Non-Steroidal Anti-Inflammatory Drug Toxicity in Dogs

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INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are a classification of drugs other than steroids that suppress substances produced during an inflammatory response. NSAIDs are widely used in both human and veterinary medicine for their anti-pyretic, anti-inflammatory, and analgesic benefits. Prescription and over-the-counter NSAID usage account for approximately 30 billion doses consumed by humans in the United States each year. [1,2] As such, it is no surprise that NSAID ingestion by animals, particularly dogs – whether dosed by dog owners or inadvertently consumed by dogs – results in a high number of reported cases of dogs presenting adverse effects. [3] The ASPCA Animal Poison Control Center hotline compiles an annual list of the top toxins most commonly ingested by pets. Human medications, both prescription and over-the-counter, are the most common reason for animal poison-related emergencies with ibuprofen, aspirin and other NSAID consumption producing more calls to animal poison control than any other drug. [6]

Acetaminophen (Tylenol) is one of the most popular human analgesic and anti-pyretic drugs in the world and is regularly reported to poison control centers for accidental consumption by dogs. Although it is commonly prescribed to relieve pain and reduce fever, it produces very little anti-inflammatory activity and is therefore not classified as NSAID. [4,5] Therefore, it will not be covered in this review, but it is important to recognize that it is used to produce similar therapeutic benefits and it has widespread availability in both veterinary and human medicine.

Although FDA-approved NSAIDs have been shown to be safe and effective when used according to the label, every drug is capable of producing an undesired effect. The FDA Center for Veterinary Medicine maintains a cumulative database of adverse drug reactions, which is defined by either an undesired side effect or a drug's lack of effect. NSAIDs are so widely used

today in the management of analgesia that they account for largest absolute number adverse drug events reported, with the gastrointestinal tract, renal, and hepatic adverse effects being the most commonly reported. [7]

HISTORY AND PRESENTATION

Dogs are exposed to NSAIDs for a number of different reasons, but typically it is due to accidental exposure or inappropriate administration. The most commonly reported clinical signs of NSAID toxicity in dogs are associated with gastrointestinal complications that range from vomiting, hematemesis, diarrhea, melena, hematochezia, inappetence, lethargy, depression, weakness, and possible abdominal pain. As the dose increases more severe sequelae can occur and include acute renal failure, severe central nervous system (CNS) depression, and hyperkalemia. [9] Idiosyncratic adverse effects that are independent of the exposed dose, such as hepatic failure, can also occur.

PATHOPHYSIOLOGY

NSAIDs are primarily absorbed in the stomach and proximal small intestines. In the intestines, they undergo enterohepatic recirculation whereby bile salts excreted by the liver are absorbed by the intestinal mucosa and returned to the liver through the portal vein. [1,3,9,10,11,12,14,21,23,24] Once absorbed, most NSAIDs have a high affinity for binding to plasma proteins, primarily albumin. As the albumin binding sites are saturated, the volume of the unbound and biologically active form of the drug increases.

NSAIDs are metabolized in the liver, with their metabolites filtered and eliminated by the kidneys, excreted via bile or feces, or a combination of both. [10,11] The major mechanism of conjugation is with glucuronic acid. [10,13] NSAIDs are eliminated from the body at various rates, with some completing elimination within a few hours and others, like naproxen, taking up

to 74 hours. [11] Neonates and animals with a renal or hepatic disease have a slower rate of elimination and an increased risk of toxic levels accumulating.

Although many mechanisms of action exist, most NSAIDs inhibit the cyclooxygenase (COX) enzyme system from converting arachidonic acid into prostaglandins (PG). To date, there have been three distinct cyclooxygenase isoenzymes (COX-1, -2 and-3) discovered. Cyclooxygenase-1, considered the endogenous form, is responsible for synthesizing prostaglandins that regulate normal cell activity ranging from repairing gastrointestinal epithelial cells, to stimulating the secretion of bicarbonate, and influencing the movement of water and electrolytes into the small intestine. [11] Cyclooxygenase-2, can be induced during inflammatory states and is involved in the recruitment of inflammatory mediators at the site of trauma, inflammation, or cellular damage. [14] However, COX-2 is also expressed in and is necessary for normal function of gastrointestinal, neural, reproductive, and renal tissues. [15] Cyclooxygenase-3 was originally thought to be a unique isomer, but it is now believed to be a subset of COX-1 and expressed primarily in the cerebral cortex of canines. [5]

The inhibition of COX-1 is associated with adverse side effects, including GI ulceration and kidney damage. Many newer NSAIDs directly inhibit COX-2 to decrease inflammation, while sparing COX-1 inhibition or minimally inhibiting it. Drugs that selectively inhibit COX-3, like acetaminophen, decrease pain and fever, but do not have anti-inflammatory activity. [5]

Aspirin has unique features that not only work by inhibiting COX-1 and COX-2 but also prevent the action of thromboxane, which is necessary for platelet aggregation in primary coagulation. Toxic amounts of aspirin result in undesired coagulopathies due to acquired thrombocytopenia.

Galliprant, a piprant class drug, is the latest veterinary approved NSAID that is the first non-COX-inhibiting prostaglandin receptor antagonist. Galliprant inhibits the prostaglandin receptor, EP4, which has been identified as the primary prostaglandin involved in osteoarthritis pain and inflammation. Since it does not produce inhibition of the COX enzymatic activity, it is not believed to disturb the endogenous prostaglandin activity that maintains homeostatic functions in the gastrointestinal tract. [16]

Gastrointestinal Adverse Effects

Gastrointestinal toxicity is a result of two mechanisms: direct irritation of the gastrointestinal mucosa and the inhibition of endogenous prostaglandin activity. Local effects are associated with the physical properties of NSAIDs. Most NSAIDs are slightly acidic and may become concentrated in the gastric mucosa through a process known as ion trapping, which can lead to direct cellular injury and ulceration. Aspirin is especially known to produce gastric ulceration. [10,11]

Systemic effects are thought to be associated with the inhibition of endogenous PG production. Decreased PG production can result in decreased mucin quality and bicarbonate content of the mucous gel layer, making the mucosa more vulnerable to acid-induced injury. NSAIDs may also cause areas of reduced blood flow within the mucosa by inhibiting endogenous PGs that have a vasodilatory effect. [3]

Renal Adverse Effects

In healthy animals, therapeutically dosed and administered NSAIDs produce minimal indirect nephrotoxic effects. Reported cases of toxicity occurred when high doses were used or when there were other complicating factors. At excessively high doses, drug accumulation has been reported to cause direct nephrotoxic effects resulting in acute kidney injury, interstitial

nephritis, and renal papillary necrosis. [17] Acute kidney injury generally occurred 36 hours or more after exposure, whereas GI signs occurred within a few hours. [18]

Renal injury occurs as a result of inhibition of renal prostaglandin production of PGE2 and PGI2. These prostaglandins cause afferent arteriolar dilation, which in turn helps maintain renal blood flow, counteracting the effect of systemic vasoconstrictors such as vasopressin, angiotensin, and norepinephrine. Clinically, important adverse renal effects of NSAIDs are primarily the result of decreased PG production.

The use of NSAIDs in the presence of hemodynamic compromise prevents the vasodilatory effects of PG to maintain renal blood flow and glomerular filtration rate when vasoconstrictors are released systemically to maintain blood pressure. This results in ischemic injury of the kidneys, which may progress to acute renal failure. [14]

NSAIDs most commonly affect the proximal tubules, although the collecting ducts may also be susceptible to NSAID-induced nephrotoxicity. [19] The mechanism is unclear, but long-term NSAID exposure may cause toxicity to the collecting ducts through either increased osmolality of the tubular fluid or further decreases to the already scant medullary blood flow. [20]

Liver Adverse Effects

Hepatotoxicity is uncommon and considered idiopathic for most NSAIDs. Aspirin and carprofen have been reported to have dose dependent intrinsic hepatotoxic reactions, but they are considered uncommon to rare. [8,21,22]

DIAGNOSTIC APPROACH

The diagnostic approach to managing NSAID toxicity may vary greatly based on the dosage consumed and the amount of time passed since consumption. Every case of suspected

(inappropriate) NSAID ingestion should include a complete blood count, chemistry panel and urinalysis. Depending on the nature of the toxicosis, laboratory results may or may not be within normal reference ranges.

Certain diagnostic abnormalities identify the presence and extent of NSAID toxicosis. Increased blood urea nitrogen (especially with normal creatinine and concentrated urine) with or without low serum proteins and an anemia support the diagnosis of gastrointestinal blood loss. Leukocytosis, with or without a left shift, may indicate a gastrointestinal perforation and peritonitis. Azotemia with isosthenuria indicates renal toxicosis. Unfortunately, normal laboratory values do not rule out NSAID toxicosis due to the timing of ingestion or nature of the injury.

If gastric ulceration is suspected, then it is prudent to consider imaging and other hemodynamic diagnostic procedures. Anemia and coagulation disorders should be monitored with reticulocyte counts, coagulation profiles, platelet counts, and bleeding time tests. Gastrointestinal imaging by ultrasound is a quick, non-invasive way to examine the stomach and proximal duodenum for evidence of ulceration. Abdominal radiographs often reveal poor visualization of serosal surfaces; however, they may be helpful to identify free gas or fluid in the peritoneal cavity. Endoscopy is the most accurate diagnostic procedure for detecting gastroduodenal ulcers, but not always clinically necessary. Because anesthesia is required to perform this endoscopic procedure, patients need to be hemodynamically stable to avoid ischemic injury of the kidneys, which may escalate to acute kidney injury. [23] While a definitive diagnosis using serum NSAID concentrations confirms absorption following an unknown exposure or ingested dose, it is not commonly performed. [24]

TREATMENT AND MANAGEMENT OPTIONS

The goals of treatment of acute NSAID overdose include aggressive decontamination, supportive care, GI protection, and monitoring of renal function.

Decontamination typically includes the induction of emesis and the administration of activated charcoal. Emesis should be induced with apomorphine or 3% hydrogen peroxide in asymptomatic dogs presenting without clinical signs of toxicosis. Apomorphine can be administered intravenously, intramuscularly or topically on the conjunctival sac of the eye, while hydrogen peroxide should be administered orally. Emesis is most effective within few hours of exposure. If emesis cannot be induced due to the presence of neurologic signs, such as coma or seizures, then gastric lavage should be considered. Once gastric contents have been evacuated, an anti-emetic, such as maropitant, should be administered. Activated charcoal should be administered to bind and limit absorption of NSAIDs from the GI tract. Since many NSAIDs are known to undergo enterohepatic recirculation, multiple doses (2–6 doses) of activated charcoal administered every 6 to 8 hours may be needed. [24] However, a recent study concluded that a single dose of charcoal was just as effective as multiple doses in reducing carprofen concentration in the blood. [28] Since this study only evaluated carprofen, additional research on other NSAIDs is still needed.

In order to prevent or treat gastrointestinal irritation or ulceration, gastrointestinal protectants are indicated and include proton pump inhibitors, such as omeprazole or pantoprazole, or histamine blockers, such as famotidine or ranitidine. Additionally, sucralfate is commonly administered to cover over and bind to existing ulcerations. Another gastroprotectant that is indicated is misoprostol, a synthetic prostaglandin analogue, to prevent GI ulcers. The use of broad-spectrum antibiotics is not routinely indicated and only required in cases where a

perforated ulcer produces peritonitis. Surgery may be indicated in severe cases of a perforated ulcer.

Fluid therapy is vital for toxin excretion and to prevent the nephrotoxic effects of NSAID consumption. Diuretic rates of twice the patient's maintenance requirement (or higher) for 48 to 96 hours are recommended. The length of fluid therapy ultimately depends on the dose and type of NSAID consumed, and if acute kidney injury (AKI) is present at the time of presentation. Acute kidney injury (AKI) is a term used to describe a loss of renal function that has the potential to cause permanent renal damage or failure. [29]

Clinically there are many indicators used to determine renal function which include creatinine, urea, urine protein:creatinine ratio, symmetric dimethylarginine (SDMA), urine specific gravity (USG), and urine output. Unfortunately, many of these indicators are not sensitive to identify the rapid damage that occurs to nephrons during AKI. For example, patients on fluid therapy will have an artificially reduced USG from diuresis. SDMA detects a reduction in glomerular filtration rate and can be used identify early stages of chronic renal failure (CRF). However, SDMA cannot distinguish between AKI or CRF, nor the various AKI staging categories. [30] Lastly, AKI patients require daily evaluation of renal function and the SDMA test take 1-2 days to obtain results since it's a test that has to be sent to a special laboratory.

The two most commonly used AKI staging schemes are the International Renal Interest Society (IRIS) and the Veterinary Acute Kidney Injury (VAKI). Both compare increases in baseline blood creatinine; however, IRIS is based on an absolute value and VAKI is based a percentage increase. [25,29] The advantage of VAKI staging is that it quantifies subtle changes in basal creatinine, even if not outside of the reference interval, which is significant in AKI patients and may not recognized by IRIS staging. Early identification of subtle changes in

creatinine are vital as creatinine elevations beyond normal reference intervals are less sensitive for AKI because they indicate nephron loss is greater than 75%.

Patients with clinical signs of liver damage should have their liver-specific enzymes (i.e. alanine aminotransferase, alkaline phosphatase, total bilirubin and gamma glutamyl transferase) monitored daily. Hepatoprotectants such as N-acetylcysteine or S-adenosylmethionine should considered if hepatotoxicity is suspected. [8,21,22]

In cases of extremely high doses that produce CNS signs, such as seizures, then diazepam or another benzodiazepine should be administered. Interestingly, naloxone has been used in cases of ibuprofen toxicity to reverse clinical signs. [8,24]

Additional NSAID toxicity treatments are being researched, which include the use of intravenous lipid emulsion and cholestyramine. Lipid emulsion therapy is performed by administering a large amount of lipid intravenously over a short period of time to compartmentalize lipid soluble drugs in the plasma and prevent their toxic action. [26] Intravenous lipid emulsion therapy is not recommended for routine cases due to the efficacy of decontamination and activated charcoal. [28] However, it may have a role with large NSAID doses or when the window for decontamination has passed. Another treatment mentioned in literature includes the administration of cholestyramine, a non-digestible ion exchange resin that binds bile in the gastrointestinal tract, which prevents enterohepatic recirculation and increases GI elimination of the toxin. [27]

PROGNOSIS

The prognosis for animals with NSAID toxicity varies, and is a determined by the dose consumed and the amount of time that passes before treatment occurs. Prognosis ranges from

good if treatment occurs quickly to guarded with AKI or if neurologic signs are seen. [6,8,29]

Ultimately, the sooner therapy is implemented, the better the prognosis.

Most Common NSAID Toxic Doses - DOGS

NSAID (Common Name)	GI Toxic Dose	Renal Toxic Dose	Hepatic Toxic Dose	CNS Toxic Dose	Other Toxic Doses
Acetamenophen (Tylenol)	50 mg/kg		100 mg/kg	200 mg/kg	Methemoglobinemia >200 mg/kg KCS - any dose (w/in 48-72 hr)
Aspirin (Bayer, BC Powder)	50 mg/kg			450 mg/kg	Metabolic Acidosis >300 mg/kg
Carprofen (Rimadyl)	20 mg/kg	40 mg/kg			
Celecoxib (Celebrex)	any dose	40 mg/kg			
Deracoxib (Deramaxx)	10 mg/kg	20 mg/kg			
Etodolac (EtoGesic, Lodine)	40 mg/kg				Lethal dose 80 mg/kg/day
Ibuprofen (Advil, Motrin)	25 mg/kg	175 mg/kg		400 mg/kg	Lethal dose >600 mg/kg
Indomethacin (Indocin)	0.5 mg/kg				Lethal dose = 160 mg/kg
Meloxicam (Metacam)	1 mg/kg	2 mg/kg			
Naproxen (Aleeve)	5 mg/kg	25 mg/kg		50 mg/kg	

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