

Glucocorticoids +/- NSAIDs: Why, Why Not, and Washout

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In this presentation, we will review possible answers to the question: Is a “Washout” period between NSAIDs or NSAIDs and glucocorticoids medically justifiable, and documented by good evidence?

About the time that the first “COX2” inhibitor carprofen (Rimadyl™) was being marketed to veterinarians, followed by deracoxib (Derramax™), promotional material published by drug companies has advocated washout times for nonsteroidal anti-inflammatory drugs (NSAIDs). The instructions included: “Consider appropriate washout times when switching from one NSAID to another or when switching from corticosteroid use to NSAID use. Only one brand of NSAID should be administered to a dog at any given time. If at some time the owner and the veterinarian decide to try a different NSAID, a wash-out period is recommended. A wash-out period is a few days long, during which the dog does not receive any NSAID. Then the dog can be switched to another NSAID. NSAIDs should not be combined with the use of a corticosteroid, either”(1). In this presentation, we will evaluate the evidence for these statements, and seek to arrive at recommendations that will maximize efficacy for and safety of your patients.

NSAIDs approved in dogs

First generation

- Aspirin –not approved as mono-product, only in combination with a glucocorticoid
- Phenylbutazone - US approval 1974
- Meclofenamic acid - US approval 1996 (no longer marketed)

Second generation

- Carprofen (Rimadyl™) - US approval 1997; Novox (generic))
- Etodolac (Etoogesic™) - US approval 1998
- Deracoxib (Deramaxx™) - US Approval 2002
- Meloxicam (Metacam™) - US approval, 2003
- Tepoxalin (Zubrin™) - 2003, removed 2012
- Firocoxib (Previcox™) - 2007

Debate point 1

“Washout” was a term introduced by pharmaceutical companies that developed the first veterinary-approved NSAIDs in response to inevitable side effects of this class of drugs. The concept has gained support primarily through discussions on internet sites, FDA-approved labels, and NSAID promotions by sponsors at conferences, without any convincing scientific evidence for support. Looking at the history of the post-marketing period for carprofen (Rimadyl™), As the FDA/CVM began to document side-effects, they requested Pfizer change the Rimadyl™ package insert to list adverse drug reactions. Pfizer complied in May of 1997, only five months after the drug was first introduced. Pfizer also mailed a ‘Dear Doctor’ letter to veterinarians that outlined the latest information available, and subsequently made several additional changes to the Rimadyl™ package insert. (2) Of all the adverse drug effect (ADE) reports the Center of Veterinary Medicine (CMV) received in 1998, 39% or 3626 involved Rimadyl®. The number of ADE reports received by CVM for Rimadyl® was considerably more than that received for any other animal drug. For any one ADE report, there is no absolute certainty that the suspected drug caused the effect. The adverse effects in these reports are consistent with those expected for NSAIDs. They typically involve the gastrointestinal system, renal/urinary system, hematopoietic (blood) system, neurological system, and the liver. Approximately 13% of the 1998 Rimadyl® ADE reports for dogs involved death of the dog, either on their own or by means of euthanasia (3).

Debate counterpoint 1: Adverse effects of NSAIDs can be serious

The concern from owners and veterinarians appeared to prompt another letter to veterinarians from Pfizer in 2000 about Rimadyl™. It pointed out that the incidence of reported possible adverse drug events in 1998 was approximately 0.2%. In addition, it noted, “Some of these side effects, like those of many other NSAID-class medications, may occur without warning and, in rare situations, may be serious, resulting in hospitalization or even death.” It is definitely true that gastrointestinal tract perforation can occur in dogs treated with a selective COX-2 inhibitor. A retrospective study of 29 cases between 2002-2003 in the Novartis Animal Health pharmacovigilance database, evaluated dogs treated with the approved dosage of deracoxib for chronic pain (1-2 mg/kg/day), for acute (post-operative) pain (3-4 mg/kg/day) for a maximum of 7 days. In these cases, 20 dogs died or were euthanatized and 9 survived due to GI perforations. The authors stated that there was an unclear correlation between deracoxib and the induction of GI ulceration. The manuscript discussion went on to state, “Deracoxib should be used at approved dosages and corticosteroids and other NSAIDs should not be administered at close temporal association with deracoxib and possibly with other selective COX-2 inhibitors” (4). While the

recommendation seemed prudent, the study did not specifically evaluate the issue addressed by this summary statement. Nonetheless, veterinarians received a letter from Novartis in 2003, "It should be noted that many of the side effects associated with Deramaxx™ administration occurred in cases in which dogs were also receiving corticosteroids or other NSAIDs....Observe appropriate washout periods when switching from one NSAID to another or when following corticosteroid use with NSAID therapy. The length of the washout period will vary, depending upon the patient's condition and other drugs involved." Following these notes of caution, one study did not find a difference in signs of toxicity when injectable carprofen was followed with either oral carprofen or oral deracoxib. Nonetheless, it was stated in the conclusion to the manuscript: "In general, veterinarians are advised to discontinue an NSAID for 24 hour to 7 days before initiating administration of a second NSAID." (5). While there are reasons to be concerned that the pharmacological effects of NSAIDs will impair normal mucus production, bicarbonate secretion, and maintenance of gastric mucosal blood flow, leading to ulcerogenic conditions in the g.i. tract, there was no evidence that the switchover from one NSAID to another would have additionally detrimental effects.

Point 2: There is no correlation between safety and pharmacokinetic half-lives of NSAIDs

Unapproved NSAIDs such as ibuprofen and indomethacin predictably produce toxicity in dogs even though they have short half-lives. Piroxicam has a long half-life of approximately 40 hours, but has been administered to dogs with relative safety when recommended dosing protocols are used. Among the small animal NSAIDs, half-lives do not correlate with the frequency of administration. Most NSAIDs are given once a day, but half-lives vary widely from 3 hours for deracoxib, to 8 hours for firocoxib and carprofen, and 20 hours for meloxicam. Anti-inflammatory and analgesic effects, and toxic effects, persist longer than the plasma half-lives predict (6,7,8). Indeed, NSAIDs persist longer in inflamed tissues (9). Because the pharmacologic effects may persist longer than predicted by the half-life, is a washout period between treatments warranted?

Point 3: Huge study not supporting a washout time for NSAIDs in dogs

In a study in 2007, "COX-1 sparing" firocoxib was administered to dogs after a wash-out period ranging from 1 day to 5 days. After analysis of 1,000 patients, there was no increased risk from switching from another NSAID to firocoxib within 7 days compared to a longer washout period. The washout time within a 7 day period varied from 0-7 days with most >2 days. Furthermore, there was no observed risk when switching from one NSAID to another within one week, compared to administration of an NSAID without any previous treatment (10).

Counterpoint 3: A COX1/2 inhibitor followed by a selective COX-2 Inhibitor DOES enhance GI risk: Selective inhibition of COX-1 or COX-2 does not result in significant gastric damage. Aspirin, a COX1/2 inhibitor, suppresses PG synthesis and inhibits the synthesis of gastroprotective prostaglandins via both COX-1 and COX-2, thereby impairing mucosal defense mechanisms and leading to hemorrhagic erosion formation. Aspirin triggers the cyclooxygenase-2-dependent synthesis of 15(R)-epi-lipoxin A4 also known as aspirin-triggered lipoxin (ATL), a substance that acts to diminish injury to the stomach. The generation of by COX-2, which partially counteracts the detrimental effects of PG suppression. Inhibition of COX-2 activity by a selective COX-2 inhibitor or a conventional non-steroidal antiinflammatory drug (NSAID) removes the formation of ATL by aspirin. In the absence of the protective effects of ATL, the extent of gastric damage is increased. Therefore, co-administration of aspirin and a selective cyclooxygenase 2 inhibitor results in more gastric damage than that induced following administration of either drug alone (11). There is indirect evidence that ATL develops in the dog: older studies have shown that after 1-2 weeks of aspirin, g.i. lesions resolved despite continued administration. High doses of aspirin may over-ride the process of adaptation. When dogs received aspirin at a high dose of 25 mg/kg every 8 hours, there was no evidence of adaptation as the lesions were as severe or worse on day 28 compared to earlier in the study (15).

Point 4

The evidence is insufficient and conflicting about NSAIDs other than aspirin: In one study, gastrointestinal lesions from administration of deracoxib and carprofen were worse early in the course of treatment (day 2), but improved by day 5. Furthermore, on day 1 of a crossover study, lesions were observed, despite a 16 day washout time designed to allow recovery of the previous crossover in the preceding weeks of the study. The investigators of this study suggested that sequential NSAID administration may exert long-term effects and requires further study (5). In another study, evidence for long-term adverse effects after 2 months of treatment was not observed, and there was evidence of g.i. adaptation (16).

Counterpoint 4: Glucocorticoids and/or then NSAIDs is a bad idea

It has also been recommended that a washout time is necessary between corticosteroid treatment and NSAID administration. These recommendations arise from studies of concurrent treatment with an NSAID and a corticosteroid showing exacerbation of g.i. lesions (17,18). Another study of 2 flunixin dosages (1.1 or 2.2 mg/kg q12h IM) or 1.1 mg/kg flunixin plus prednisone (0.55 mg/kg q12h po) showed gastric mucosal lesions visible via endoscopy within 4 days of initiating therapy in all treated dogs. All the treated dogs had occult blood in their feces by day 5. However, the flunixin+prednisone groups developed the earliest and most severe lesions (5). Another study evaluated healthy dogs treated for 30 days with meloxicam (0.1 mg/kg) and prednisolone (0.5 mg/kg) (MP), ketoprofen

(0.25 mg/kg) and prednisolone (0.5 mg/kg) (KP) compared to normal control (NC) animals. Severe grades of endoscopic lesions and fecal occult blood were observed in the KP group with clinical signs of anorexia, vomiting, diarrhea or melena. The MP group also developed some invasive erosions, but there was no significant difference between the dogs in MP and NC groups. (19). A similar study of simultaneous administration of meloxicam and dexamethasone in healthy dogs. The total endoscopic score of dexamethasone-meloxicam group was significantly greater than the other groups scores. Meloxicam alone seemed safe on GI tract (similar to saline group). Dexamethasone alone causes GI lesions, and the effect was significantly increased with the addition of meloxicam (17). Therefore, even in healthy dogs, concurrent administration of NSAIDs with corticosteroids may be contraindicated, even if the NSAID is a COX-2 selective.

Point 5: Inconsistent and imprudent use of NSAIDs and glucocorticoids

Interestingly, aspirin is not approved as a mono-drug product for dogs. However, a combination of 0.5 mg methylprednisolone/300 mg of aspirin (Cortaba™, Pfizer) has been approved, and used for years. In response to Counterpoint 4, the 0.5 mg/kg per day dexamethasone dosage used in the study above was much higher than a typical anti-inflammatory dose and the NSAID used, and flunixin is inherently ulcerogenic in dogs. A washout time between corticosteroid and NSAID therapy has not been established and it is not known if one is needed when low-dose anti-inflammatory doses of a corticosteroid is administered with an NSAID that has a good safety profile in dogs. A retrospective clinical report described g.i. lesions in dogs associated with administration of deracoxib. Many of the dogs had severe ulceration and had received either a high dose, concurrent treatment with a corticosteroid, or another NSAID in close temporal association with deracoxib (4). However, the NSAID therapy reported in that study was variable and consisted of different drugs and doses, making it difficult to determine whether or not these dogs were predisposed to NSAID-induced injury, or if the NSAID therapy compounded the toxicity from deracoxib.

Point 6: Wean, don't "washout" glucocorticoids

When deciding to remove an animal from glucocorticoids, the HPA suppressive action of glucocorticoids should be remembered: wean, don't "washout" an cold turkey from glucocorticoids, or there is the potential to cause gastrointestinal signs including vomiting, diarrhea and melena due to iatrogenic hypoadrenocorticism.

Recommendations based upon best evidence

If a COX2 inhibiting drug follows a gastroduodenal injury or ulcerogenic NSAID, there may be increased risk of delayed healing and further injury because of the beneficial role of COX-2 in the gastrointestinal mucosa for injury repair and mucosal protection. Most agree that washout following aspirin is a unique situation, due in part to the phenomena of Aspirin Triggered Lipoxin (ATL). The issue of "washing out" between NSAIDs is poorly researched and requires further careful evaluation. Five to seven days washout following aspirin is probably adequate. If adverse effects have occurred such as g.i. ulceration, a minimal washout time should be no less than the time required to recover from those adverse effects. Extra caution seems appropriate when switching between a COX-nonspecific inhibitor or glucocorticoid, and a COX-2 inhibitor. Finally, be sure to consider endocrine effects of glucocorticoids and wean, do not remove precipitously. When serious pain management is needed between NSAIDs, consider other agents: e.g. gabapentin, fentanyl, codeine, or tramadol.

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