

Corticosteroid & Nonsteroidal Antiinflammatory Drug Interactions

Both corticosteroids and nonsteroidal antiinflammatory drugs (NSAIDs) are known to cause adverse effects in dogs and cats. The theoretical risk for toxicity is increased when these drugs are used concurrently and this practice is generally contraindicated.

However, corticosteroids and NSAID combinations may have additive therapeutic benefits when treating some disease conditions because they sequentially block the arachidonic acid cascade production of prostaglandins (PGs). This effect may be adverse, though, as PGs also benefit and protect the gastrointestinal (GI) tract, hemostasis, and renal function.

PATHOPHYSIOLOGY

The mucosa of the GI tract is regularly exposed to a wide range of potentially damaging substances, including those that are ingested (bones, drugs, etc) and endogenous secretions (gastric acid, bile salts). The GI mucosa is not only able to resist damage by these substances for the most part, but it has tremendous reparative capacity when damage does occur.

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CONTINUES

COX = cyclooxygenase; GI = gastrointestinal; NSAID = nonsteroidal antiinflammatory drug; PG = prostaglandin



Postmortem stomach specimen from a Great Dane that was administered 2 doses of naproxen shows multiple NSAID-induced mucosal erosions.

Courtesy Dr. Michael Schaer

mucosa defense and repair, with COX-1-derived PGs supporting mucosal blood flow, mucus and bicarbonate secretion, and normal platelet aggregation, while COX-2-derived PGs modulate the inflammatory response so that normal healing can occur. Hemostasis is highly influenced by PGs, with platelet aggregation and vasoconstriction promoted by platelet-derived thromboxane A₂ and inhibition of platelet aggregation and vasodilation promoted by endothelium-derived prostacyclin. Renal PGs help maintain normal blood flow and glomerular filtration rate (GFR).

There are significant interspecies differences in the presence and distribution of COX isoforms. In dogs, both COX isoforms have major roles in normal renal function, with COX-1 expressed at high levels in the collecting ducts and renal vasculature, and basal levels of COX-2 present in the maculae densa, thick ascending limbs, and papillary interstitial cells. COX-2 expression is markedly increased in volume-depleted dogs.¹

Currently, there is no published information regarding the distribution of COX isoforms in the cat, but clinical experience suggests that they are more susceptible to drug-induced nephrotoxicity than dogs.

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GASTROINTESTINAL COMPLICATIONS

Corticosteroids

- Corticosteroids are known to induce GI ulceration and hemorrhage in dogs.²⁻⁵ It is thought that ulceration is caused by blockage of PG synthesis at the level of phospholipase A.
- Corticosteroids also inhibit ulcer healing by altering gastric mucous composition, decreasing the rate of mucosal cell turnover, reducing capillary and fibroblast proliferation, and enhancing collagen breakdown.

NSAIDs

- Through PG inhibition, NSAIDs reduce mucus and bicarbonate secretion, increase gastric acid secretion, and reduce mucosal blood flow.
- NSAIDs also trigger an increase in adhesion of leukocytes to the vascular endothelium in the GI microcirculation, which is an early and critical event in the pathogenesis of NSAID-induced mucosal ulceration.⁶
- NSAID-induced GI bleeding is increased by NSAIDs that have COX-1 activity, which reduces platelet aggregation.

Corticosteroids + NSAIDs

- Retrospective studies have associated the concurrent use of corticosteroids and NSAIDs with GI ulceration and perforation in dogs and cats.^{7,8} Concurrent administration of an

immunosuppressive dose of prednisone and ultralow-dose aspirin in healthy dogs increased the frequency of mild, self-limiting diarrhea but did not increase the severity of GI lesions compared with prednisone alone or placebo.⁵

- In a study comparing concurrent administration of ketoprofen (a COX-1 selective NSAID) and prednisolone with meloxicam (a COX-2 selective NSAID) and prednisolone, the ketoprofen-treated dogs had significantly more severe GI lesions compared with the meloxicam-treated dogs or untreated controls. All ketoprofen-treated dogs had positive fecal occult blood tests, but only 1 meloxicam-treated dog had a positive test.⁹
- In a comparison of the effects of flunixin and flunixin plus prednisone on the GI tract of dogs, dogs given prednisone and flunixin developed GI lesions more rapidly and lesions were more severe than those in dogs given flunixin alone.¹⁰

Complications of GI ulceration include intraluminal hemorrhage, ulcer perforation, and stenosis of affected areas. Perforation and septic peritonitis are the most common life-threatening sequelae of GI ulcers in dogs and cats.⁷

HEMOSTATIC & RENAL COMPLICATIONS

Little is known about the adverse hemostatic or renal effects of corticosteroid/NSAID combination therapy.

- In dogs, the combination of ketoprofen and prednisolone caused significant decreases in GFR and renal plasma flow, hyperalbuminuria, an increased urine albumin:creatinine ratio, and enzymuria with exfoliation of renal tubular epithelial cells.
- Some abnormal enzymuria and exfoliation of renal tubular epithelial cells were seen in dogs receiving meloxicam and prednisolone, but no other indications of renal dysfunction were documented.
- The combination of meloxicam and prednisolone did not cause demonstrable changes in bleeding times, while the ketoprofen/prednisolone combination caused greatly prolonged mucosal and cuticular bleeding times with no effect on measures of secondary hemostasis

(prothrombin time, activated partial thromboplastin time, fibrinogen concentration).⁹

PREVENTION OF COMPLICATIONS


Currently there is insufficient evidence to recommend prophylactic gastroprotective drugs in all dogs or cats receiving NSAIDs and/or corticosteroids, but prophylactic therapy may be warranted in patients that are at risk for GI ulcers and receiving both types of drugs.

- Prophylactic administration of misoprostol (a PG analogue), histamine-2 receptor antagonists (eg, cimetidine, ranitidine, or famotidine) and proton pump inhibitors (eg, omeprazole, pantoprazole) has been evaluated in humans and dogs.
- In a study of healthy dogs, famotidine, pantoprazole, and omeprazole significantly suppressed gastric acid secretion, but only twice daily administration of a suspension of omeprazole met the criteria for therapeutic efficacy for acid-related disease as assessed in human patients.¹¹
- Misoprostol has shown efficacy in preventing aspirin-induced gastric mucosal ulceration in dogs.¹² However, in dogs with intervertebral disk disease treated with dexamethasone, neither omeprazole nor misoprostol was effective in healing or preventing the further development of gastric ulcers.¹³
- In dogs undergoing spinal surgery that received methylprednisolone sodium succinate, neither cimetidine, sucralfate, nor misoprostol reduced postoperative GI bleeding.^{3,4}

TREATMENT OF COMPLICATIONS

Treatment of GI toxicity is intensive and mainly symptomatic. Anorexia and/or vomiting are frequently the first indication of GI ulceration and perforation. Any dog or cat that becomes anorectic or vomits while on combination NSAID and corticosteroid therapy should be promptly evaluated by a veterinarian.

- **Vomiting & Diarrhea:** Fluid and electrolyte losses from vomiting or diarrhea are managed with commercially available intravenous fluids.
- **Hemostasis Complications:** Blood transfusions are necessary in patients with hemostatic complications.



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CONTINUES



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- **Hypoproteinemia:** Hypoproteinemia that results from loss of plasma proteins into the ulcerated GI tract can be corrected with intravenous infusions of plasma.
- **Renal Failure:** The general principles of managing drug-induced renal failure include treatment of life-threatening features, such as shock, respiratory failure, hyper-

kalemia, pulmonary edema, metabolic acidosis, and sepsis. Further administration of nephrotoxic drugs should be avoided and drug dosages should be adjusted as appropriate for the patient's GFR.

- **Peritonitis & Bacterial Septicemia:** Broad-spectrum antimicrobials are indicated when there is evidence of peritonitis or bacterial septicemia.
- **Pain:** Pain must be managed with opioid analgesics.
- **GI Perforation:** If GI perforation is suspected or diagnosed based on abdominal fluid cytology, abdominal radiography or ultrasound, or endoscopy, prompt surgical exploration and correction are necessary. Open abdominal drainage may be necessary as well.⁷ Even with prompt surgical correction, GI perforation has a high mortality rate.
- **GI Ulcers:** Antiulcer medications may be beneficial and speed healing of GI ulcers.
 - The clinical "efficacy" of antiulcer drugs is typically evaluated by comparing endoscopically detectable mucosal damage and ulcers in treated patients control animals. However, a true ulcer is deep enough to reach or penetrate the muscularis mucosa, which cannot be measured endoscopically. The NSAID-induced endoscopic "ulcers" seen in these studies may not be relevant, as clinically significant GI hemorrhage is rarely seen in humans or dogs with these lesions.¹⁴

- Currently, there are limited efficacy data on these drugs in dogs and none of the antiulcer drugs has been evaluated in cats.
- In humans, proton pump inhibitors are preferred for healing and prevention of GI ulcers in patients taking both traditional NSAIDs and selective coxibs, and who have risk factors associated with more frequent or severe GI complications, including patients with previous ulcers, the elderly, and those receiving concomitant corticosteroids or anticoagulants.¹⁵
- Omeprazole, sucralfate, and misoprostol are limited to oral formulations, which are not feasible in actively vomiting patients or if GI perforation is likely.
- H2-blockers and pantoprazole are available in injectable formulations.

SUMMARY

It is very difficult to predict which corticosteroid/NSAID combinations (drug formulation, dose, dosing frequency, treatment duration) will result in adverse effects in any individual patient. Therefore, concurrent therapy should only be done when medically necessary and with close and careful patient monitoring. Further evaluation in dogs and cats is needed, but proton pump inhibitor drugs, such as omeprazole, appear to be the best choice for pharmacotherapy of GI ulceration because their effects are therapeutic as well as prophylactic. Management of adverse hemostatic and renal effects is mainly supportive.

See Aids & Resources, back page, for references & suggested reading.

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