SAND2013-1572P

Veterinary Pharmacology

ANTI-INFLAMMATORY AGENTS

Sandia National Laboratories is a multi-program laboratory managed and operated by Sandia Corporation, a wholly owned subsidiary of Lockheed Martin Corporation, for the U.S. Department of Energy's National Nuclear Security Administration under contract DE-AC04-94AL85000.**SAND**

International
BIOLOGICAL THREAT REDUCTION

Anti-inflammatory Agents: Introduction

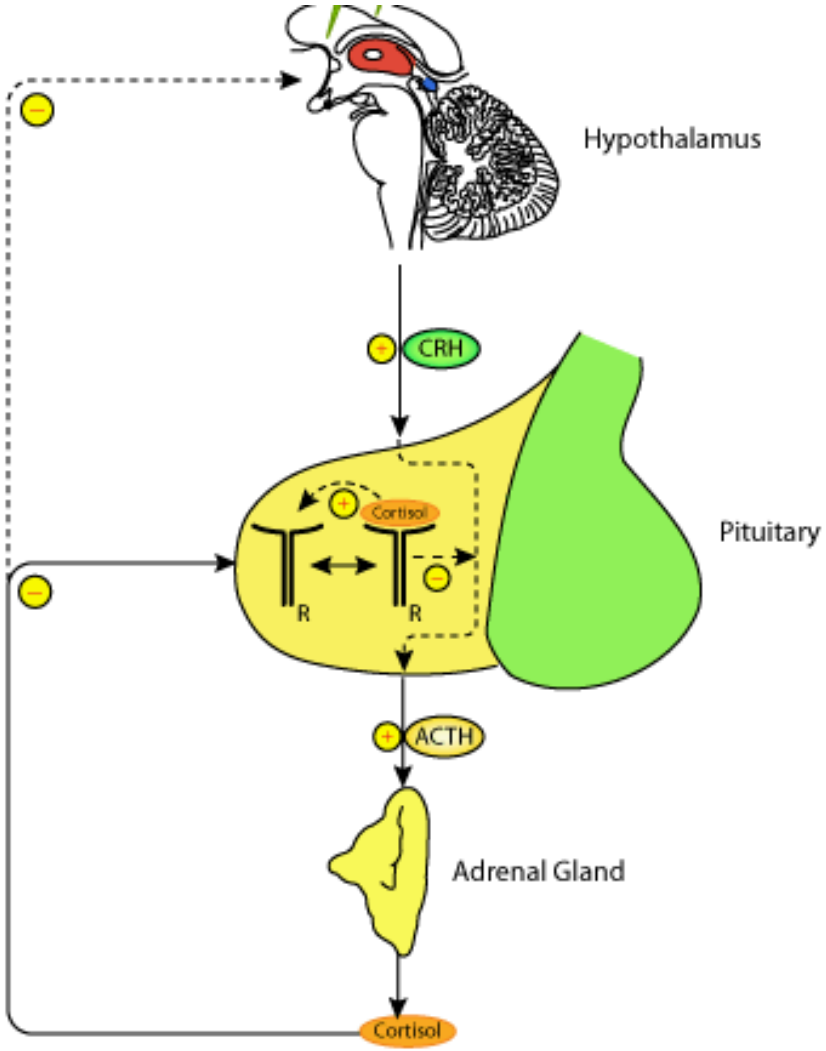
- **Anti-inflammatory agents are widely use in veterinary medicine and are characterized based on their mechanism of action**
  - Steroidal anti-inflammatory agents
    - **Corticosteroids**
  - Nonsteroidal anti-inflammatory agents
    - **Prostaglandin inhibitors**
      - Selective and nonselective prostaglandin inhibitors
    - **Leukotriene inhibitors**

- **New generation anti-inflammatory agents have been developed in recent years due to the adverse reactions caused by long term use**
  - Horses and dogs seem to be especially sensitive to the adverse effects of anti-inflammatory agents

Corticosteroids

- **Corticosteroids or glucocorticoids are produced by the adrenal glands in response to signals from the hypothalamus and pituitary gland**
  - Potent inhibitors of inflammation and are widely used in veterinary medicine to reduce the inflammatory response
  - Play significant roles in the metabolism of carbohydrates, proteins, and lipids
  - Increased in response to stress
  - Affect fluid and electrolyte balance
  - Modulate the immune response
    - **Increases in glucorticoids reduce the immune response by reducing the production of inflammatory mediators**
      - Inflammatory mediators regulate the immune response

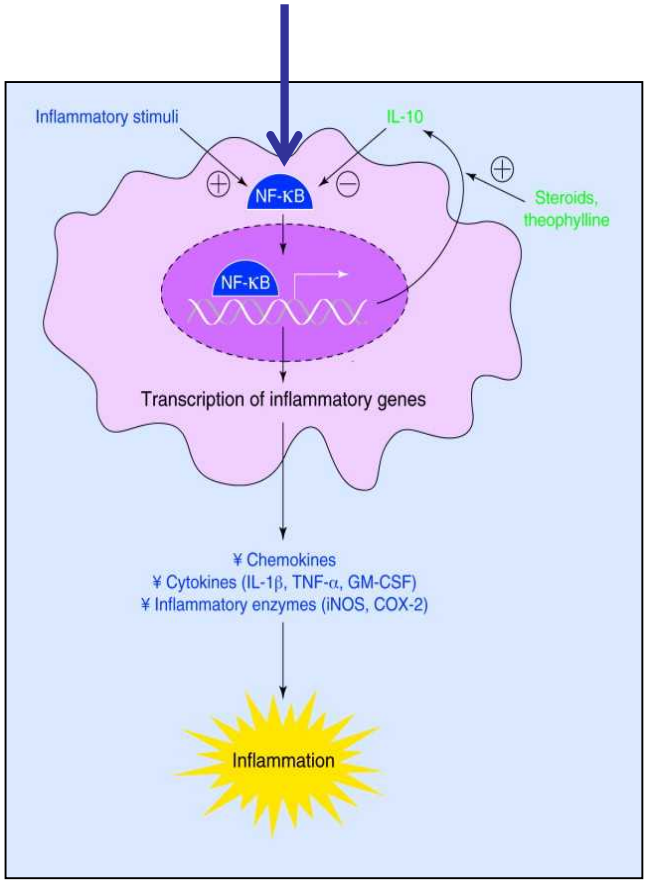
Production of Glucocorticoids



Corticosteroids: Anti-inflammatory Activity

- **Mechanism of action**
  - Corticosteroids act on inflammatory cells to inhibit the production of inflammatory mediators
    - **Corticosteroids bind to glucocorticoid receptors on the cell surface**
    - **Activation of the glucocorticoid receptor initiates a series of events leading to the inactivation of the gene transcription factor that encodes pro-inflammatory mediators**
    - **Reduced production inflammatory mediators that activate the immune response dramatically reduces inflammation**
      - Reduction is highly dose dependent

Steroids inhibit the activity of NF-kB



Corticosteroids

- **Absorption**
  - Many formulations of corticosteroids are available for use in animals and humans
    - **Orally administered formulations are not absorbed in ruminants**
    - **Ruminants can only be given injectable forms**
- **Distribution**
  - Corticosteroids are well distributed through the body
  - Effect of the drug is dependent on the formulation
- **Elimination**
  - Corticosteroids are metabolized by the liver and eliminated by the liver and kidneys

Corticosteroids

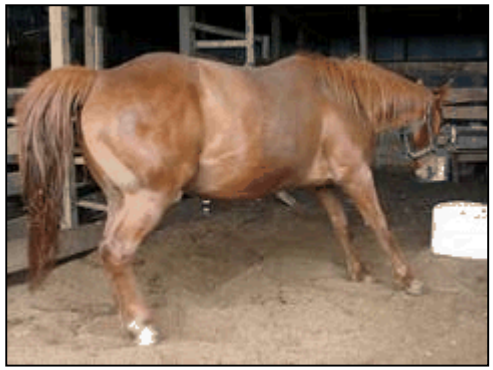
- **Potency**
  - Corticosteroid potency varies depending on the drug formulation
    - **Betamethasone is about 30 times more potent than cortisol**
      - Betamethasone is primarily used topically
    - **Dexamethasone is about 30 times more potent than cortisol**
    - **Prednisolone is about 4 times more potent than cortisol**
    - **Triamcinolone is about 5 times more potent than cortisol**
      - Mostly used topically or in ocular formulations to reduce inflammation of the eye or for intra-articular injections in horses

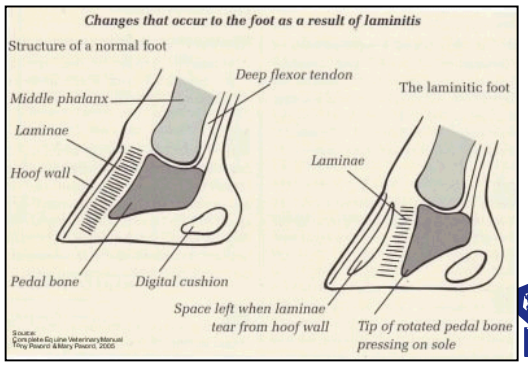
BEP

International
BIOLOGICAL THREAT REDUCTION

Corticosteroids

- **Precautionary information**
  - Adverse reactions and side effects
    - **Do not use in pregnant animals – can cause induction of parturition or abortions**
    - **Long-term use can result in polyphagia, polydipsia and polyuria**
    - **Gastric ulceration, delayed wound healing, diabetes, and weakened immunity can occur with long-term use**
    - **Corticosteroid use in horses can cause laminitis – must use corticosteroids with caution in horses**
    - **Use sparingly in animals with infectious diseases as immune suppression can worsen the course of disease**





Corticosteroids: Dexamethasone

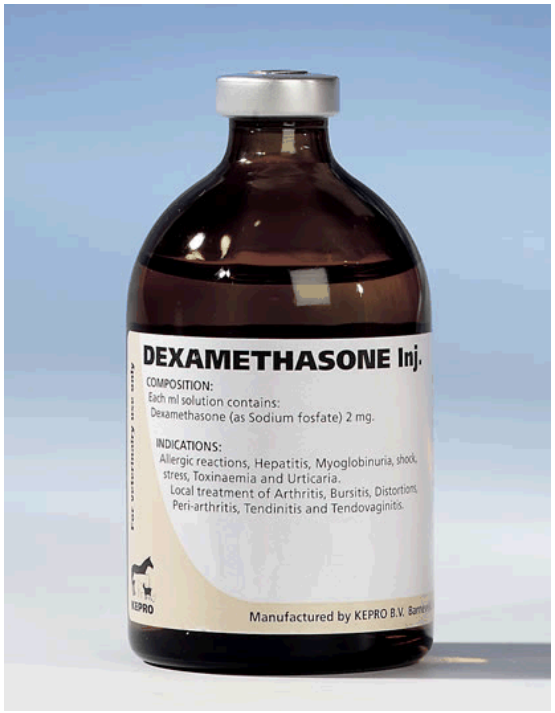
- **Clinical use**
  - Dexamethasone is used to reduce inflammation in large animals
    - **Infectious and allergic diseases**
  - Treat and test for endocrine disorders in small animals
  - Treat autoimmune and allergic disorders
  - Induce parturition in cattle – may enhance surfactant production in calves of near term cows
- **Formulations**
  - Dexamethasone sodium phosphate (4 mg/ml)
    - **The only injectable form that can be administered intravenously – it is water soluble**
  - Dexamethasone
    - **Injectable form (2 mg/ml) that can only be administered subcutaneously or intramuscularly – not for intravenous use because it contains propylene glycol**
    - **Oral tablets are available for use in small animals**

Dexamethasone

- **Dose**
  - Cattle and Horses
    - **0.04 – 0.15 mg/kg, given intramuscularly**
      - Dexamethasone sodium phosphate can be given intravenously at the same dose
      - Specific dose is based on clinical presentation
      - Chronic airway disease in horses: 0.05 – 0.1 mg/kg every 24 hours or 0.165 mg/kg orally every 24 hours for 2 – 3 days
      - Induction of parturition in cattle: 0.05 mg/kg (25 mg/animal) as a single dose during the last week of pregnancy
  - Sheep
    - **Induction of parturition: 0.15 mg/kg intramuscularly for 1 – 5 days during the last week of gestation**
- **Always use steroids with caution**
  - Immunosuppression
  - Laminitis in horses

Dexamethasone

- **Withdrawal times**
  - Withdrawal times have not been established in cattle
    - **Use 4 – 5 days for meat and 96 hours for milk**

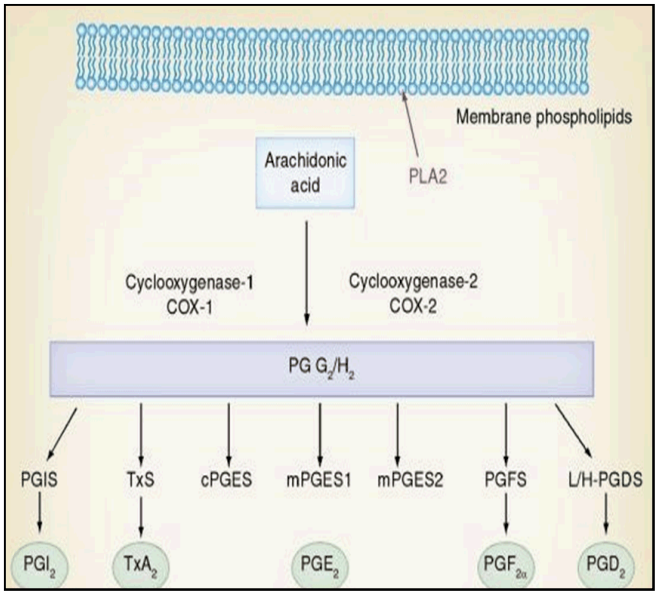


Nonsteroidal Anti-inflammatory Agents

- **Nonsteroidal anti-inflammatory agents act by inhibiting the production of prostaglandins**
  - Prostaglandins are produced from cell membranes
    - **Prostaglandin PGE_2, PGD_2, $PGF_{2\alpha}$, thromboxane, and prostacyclin**
  - Prostaglandins are important for normal cellular and physiological processes, and also for pathological processes including:
    - **Protection of the stomach lining**
    - **Maintenance of renal blood flow**
    - **Maintaining normal platelet function**
    - **Erosions of cartilage**
    - **Modulation of the inflammatory response**
  - Prostaglandin inhibition can reduce inflammation but at the same time disrupt normal physiological processes that are damaging to the patient

Nonsteroidal Anti-inflammatory Agents: Prostaglandin Production

- **Break down of cell membranes results in release of arachidonic acid**
- **Arachadonic acid is an intermediate in the cellular pathway that results in the production of prostanoids**
- **Cyclooxygenase-1 and cyclooxygenase-2 are enzymes that convert arachidonic acid into prostanoids**
  - Cyclooxygenase-1 is primarily involved in producing prostanoids that support normal physiological processes
  - Cyclooxygenase-2 is primarily involved in producing prostanoids that cause inflammation



Nonsteroidal Anti-inflammatory Agents: Mechanism of Action

- **Nonsteroidal anti-inflammatory agents act by inhibiting cyclooxygenase**
  - Older anti-inflammatory agents are not selective and inhibit both cyclooxygenase-1 (COX1) and cyclooxygenase-2 (COX2)
    - **Adverse affects such as gastric ulcers and kidney failure results because of inhibition of cyclooxygenase-1**
    - **COX1 and COX2 inhibitors include: aspirin, flunixin meglumine, ibuprofen, phenylbutazone**
  - New generation anti-inflammatory agents selectively inhibit cyclooxygenase-2
    - **Reduced adverse affects by maintaining the activity of cyclooxygenase-1**
    - **COX2 inhibitors: carprofen and meloxicam**
- **Horses and dogs are very susceptible to ulceration caused by use of nonselective cyclooxygenase inhibitors**
  - Gastric ulceration and renal failure are associated with adverse side effects associated with use

Nonsteroidal Anti-inflammatory Agents: Adverse Effects

- **Gastric ulcers**
  - COX1 is required for production of mucous and bicarbonate in the stomach, which protects the stomach lining from stomach acid
  - COX1 maintains blood flow to the stomach which supports the production of stomach bicarbonate and mucous
  - Inhibition of COX1 reduces the mechanisms in the stomach that are protective against the stomach acid
    - **Gastric ulcers result**
- **Renal failure**
  - COX1 maintains blood flow to the kidneys even during times of dehydration
    - **Renal tubular cells are very vulnerable to damage caused from reduced blood flow**
  - COX1 inhibition greatly reduces the body's ability to maintain blood flow to the kidneys, especially during times of dehydration
    - **When blood flow is reduced, renal tubular cells undergo necrosis**

Aspirin

- **Mechanism of action and use**
  - Aspirin is a nonselective inhibitor of cyclooxygenase
  - Used to treat inflammation and pain, also inhibits platelet aggregation
- **Absorption**
  - Aspirin is absorbed from the stomach of most species including ruminants
- **Formulations**
  - 81 mg, 325 mg, 3.9 gram, 15.6 gram, and 31.2 gram tablets and 240 grain boluses (1 grain = 65 mg)
- **Dose**
  - Dogs: 20 – 25 mg/kg, orally every 12 hours
  - Ruminants: 100 mg/kg, orally every 12 hours
  - Horses: 25 – 50 mg/kg orally every 12 hours
- **Withdrawal time**
  - 1 day for meat and 1 day for milk

Flunixin Meglumine

- **Mechanism of action**
  - Nonselective COX1 and COX2 inhibition
  - Treatment inflammation, pain, and inhibits some of the effects of endotoxin
    - **Treatment of signs caused by bronchopneumonia and colic**
- **Absorption**
  - Oral absorption occurs in horses and cattle, injectable is preferred in cattle
- **Formulation:**
  - Oral granules, paste, and injectable
- **Dose**
  - Dogs and cats: 1.1 mg/kg once intravenously, intramuscularly, or subcutaneously
  - Horses: 1.1 mg/kg every 24 hours for five days, can be given intravenously, intramuscularly, or orally
  - Cattle: 1.1 to 2.2 mg/kg once a day for 3 days, can be given intravenously or subcutaneously
    - **Is often given in combination with fluorfenicol**

Meloxicam

- **Mechanism of action and use**
  - Primarily inhibits COX2
  - Used to treat pain and fever in animals
- **Formulations**
  - 0.5 and 1.5 mg/ml oral suspensions, 5 mg/ml injection, and 7.5 and 15 mg tablets
- **Dose**
  - Dogs: 0.2 mg/kg initially and then 0.1 mg/kg once daily after the loading dose
  - Horses: 0.6 mg/kg every 24 hours, given orally or intravenously
  - Cattle: 0.5 mg/kg every 24 hours, given intramuscularly, intravenously, or subcutaneously
- **Withdrawal time**
  - Cattle: the recommended withdrawal time is15 days for meat and 5 days for milk

Phenylbutazone

- **Mechanism of action and use**
  - Inhibits COX1 and COX2
  - Primarily used to treat musculoskeletal pain
- **Formulation**
  - Oral tablets and paste and injectable form for intravenous use only
    - **Perivascular injections are severe – critical not get outside of the vein**
- **Dose**
  - Horses: 4.4 to 8.8 mg/kg every 24 hours orally or intravenously, should not exceed 3 days treatment
  - Cattle: 17 – 25 mg/kg loading dose, then 2.5 – 5 mg/kg every 24 hours or 10-14 mg/kg every 46 hours, can be given orally or intravenously
- **Withdrawal time**
  - Prohibited from use in female dairy cattle
  - Recommended meat withdrawal times are 50 - 55 days in cattle
    - **Has been associated with aplastic anemia in humans**