Non-steroidal antiinflammatory drugs (NSAIDs) are often used in veterinary medicine for their anti-inflammatory, analgesic and anti-pyretic properties. NSAIDs inhibit the cyclooxygenase (COX) pathway of arachidonic acid metabolism and production of the prostaglandins PGE₂ and PGF₂α, prostacyclin (PGI₂) and thromboxane A₂(TxA₂). These products, while playing a role in inflammation and pain transmission, also participate in many important physiologic functions. The particular final product formed depends on the cell type being stimulated, the stimulus, and the presence of specific synthases within that cell.

At least two distinct isoforms of the COX enzyme, COX-1 and COX-2, occur. COX-1 is constitutively expressed in most tissues, including the gastric mucosa, liver, kidneys and platelets, and is involved in gastric mucosal barrier protection, maintenance of liver and renal blood flow (particularly in low perfusion conditions) and normal platelet aggregation. COX-2 is primarily an inducible enzyme found within inflammatory cells, endothelial cells, articular chondrocytes and synovial fibroblasts, peripheral nerves and the central nervous system (CNS). COX-2 is also found constitutively in the CNS and renal vasculature, and synovial chondrocytes in some species. Newer NSAIDs that target the COX-2 enzyme and “spare” the COX-1 enzyme result in selective antiinflammatory effects with decreased gastric side effects and minimal effects on coagulation. However, GI and renal side effects may still occur.

New information and the availability of new drugs have changed the way NSAIDs are used perioperatively as part of a multimodal approach to pain management. While inhibiting COX activity and inflammation peripherally contributes to the analgesic effect, a large part of the analgesic effect is related to inhibiting COX activity, more specifically COX-2 activity, in the CNS. It may take up to two hours after drug administration to achieve effective inhibitory levels within the dorsal horn of the spinal cord. This time lag should be taken into account when using NSAIDs “pre-emptively”. This is especially true perioperatively, when measuring the risk/benefit ratio of using these drugs at a time when anesthetic agents may adversely affect blood pressure and/or renal blood flow and oxygen delivery.

Most NSAIDs are metabolized in the liver and excreted via the biliary system or kidney. Since cats have a low hepatic glucuronidase activity, many of the drugs metabolized by this pathway (e.g. aspirin, carprofen) have a prolonged half-life in cats. In dogs, the most common adverse drug experiences reported to the FDA are related to GI, renal and hepatic systems.

**GI ulceration and hemorrhage:** The most common side effects of NSAID use are GI ulceration and hemorrhage, due both to direct irritation of the gastric mucosa and as a sequelae to PG inhibition. The incidence of ulceration is greatly increased in animals receiving NSAIDs in combination with steroids or other NSAIDs or in animals with a history of previous GI bleeding. The use of aspirin in combination with other NSAIDs GREATLY increases the incidence of aspirin-induced gastric injury. Although COX-2 preferential inhibitors generally cause less GI ulceration than non-selective NSAIDs, signs of GI irritation (vomiting, diarrhea) still occur in about 10% of dogs. Few studies have been done on NSAID-associated GI ulceration in cats.

**Nephrotoxicity:** Although prostanoids do not play a major role in regulating blood flow in the normal healthy kidney, PGE₂ and PGI₂ help maintain renal perfusion during low-flow states (e.g. hypotension, dehydration, anesthesia, renal disease). Therefore, both non-selective and COX-2 preferential NSAIDs should be avoided in these conditions. Repeated use (off-label) of...
Meloxicam has been associated with acute renal failure in the cat and should be discouraged. Prostanoids also play an important role in sodium and water regulation and NSAID use should be avoided in patients with heart failure or hypertension.  

**Hepatotoxicity:** Prostanoid production may also play a role in maintaining blood flow to the liver. Hepatotoxicity caused by NSAIDs is generally considered idiosyncratic. Most dogs recover with discontinuation of the drug and supportive care.  

**Decreased platelet function:** NSAIDs inhibit platelet function by inhibiting TxA2 production, a COX-1-mediated event and may cause increased bleeding. This is especially true when using aspirin, which causes irreversible inhibition of the COX enzyme by acetylation so new platelets must be produced before clotting function returns to normal. COX-2 preferential drugs should not affect hemostasis when given preoperatively.  

**Specific NSAIDs**

**Aspirin (acetylsalicylic acid):** Nonselective COX inhibitor. May cause GI ulceration. Not approved for use in the dog  

**Flunixin meglumine (Banamine ®):** Nonselective COX inhibitor. May cause cause GI ulceration after only a few doses. Nephrotoxicity has also been reported after prolonged use.  

**Phenylbutazone:** Nonselective COX inhibitor. Causes GI ulceration in dogs and potentially fatal blood dyscrasias in humans. Approved for use in the dog.  

**Ketoprofen (Ketofen ®):** Injectable nonselective COX inhibitor.  

**Piroxicam (Feldene®):** Nonselective COX inhibitor. May cause GI ulceration (significant enterohepatic cycling). Long elimination half life (40 hours). Immunomodulatory as well as anti-inflammatory, piroxicam is frequently used as an antineoplastic agent in dogs.  

**Meloxicam (Metacam ®):** Preferential COX-2 inhibitor. Care must be taken with dosing due to a relatively narrow margin of safety (i.e. GI ulceration with perforation has been reported at twice the label dose). Approved for use in the dog and cat (one dose)  

**Carprofen (Rimadyl ®):** Preferential COX-2 inhibitor. Selectivity progressively lost at larger doses. May cause GI ulceration. An idiosyncratic hepatocellular reaction with anorexia, vomiting and icterus has been occasionally reported with it’s use. Approved for use in the dog.  

**Etodolac (Etogesic®):** Marketed as a COX-2 preferential NSAID. May cause GI ulceration (significant enterohepatic cycling). Approved for use in the dog  

**Deracoxib (Deramaxx®):** Targeted COX-2 inhibitor (“coxib”), with relatively little activity at the COX-1 enzyme site at clinically used doses. May cause GI ulceration. Approved for use in the dog  

**Firocoxib (Previcox®):** Targeted COX-2 inhibitor (“coxib”), with relatively little activity at the COX-1 enzyme site at clinically used doses. Efficacy and safety reportedly similar to that of other COX-2 selective drugs. May cause GI ulceration. Approved for use in the dog  

**Robenacoxib (Onsior®):** First targeted COX-2 inhibitor (“coxib”) approved for perioperative use in the cat (up to 3 days). Rapidly cleared from the blood with a long residence time at sites of inflammation (“tissue selective”)  

**Tepoxalin (Zubrin®):** Nonselective COX inhibitor. Lipoxygenase inhibitor, which decreases inflammation in the gastric mucosa and gastric ulcer formation. Approved for use in the dog.  

**Naproxen (Aleve ®):** Naproxen is not recommended for use in dogs. Perforated gastric ulcers have been reported after only one dose.