. Platelet dysfunction and bleeding
A. Classical NSAID's inhibit platelet function most readily
1. Aspirin, ketoprofen, piroxicam
    a. Impaired platelet function via inhibition of COX-1 mediated TXA_2 generation.
    b. Prolonged bleeding times with ketoprofen in dogs undergoing elective orthopedic surgery (Grisneaux 1999); one ketoprofen-treated dog developed a hematoma at the surgical site.
    c. Bleeding from gingival or enhanced surgical hemorrhage
    d. GI hemorrhage most common
        1) Impaired platelet function *and* altered gastric mucosa

B. COX-2 preferential agents have less inhibitory effects on platelets
1. Carprofen leads to mild subclinical decreases in platelet aggregation, but neither carprofen nor meloxicam prolong buccal mucosal bleeding times in healthy dogs
2. However, etodolac has been associated with excessive bleeding in dogs during experimental surgery (Etodolac label).

C. COX-2 selective coxibs do not inhibit platelet function in dogs
1. Deracoxib and firocoxib does not affect buccal mucosal bleeding time in dogs (Deramaxx label; Steagall 2007)
2. Coxibs may be better NSAID choices in dogs with pre-existing coagulopathies (e.g. von Willebrand's disease)
3. Clinical monitoring for bleeding is always important

D. What about coxibs in patients with **hyper**coaguable states?
1. Traditional non-selective NSAIDs (esp. low dose aspirin) have a theoretical advantage in patients prone to thrombosis
2. Coxibs are, in theory, contraindicated in these hypercoaguable patients
    a. Unopposed activity of COX-1 may lead to platelet over-reactivity and impaired small vessel dilation, resulting in thrombosis in at-risk patients
    b. Until more is known, avoid coxibs in patients with protein losing nephropathy, immune mediated hemolytic anemia, vasculitis, and hyperadrenocorticism

V. Hepatopathy
A. In humans, both cholestasis and fulminant hepatic failure have been reported with coxibs and etodolac.
B. In dogs, carprofen has been associated with rare acute hepatic necrosis
1. Very high ALT with typically lesser increases in SAP
2. It is very unlikely that modest increases in SAP, with a normal ALT, are due to carprofen

C. Icterus and hepatic enzyme elevations have also been reported with all other veterinary NSAIDs in dogs (see drug labels), although the incidence is not clear.
1. Any NSAID has the potential to cause hepatopathy
2. Baseline CBC and chem. panel indicated in older dogs
3. Careful clinical monitoring is key
    a. Watch for vomiting, inappetence, lethargy, diarrhea, dark urine
    b. If even mild clinical deterioration during NSAID administration, evaluate blood work, with a focus on new elevations in ALT

4. With idiosyncratic reactions such as these, careful clinical observation is probably a more effective monitoring tool than routine liver enzyme evaluations

VI. Drug interactions with NSAID's

A. Benzodiazepines

1. Most NSAID's, including coxibs, are highly protein bound (> 90-95%)
   a. Can lead to displacement and increased toxicity from other highly protein bound drugs, such as benzodiazepines
      1) Also: warfarin, valproic acid, methotrexate
2. Most likely to be clinically significant when giving single or loading doses of NSAIDs to animals that:
   a. Have low serum albumin concentrations
   b. Are being treated with single dose of an NSAID and a benzodiazepine
3. Protein binding drug interactions are less likely with chronic NSAID administration, since increases in free drug are offset over time by increased elimination of the extra free drug

B. Acetaminophen and phenobarbital

1. Acetaminophen is metabolized to its toxic metabolite by a cytochrome P450 (CYP2E1) that is induced by phenobarbital
   a. Chronic phenobarbital administration increases the hepatotoxicity of acetaminophen in experimental studies
   b. Acetaminophen should probably be avoided in dogs treated with phenobarbital

C. Aminoglycosides and furosemide

1. NSAIDs increase the nephrotoxicity of both aminoglycosides and furosemide
   a. Inhibition of compensatory renal prostaglandin production

D. Herbs and NSAIDs

1. Herbs that contain salicylate, such as meadowsweet and willow, could exacerbate the side effects of aspirin and other traditional non-selective NSAID's
2. Gingko, garlic, ginger, and ginseng inhibit platelet aggregation
   a. Gingko has lead to spontaneous bleeding in humans in combination with aspirin

Minimizing NSAID complications

- Obtain screening CBC and panel in older patients prior to starting NSAIDs
  - Rule out significant pre-existing azotemia, anemia, or hepatic dysfunction
- Maintain hydration
- Absolutely no concurrent glucocorticoids (including budesonide or high dose topicals)
- Never use multiple NSAIDs concurrently
  - Use at least a one-week washout between an NSAID and either glucocorticoids or other NSAIDs
  - Consider bridging with tramadol and omeprazole during that week
- Client education and careful monitoring for GI upset, darkened stools, inappetence, or lethargy in any treated patient
- Periodic monitoring of CBC and chem. panels in older patients or those with underlying risk factors for GI bleeding, such as hepatic disease or early renal insufficiency.

NSAID	Relative COX inhibition	Advantages and disadvantages
Non-selective agents		
Aspirin	Both COX-1 and COX-2	Low doses selectively inhibit platelet function (0.5– 1 mg/kg q. 12 h) May be useful for pro-thrombotic states (cardiomyopathies in cats, protein losing nephropathy in dogs) GI upset and bleeding at higher dosages
Ketoprofen	Both COX-1 and COX-2	Short term analgesia, but has been associated with bleeding and azotemia There are safer agents
Piroxicam	Both COX-1 and COX-2	Effective to slow growth of transitional cell, nasal, and colon carcinomas in dogs and cats Avoid if coagulopathy present

COX-2 preferential agents		
Carprofen (Rimadyl)	COX-2 > COX-1	Good pain control with minimal risk of bleeding Risk of renal decompensation remains Rare risk of idiosyncratic hepatic necrosis
Meloxicam (Metacam)	COX-2 > COX-1	Good pain control with minimal risk of bleeding Risk of renal decompensation remains Acute renal failure with chronic dosing at label dose in cats
Etodolac (Etogesic)	COX-2 > COX-1	Approved for dogs but not as popular as carprofen or meloxicam Excessive bleeding in dogs during experimental surgery (Etogesic label) Fall in serum total T4 in dogs with orthopedic disease, sometimes into the hypothyroid range (Ness 2003)
COX-2 selective agents		
Deracoxib (Deramaxx)	COX-2 >>> COX-1	Good pain control with apparent low risk of new GI ulceration COX-2 selective agents can impair healing of pre-existing ulcers Minimal risk of bleeding Risk of renal decompensation remains
Firocoxib (Previcox)	COX-2 >>> COX-1	Good pain control with apparent low risk of new GI ulceration COX-2 selective agents can impair healing of pre-existing ulcers Minimal risk of bleeding Risk of renal decompensation remains
Other NSAIDs		
Tepoxalin (Zubrin)	Both COX-1 and COX-2 Also inhibits 5-lipoxygenase	Safer than coxibs for dogs with pre-existing ulcers? Unfortunately, manufacture has been stopped
Acetaminophen (Tylenol)	Weak, reversible COX inhibition No significant anti-inflammatory effects	Antipyretic or analgesic in dogs intolerant of NSAIDs (acetaminophen 10-15 mg/kd q. 8 h; if combined with codeine, dose codeine at 1-2 mg/kg q. 8 h.) Acetaminophen contraindicated in cats, of course