

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)



BASICS

OVERVIEW

- NSAIDs comprise a group of over 30 compounds with analgesic, antipyretic, and anti-inflammatory effects.
- Aspirin, flunixin meglumine, ketoprofen, carprofen, phenylbutazone, and dipyrone are NSAIDs that are commonly used in ruminants. Of these, only flunixin is specifically labeled for use in beef and dairy cattle in the USA. Phenylbutazone and dipyrone should not be used. Meloxicam and tolfenamic acid are new NSAIDs not yet approved for use in ruminants in the USA.

SYSTEMS AFFECTED

- Musculoskeletal
- Digestive
- Urinary
- Hematopoietic

PATHOPHYSIOLOGY

- In general, NSAIDs inhibit one or more steps in the arachidonic acid cascade (*see Figure 1*)
- Arachidonic acid (AA) is a polyunsaturated fatty acid found within cell membranes.
- Under the influence of cyclooxygenases, either cyclooxygenase 1 (COX 1) or cyclooxygenase 2 (COX 2), AA is converted into several prostaglandin products (PGG₂, PGH₂, PGD₂, PGE₂, PGI₂) at a variety of sites including gastrointestinal and renal tissues, endothelial cells and platelets.
- Prostaglandin products produced via the COX 1 pathway are constantly present within the body, and provide a range of physiologic effects including protection of the GI mucosa, vascular hemostasis and protection of renal tissue from ischemia during hypotensive events. Prostaglandins produced via the COX 2 pathway are not constantly present, are induced when needed and generally potentiate inflammation.
- COX inhibition
 - Most NSAIDs currently available for veterinary use are nonselective COX inhibitors.
 - Blockage of the COX 1 pathway is generally considered to create the toxic effects associated with NSAIDs, including GI ulceration and bleeding, renal damage and interference with clotting.
 - From a therapeutic perspective, inhibition of COX 2 is desirable since blocking this pathway provides anti-inflammatory and analgesic results.
- Lipooxygenases
 - Located within cells and can stimulate the formation of inflammatory mediators via metabolism of AA. The resulting leukotrienes are potent inflammatory mediators, chemotactic agents and have the ability to influence leukocyte function.
 - NSAID interference with the cyclooxygenase pathways may create increased production of leukotrienes.

- Other effects: NSAIDs may inhibit neutrophilic release of inflammatory cellular enzymes, inhibit cellular adhesion and movement, and influence lymphocyte activity (immunomodulation).

ARACHIDONIC ACID

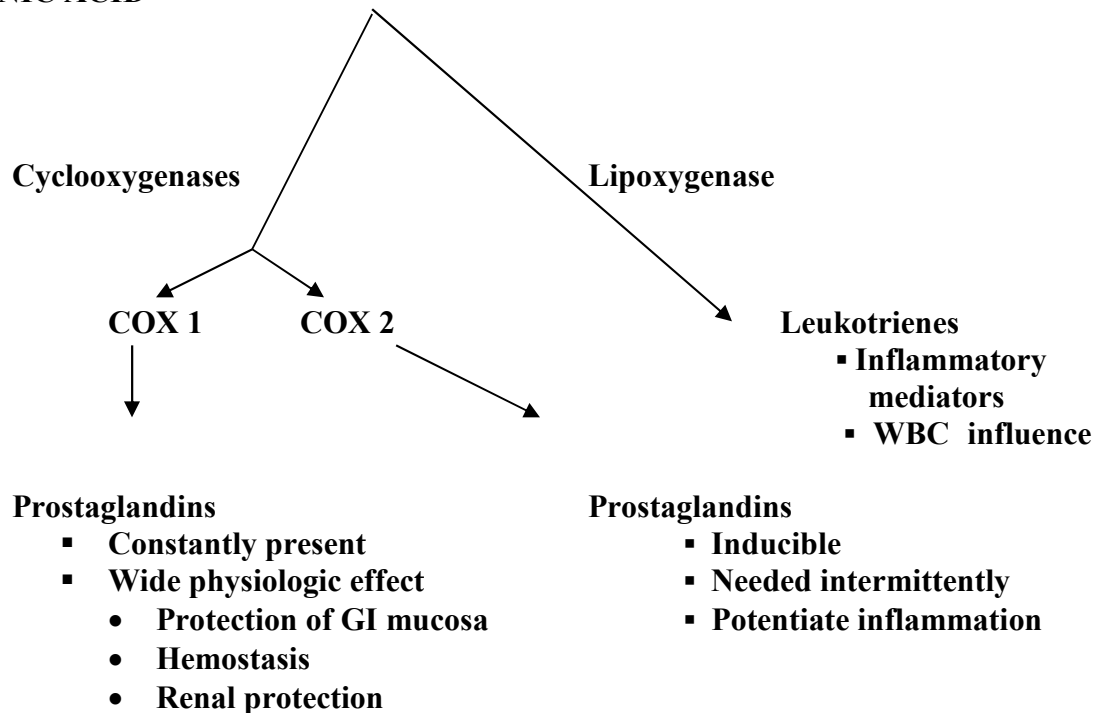


Figure 1: *Abbreviated schematic of the arachidonic acid cascade*

- Reports of adverse effects from NSAID use in ruminants are uncommon; however, all NSAIDs have the potential to induce serious, and potentially life-threatening side effects.
- Effects primarily reflect the influence of NSAIDs on prostaglandin activity in the GI, urinary (renal), and hematopoietic systems.
- Gastrointestinal
 - Specific prostaglandins (PGE₂ and PGI₂) regulate blood flow to the GI mucosa, and stimulate mucus and bicarbonate production, which provide protection to the gut.
 - Inhibition of these prostaglandin products produces damage reflective of disruption of the mucosal barrier with subsequent erosion and ulceration.
 - GI bleeding and changes in mucus, acid and bicarbonate production may occur.
- Renal
 - Similarly to the GI system, vasodilatory prostaglandins protect the kidneys from adverse hemodynamic events such as hypotension, dehydration and other conditions that influence renal blood flow
 - Blockage of these prostaglandins by NSAIDs may result in acute renal failure
 - Interstitial nephritis and renal crest necrosis can occur
- Hematopoietic
 - NSAIDs inhibit platelet activity due to their influence on thromboxane production. This effect appears to be drug and dose dependent, and may be either reversible or irreversible, depending on the agent.
 - Inhibition of platelets may result in abnormal clotting and problems with hemostasis.

CAUSES AND RISK FACTORS

- Very young and very old animals may be more susceptible to adverse effects of NSAIDs
- Administration of NSAIDs to dehydrated or hypotensive animals may increase the risk of renal toxicity
- Administration of combinations of different NSAIDs, or the combination of NSAIDs with other nephrotoxic drugs may increase the risk of toxic effects
- Administration of NSAIDs at erroneously high doses or for prolonged durations may increase the risk of toxic effects
- Discontinuation of NSAIDs for a minimum of ten days before anticipated elective surgical procedures is recommended to avoid intra- and post-operative bleeding concerns



DIAGNOSIS

- Suspected NSAID toxicity can be suggested by a history of ingestion/treatment, clinical signs and specific laboratory abnormalities

DIFFERENTIAL DIAGNOSES

- Abomasal ulceration
- Neoplasia
- Parasitism
- Other causes of renal failure

CBC/BIOCHEMISTRY/URINALYSIS

- Mild to severe anemia
- Hypoproteinemia (hypoalbuminemia); azotemia and serum electrolyte abnormalities (hypocalcemia, hyponatremia, and hypochloremia in chronic cases)
- Hematuria

OTHER LABORATORY TESTS

- N/A

IMAGING

- Gastroscopy in pre-ruminants

OTHER DIAGNOSTIC PROCEDURES

- Fecal occult blood analysis

PATHOLOGIC FINDINGS

- Mucosal edema, irritation, petechiation, and ulceration of alimentary tract
- Bilateral renal papillary necrosis
- Interstitial or tubular nephritis



TREATMENT

THERAPEUTIC APPROACH

- In cases where NSAIDs are indicated, before their administration, renal hemodynamics should be considered in case a fluid therapy plan and electrolyte evaluation is appropriate.
- Toxicity can be addressed by supplying IV fluids (1.5 to 2X maintenance), activated charcoal (1-5 g/kg PO as slurry) to treat oral overdose situations, and provision of antacids (magnesium hydroxide, 1 g/kg PO in 2-3 gallons of warm water) if abomasitis is suspected.



MEDICATIONS

DRUGS OF CHOICE

- Aspirin
 - 100 mg/kg PO BID or TID
 - No FDA approved formulation on market
 - In general, aspirin has a wide margin of safety. Slow oral absorption ($t_{1/2} = 3$ hours)
 - Bioavailability approximately 70%
 - Elimination is rapid (elimination $t_{1/2} = 0.5 - 6$ hours)
 - No published meat and milk withdrawal time; general FARAD recommendation of 24 hours
- Flunixin meglumine
 - 1.1 – 2.2 mg/kg slow IV q day or divided BID for 3 days.
 - Similar dosage is used in other ruminant species but is extra-label
 - Oral formulations available but not FDA approved for ruminants
 - Elimination cattle $t_{1/2}$ ranges from 3.1 – 5.2 hours, sheep from 3.4 – 3.8 hours, and llamas 1.4 hours.
 - FARAD recommended withdrawal (IV use only) of 4 days for meat and 36 hours for milk.
- Ketoprofen
 - 3 mg/kg, IV or IM q 24 hours for up to 3 days (extra-label in USA) for cattle, sheep, goats
 - Rapid elimination (elimination $t_{1/2} = 30$ minutes)
 - FARAD withdrawal recommendation of 7 days for meat and 24 hours for milk at dosage above
- Carprofen
 - 1.4 mg/kg IV or SC x 1 dose (extra-label in USA)
 - Long elimination cattle $t_{1/2}$ of 30-40 hours; 26-33.7 hours in sheep
 - Slaughter withdrawal = 21 days; should not be used in ruminants producing milk for human consumption.
 - Rarely used in USA where flunixin is available
- Phenylbutazone
 - In 2002, the United States FDA added phenylbutazone to the list of drugs that not allowed to be used in food-producing animals.
- Dipyrone
 - In 1996, the United States FDA issued a statement that dipyrone is not approved for use in any animal and its use constitutes an illegal drug use.

CONTRAINDICATIONS

- Bismuth subsalicylate containing products should not be given in NSAID toxicity situations

PRECAUTIONS

- Appropriate milk and meat withdrawal times must be followed for all compounds administered to food producing animals
- Diclofenac has caused death in vultures scavenging the carcasses of treated ruminants

POSSIBLE INTERACTIONS

- Different NSAID drugs should not be combined



FOLLOW-UP

EXPECTED COURSE AND PROGNOSIS

- Generally good if NSAIDs are stopped at first signs of adverse effects

POSSIBLE COMPLICATIONS

- Perforation of abomasal or colonic ulcers with subsequent bleeding and/or peritonitis

CLIENT EDUCATION

- Focus on appropriate NSAID drug options and dose regimens

PATIENT CARE

- CBC, serum electrolytes and serum chemistry as needed

PREVENTION

- Stop using NSAIDs at the first signs of adverse effects – anorexia, depression, colic, hematuria, hematochezia
- Correction of dehydration and/or hypotensive conditions, before treatment with NSAIDs will minimize the secondary nephrotoxic effects of potent drugs.



MISCELLANEOUS

ABBREVIATIONS

- AA = arachidonic acid
- COX= cyclooxygenase 1 (COX 1) or cyclooxygenase 2 (COX 2)
- FARAD= Food Animal Residue Avoidance Database
- FDA= United States Food and Drug Administration
- GI = gastrointestinal
- NSAIDs= nonsteroidal anti-inflammatory drugs
- PG= prostaglandin products (PGG₂, PGH₂, PGD₂, PGE₂, PGI₂)

Suggested Reading

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