THE RENAL EFFECTS OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) IN DOGS WITH CHRONIC KIDNEY DISEASE (CKD)

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Abstract

Prostaglandins play many important roles in the kidney including regulation of renal blood flow, glomerular filtration, renin release, and sodium excretion. Upon activation of the renin angiotensin aldosterone system (RAAS), prostaglandin upregulation becomes critical to offset the vasoconstrictive effects of norephinephrine, angiotensin II, and vasopressin. Nonsteroidal anti-inflammatory drugs (NSAIDs) produce both their beneficial and detrimental effects through inhibition of the cyclooxygenase enzyme and subsequent interference with prostaglandin production.

Healthy canine kidneys express both COX-1 and COX-2, although basal COX-2 expression in dogs is significantly higher than in other species. Nonsteroidal anti-inflammatory drugs that spare COX-1 have exhibited less gastrointestinal toxicity, but no NSAID has been proven safe for the kidney. The kidney is the organ with the second highest reports of adverse drug events, which is usually manifested as functional changes. However, structural changes including renal papillary necrosis, can occasionally be observed.

Dogs with chronic kidney disease could be expected to be at increased risk for NSAID-related adverse drug effects. As nephrons and renal reserve are lost in chronic kidney disease, the canine kidney becomes more dependent on COX-2 for production of prostaglandins. Inasmuch as the prevalence of both CKD and OA increases with age, it is expected that many dogs being treated with NSAIDs for OA will have loss of renal reserve and/or early stage CKD. If administration of an NSAID is required for long term treatment of osteoarthritis, frequent monitoring of blood pressure and renal parameters, as well as hepatic enzymes are recommended.

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Chapter 1 - The Renal Effects of NSAIDs in Dogs and Cats

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used in veterinary medicine to control chronic pain associated with osteoarthritis (OA). Although the quality of life for dogs with OA can often be improved with NSAIDs, the number of adverse drug events (ADE) associated with NSAID use reported to the Federal Drug Administration Center for Veterinary Medicine is higher than for any other companion animal drug; gastrointestinal, renal, hematologic, and hepatic adverse reactions are most commonly reported.[1] NSAIDs are frequently administered to large numbers of animals for routine procedures such as spays and neuters and are also administered to many patients for chronic conditions such as OA, therefore it is not unexpected to have a large absolute number of adverse effects reported. The purpose of this review was to evaluate the literature to determine the renal effects of NSAIDs in dogs.

Nonsteroidal anti-inflammatory drugs produce analgesic as well as adverse effects via inhibition of cyclooxygenase (COX) which decreases production of prostanoids. In the kidney, prostaglandins can influence renal blood flow (RBF), glomerular filtration rate (GFR), renin release, and sodium excretion.[2] Prostaglandins are synthesized by both the cyclooxygenase 1 (COX-1) and cyclooxygenase 2 (COX-2) enzymes in the healthy kidney. There are important species differences in the renal expression of COX-1 and COX-2. For example, rats and dogs have higher basal levels of COX-2 expression in the kidney compared with human beings.[2] In addition, in mice with RAAS activation and in dogs with CKD, an increase in COX-2 expression occurs in the macula densa and thick ascending loop, and synthesis of prostacyclin (PGI_2) and prostaglandin E2 (PGE_2) shifts to the COX-2 pathway.[3,4] For these reasons, NSAIDs that target COX-2 may be expected to adversely affect renal function in dogs, especially dogs with CKD.

Renal Hemodynamics

Renal blood flow (volume of blood delivered to the kidney per unit of time) and GFR (volume of fluid filtered by the kidneys per unit of time) are two important renal hemodynamic parameters. Although the kidneys account for only 0.5% body weight, they receive

approximately 25% of cardiac output.[5] A majority (90%) of renal blood flow supplies the cortex, with the inner medulla and papilla receiving only 1%. Renal blood flow is relatively constant over a broad range of mean arterial blood pressure (80-170 mmHg) in dogs.[5] GFR is less well maintained than renal blood flow during decreases in arterial blood pressure.[6] For example, at a mean arterial pressure of 75 mmHg, renal blood flow is preserved, but decreases in GFR occur over a mean arterial pressure of 75-100 mmHg. The end result is maintenance of renal perfusion at the expense of filtration of solutes.

In normal healthy dogs, GFR is largely regulated by tubuloglomerular feedback mechanisms. These mechanisms involve the juxtaglomerular complex, composed of a sodium-sensing macula densa in the distal tubule and juxtaglomerular cells located predominantly in the walls of the afferent arterioles.   A decrease in GFR slows the flow of filtrate through the loop of Henle, allowing increased time for sodium (and chloride) reabsorption. Consequently, less sodium reaches the macula densa stimulating vasodilation of the afferent arteriole which increases renal hydrostatic pressure and restores GFR. During this process, renin is released from the juxtaglomerular cells to increase formation of angiotensin I. Conversion of angiotensin I to angiotensin II constricts the efferent arteriole to further increase hydrostatic pressure within the glomerulus.

The sympathetic nervous system and arachidonic acid metabolites also influence vascular tone in the kidneys. Activation of the sympathetic nervous system secondary to hypotension or decreased circulating volume results in vasoconstriction of both the afferent and efferent arterioles. The end result is a transient (minutes to hours) decrease in RBF and GFR. Prostaglandins and bradykinins counter renal vasoconstriction and tend to enhance RBF and GFR. The most abundant prostanoid in the kidney is PGE_2 with lesser amounts of vasodilatory PGI_2 and $PGF_{2\alpha}$.[7] PGI_2 synthesis is localized to the cortex, while PGE_2 is found primarily in the medulla.[7]

The renal prostanoids do not play a leading role in hemodynamics in the dog unless hyponatremia and/or hypovolemia occur. In these situations, synthesis of renal prostaglandins is upregulated. PGE_2 and PGI_2 are produced in the renal tubules and glomeruli, respectively, to offset vasoconstriction caused by angiotensin II, norepinephrine, and vasopressin.[8] Prostaglandin E_2 also acts directly on renal tubules to increase excretion of sodium and water as well as stimulate renin secretion from the macula densa.[9]

COX and the Kidney

Primary beneficial and adverse renal effects of NSAIDs can be associated with their interference with prostaglandin synthesis. Prostaglandins are produced from the arachidonic acid pathway. Arachidonic acid is released from cell membranes into the cytoplasm where it acts as a substrate for cycloxygenase, lipoxygenase, and other enzymatic reactions. The precursor prostaglandin PGH_2 is then converted to the prostanoids (PGE_2, PGI_2, $PGF_2\alpha$, and TxA_2) that exert their biologic effects in close proximity to their site of synthesis.[7] PGE_2 is believed to be at the forefront of the inflammatory process and is associated with a decreased nociceptive threshold in addition to producing vasodilation, increased vascular permeability, and edema.[10] In the kidney however, PGI_2 and PGE_2 help protect RBF and GFR via renal vasodilation. This protective mechanism can be compromised in dogs treated with NSAIDs.

The COX-1 and COX-2 isoforms were discovered in the 1990s. COX-1 is normally present in most healthy tissues. COX-2 can be induced during inflammatory states; however, it is also expressed in and is necessary for normal function in gastrointestinal, neural, reproductive, and renal tissues. Certain species such as rats and dogs have higher basal levels of COX-2 expression in the kidney as compared to humans. Dogs have been shown to have increased COX-2 expression in the thick ascending limb of the loop of Henle, macula densa, and collecting ducts.[11] In a normal canine kidney, the prostanoids are synthesized in both the COX-1 and COX-2 pathways. When hypovolemia occurs in dogs, COX-1 and COX-2 maintain renal blood flow while COX-2 controls tubular function and renin release.[8]

COX-2 derived prostanoids are important for sodium excretion and thus blood pressure regulation under normal healthy conditions as well as in CKD. Inhibition of the COX-2 pathway decreases medullary blood flow and results in sodium retention. COX expression in the kidney can be affected by dietary salt intake. Metabolites of COX-2 have a minor role in regulation of RBF and GFR in dogs when sodium intake is normal or high, but they play a major role in sodium-depleted dogs.[11] Even though dogs have comparatively high basal COX-2 expression, the COX-2 pathway does not become important in regulation of renal hemodynamics until hypovolemia or hyponatremia occurs and RAAS is activated.[8] COX-2 expression in the thick ascending loop of Henle can then triple in dogs, resulting in a 10-fold increase in plasma renin.[12]

A variety of terminology (nonselective, COX-2 selective, COX-2 specific, COX-1 sparing, etc.) has been coined in an attempt to classify NSAIDs according to their ratio of COX activity, but no standardized definition exists for these terms. COX-2 inhibitors have exhibited decreased gastrointestinal toxicity as compared to nonselective NSAIDs.[13] However, this advantage may be lost in vivo when NSAIDs are administered at recommended dosages.[14] Furthermore, renal impairment in dogs can occur in dogs after administration of preferential or nonselective NSAIDs.[15]

COX versus LOX

In addition to expression of COX-2, increased levels of 5-LOX occurred in a study of canine coxofemoral osteoarthritis.[16] Dual inhibitors, NSAIDs that can inhibit both the COX and LOX pathways, may therefore provide additional beneficial effects in decreasing pain and inflammation. The 5-lipoxygenase pathway may have the most clinical significance in chronic inflammatory disease since its end product, LTβ4, attracts leukocytes via chemotaxis.[17] LTβ4 can also result in decreased RBF.[18] A dual inhibitor in phase III trials for approval in humans, ML-3000 (licofelone), decreased IL-1β and collagenase 1 synthesis, reducing experimental evidence of osteoarthritis in a group of mongrel dogs treated for 8 weeks. PGE_2 and LTβ4 production was also significantly decreased.[19]

Chronic Kidney Disease and Osteoarthritis

Chronic kidney disease (CKD) affects 0.5%-1.5% of the dog population and is defined as structural or functional changes of the kidneys, usually present for at least 3 months.[20,21] Both OA and CKD are more common in older dogs, so it's reasonable to assume that some subset of dogs with OA will also have subclinical (IRIS Stage 1/early Stage 2) CKD. Control of pain associated with OA usually requires long-term treatment with NSAIDs. Although NSAIDs are often used for chronic management of OA, few long term safety studies exist. A recent review of the safety and efficacy of long-term NSAID use in the treatment of canine OA identified 15 trials that evaluated treatment of 28 days or more in duration, with the longest study being 120 days. More research to assess the effects of long-term NSAID administration in dogs would provide beneficial information on adverse drug events and could direct monitoring guidelines.

Renal Effects and Toxicity

The kidney is the organ with the second most common number of adverse effects from NSAIDs. Most of these adverse effects occur secondary to interference with renal fluid and electrolyte balance due to decreased prostanoid synthesis. Within the kidney, decreased prostanoid synthesis commonly manifests as decreases in RBF and/or GFR and in severe cases, acute tubular injury that may lead to acute renal failure. Acute kidney injury from NSAIDs is more likely to occur in dogs that already have decreased renal function.[22] Chronic kidney disease, salt depletion, and hypotension result in RAAS activation and make the kidney susceptible to vasoconstriction in the face of decreased production of prostaglandins secondary to use of NSAIDs.[23] Concurrent medication administration may also change renal hemodynamics. Potent diuretics like furosemide may enhance adverse effects in dogs treated with NSAIDs.

Dogs with CKD and concurrent hypertension and/or proteinuria are frequently treated with angiotensin converting inhibitors (ACEi). The effects of combined ACEi and NSAID treatment in dogs with CKD is largely unknown, although in one study, no change in GFR or RBF were observed when tepoxalin and an ACEi were administered to healthy beagles for 28 days.[24] Many older dogs with OA also have other conditions that could predispose them to NSAID adverse effects such as liver or cardiac disease and neoplasia in addition to CKD. Since NSAIDs are highly protein-bound, their half-lives could be decreased in hypoalbuminemic states and liver or kidney disease. Other concurrent conditions such as decreased metabolic rate, and altered volumes of distribution are risk factors for NSAID toxicity in elderly humans and may have a role in dogs as well.[10]

The renal effects of ibuprofen and carprofen have been investigated in euvolemic and volume-depleted healthy dogs.[25] No difference was found between ibuprofen (a nonspecific NSAID) and carprofen (a COX-2 preferential NSAID) in dogs that had received furosemide, indicating that both nonspecific and preferential NSAIDS are capable of hemodynamic renal impairment. To determine whether COX selectivity had any effect on the previous results, a similar randomized crossover study was performed comparing carprofen and etodoloac in euvolemic and volume-depleted healthy dogs.[26] Dogs that received either NSAID in

combination with furosemide experienced a statistically significant increase in creatinine and decrease in GFR which was reversible when treatment was discontinued. Renal plasma flow, the volume of plasma reaching the kidneys per unit time, was preserved, however. A decrease in GFR without a decrease in RPF indicated pre and postglomerular vasoconstriction.

Although the renal distribution of expression of the COX-1 isoform is fairly uniform across animal species, interspecies differences in renal COX-2 expression have been recognized. In order to elucidate these differences, dogs and monkeys were given naproxen at 50 mg/kg/day and 150 mg/kg/day, respectively, for 2 weeks in order to reach a plasma concentration that would maximally inhibit renal COX.[15] Plasma concentrations were 763 μg/ml/hr and 1918 μg/ml/hr in dogs and monkeys, respectively. Naproxen is a nonspecific COX inhibitor with a narrow margin of safety and renal toxicity can be observed at 10 mg/kg in dogs. Despite similar reductions in renal prostaglandin levels, dogs had more significant renal toxicity, manifest by decreases in RBF and sodium excretion, than did monkeys presumably due to a greater degree of COX-2 inhibition. Immunohistochemistry analysis indicated COX-2 was prominent in the macula densa, thick ascending loop of Henle, and papillary interstitial cells of canine but not monkey kidneys.[15] Postmortem exam at 6 weeks showed dogs had developed tubular atrophy and interstitial fibrosis in addition to renal papillary necrosis. Dogs may be especially sensitive to COX-2 induced ischemia due to sluggish blood flow through the renal papilla.[15]

Reversible hemodynamic changes are the most common renal effects of NSAIDs, but structural changes to the kidney can also occur. Acute kidney injury, interstitial nephritis, and renal papillary necrosis are all renal effects of NSAIDS that have been reported in dogs.[15] Nonsteroidal anti-inflammatory drugs most commonly affect the proximal tubules, although the collecting ducts may also be susceptible to NSAID induced nephrotoxicity. The mechanism is unclear, but long term NSAID exposure may cause toxicity to the collecting ducts through increased osmolality or further decreases to the already scant medullary blood flow.[27] At excessively high NSAID doses, drug accumulation may also have a direct toxic effect in the kidney as in renal papillary necrosis.

Clinical Safety Studies

Adverse renal effects of veterinary NSAIDs in the literature are commonly associated with high doses and/or prolonged administration. When deracoxib was dosed to dogs (n = 10/group at 2 mg/kg/day [labeled dosage] and 4 mg/kg/day for 6 months), no adverse clinical effects were noted, although GFR was not measured. When administered to dogs at 6 mg/kg/day (3 times the label dose) for 6 months, two dogs developed hyposthenuria. Increases in BUN and dose dependent renal tubular degeneration occurred with dosages of 6 (n=2), 8 (n=2), and 10 (n=4) mg/kg/day. Renal papillary necrosis developed at six months in one dog receiving 8 mg/kg/day and in three dogs receiving 10 mg/kg/day.[28]

In a placebo-controlled study, ketoprofen was administered at 1 mg/kg to five clinically healthy beagle dogs for 30 days.[29] The labeled dosage is 1 mg/kg daily for up to five days.[30] No significant differences were observed in RPF or GFR between pre and post-NSAID treatment, although one dog in the ketoprofen group was below the reference range for RPF at 20 and 30 days and developed mild to moderate renal proteinuria and urine sediment abnormalities. Renal tubular epithelial cells (2-3/hpf) were present on urine sediment exam. Two dogs in the ketoprofen group also had increased urinary N-acetyl-β-D-glucosaminidase and/or gamma glutamyl transpeptidase excretion; one dog showed increased urine NAG and GGT excretion between days 6 and 18 while the other dog only had an increased urine GGT excretion at day 30. At necropsy these same two dogs had mild lymphoid cell infiltration in the renal medulla.[28] In another ketoprofen study, the effects of a low dose of (0.25 mg/kg PO) given once daily for 30 days on urinary enzyme excretion was assessed. No increase in urinary NAG or GGT occurred in this study suggesting renal tubular cell injury did not occur at this dose; however histopathology was not performed to corroborate the laboratory findings.[31]

A study in dogs with IRIS Stage 2 or 3 CKD given tepoxalin for 28 days (n=16, acute phase) and an additional 6 months (n=10, chronic phase) found no differences in renal parameters (assessed by serum biochemical analysis, urinalysis, urine protein-to-creatinine concentration ratio, urine γ-glutamyl transpeptidase-to-creatinine concentration ratio, iohexol plasma clearance, and indirect blood pressure measurement) over time in dogs that completed the two phases (n = 14 and 7 for the acute and chronic phases, respectively).[32] Adverse drug events (ADEs) resulting in discontinuation of tepoxalin and/or withdrawal from the study included increased serum creatinine concentration (1 dog; week 1), collapse (1 dog; week 1), increased

liver enzyme activities (1 dog; week 4), vomiting and diarrhea (1 dog; week 8), hematochezia (1 dog; week 24), and gastrointestinal ulceration or perforation (1 dog; week 26).[32] Some of the dogs that experienced adverse events had preexisting medical conditions and/or were receiving other medications in addition to tepoxalin during the study period.

Studies evaluating the renal effects of NSAIDs have also been performed in healthy cats and cats with CKD.[33-37] Meloxicam has been shown to be safe for long-term administration in cats at a maintenance dose of 0.01-0.03 mg/kg/day.[33] In this study, coexisting conditions such as CKD (n=3), diabetes mellitus (n=3), and hyperthyroidism (n=4) did not preclude inclusion as long as those conditions were being appropriately managed.[33] Interestingly, the administration of meloxicam for longer than 6 months at a dose of 0.02 mg/kg (20% of an extralabel dose) did not adversely affect survival of cats with IRIS Stage II or III CKD.[34] Furthermore, in another study, serum creatinine increased more slowly over 327 days in meloxicam treated CKD cats as compared to control CKD cats.[35] The authors speculated that the delayed azotemia may have been due to improved quality of life and appetite or to a direct effect on the kidney in decreasing interstitial inflammation and fibrosis.

Six young, healthy cats given high-dose meloxicam (0.2 mg/kg PO on day 1, 0.1 mg/kg PO on days 2-5) showed no change in plasma iohexol clearance at the end of six days compared to placebo.[36] In another study, the renal effects of both vedaprofen and tolfenamic acid in healthy cats were evaluated by renal scintigraphy and serial hematologic evaluations and no change in renal function occurred following 14 day administration of vedaprofen (0.5 mg/kg/day) or tolfenamic acid (4 mg/kg/day).[37]

Recommendations

Using the lowest effective dose of a veterinary approved NSAID to control pain and improve mobility is recommended for all older dogs necessitating NSAID treatment but especially for dogs with concurrent health problems such as CKD. Alternate forms of analgesia such as opioids should first be administered before determining if an NSAID is required. The administration of non-veterinary approved NSAIDs is not recommended in dogs and cats due to increased elimination times and an extremely narrow margin of safety. Evaluation of blood pressure, hematocrit, renal and hepatic parameters are recommended prior to prescribing an

NSAID in a dog or cat with decreased renal function. Repeat evaluation of laboratory parameters 2 weeks after initiating treatment with periodic monitoring during treatment has been recommended.[38] Re-evaluation after a month of NSAID administration should also be considered since some ADEs (hepatocellular injury) can be clinically silent.[32] If all parameters are stable, rechecks every 3 months should occur, both to evaluate any clinical changes and to monitor CKD progression. Adverse effects of NSAIDs are more likely to occur in the first 14-30 days of administration but have been reported from 3-182 days.[1,32] Since it is impossible to predict which animals will experience an adverse event, the owner of every animal receiving NSAIDs should also be educated on NSAID side effects such as vomiting, diarrhea, inappetance, and dark stools. By practicing vigilance, the quality of life for dogs with severe OA can be improved without overlooking the warning signs that could lead to more serious problems.

Chapter 2 - Acute and Chronic Effects of Tepoxalin on Renal Function in Dogs with Chronic Kidney Disease and Osteoarthritis

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used in veterinary medicine to control chronic pain associated with osteoarthritis (OA). Although the quality of life for dogs with OA can be improved with NSAIDs, the number of adverse drug events (ADE) associated with NSAID use reported to the Federal Drug Administration Center for Veterinary Medicine is higher than for any other companion animal drug; gastrointestinal, renal, hematologic, and hepatic adverse reactions are most commonly reported.[1] There are several studies suggesting "long-term" use of NSAIDs is well tolerated in dogs with OA, however, the length of these studies is 30-60 days.[39-42]

Nonsteroidal anti-inflammatory drugs produce analgesic and toxic effects via inhibition of cyclooxygenase (COX) resulting in decreased production of prostanoids. In the kidney, prostaglandins have a role in regulation of glomerular filtration rate (GFR), renin release, and sodium excretion.[2] Prostaglandins are synthesized by both the cyclooxygenase 1 (COX-1) and cyclooxygenase 2 (COX-2) enzymes in the healthy kidney, however, when the mouse kidney is stimulated by angiotensin, an increase in COX-2 expression occurs in the macula densa and thick ascending loop,[4] and synthesis of prostacyclin (PGI_2) and prostaglandin E_2 (PGE_2) shifts to the COX-2 pathway. There are important species differences in the renal expression of COX-1 and COX-2. For example, rats and dogs have higher basal levels of COX-2 expression in the kidney compared with human beings,[2] and dogs with chronic kidney disease (CKD) have increased expression of COX-2.[3] For these reasons, NSAIDs that target COX-2 may be expected to adversely affect renal function in dogs, especially dogs with CKD.

In addition to COX-1 and COX-2, the lipoxygenase (LOX) pathway is another route for arachidonic acid metabolism. The 5-LOX enzyme may have the most clinical significance in promoting inflammation since one of its end products, leukotriene β4 (LTβ4), attracts leukocytes via chemotaxis.[17] This pathway may also influence renal function as synthesis of the vasoconstrictor leukotriene C4 has been shown to decrease renal blood flow (RBF) in a rat glomerulonephritis model.[43] Therefore, dual inhibitor NSAIDs that can inhibit both the COX and LOX pathways may have increased analgesic effects in OA with fewer adverse renal effects.

Tepoxalin is the first dual inhibitor approved for use in veterinary medicine.[44] The objective of this study was to assess renal functional parameters in dogs with OA and stable IRIS Stage 2 or 3 CKD treated with tepoxalin.

Materials and Methods

Animals

Client-owned dogs with OA and IRIS Stage 2 or 3 CKD were enrolled in a prospective clinical trial at Kansas State University Veterinary Medical Teaching Hospital (KSU-VMTH). Patients were recruited from referring veterinarians and from within KSU-VMTH. The study was approved by the KSU Institutional Animal Care and Use Committee, and all owners signed a consent form prior to enrollment.

Inclusion Criteria

Dogs with OA as well as stable IRIS Stage 2 or 3 (serum creatinine [SrCr] of 1.6-3.5 mg/dl) CKD were eligible for inclusion in the study. Osteoarthritis was suspected based on history and by pain and/or crepitus on orthopedic examination and confirmed by radiography of the affected joint(s). In addition, owners were asked to fill out a questionnaire that detailed their dog's mobility and activity level. A diagnosis of CKD was based on a combination of the following: chronic history ($\geq$ 2 months) of weight loss, polydipsia/polyuria, and/or persistent azotemia (SrCr $\geq$ 1.6 but $\leq$ 3.5 mg/dl) superimposed on isosthenuric or minimally concentrated urine. In addition, abdominal radiographs and ultrasound evaluations, indirect blood pressure determination (Doppler)[a], urine culture, urine protein/creatinine ratio (UP/C), urine γ-glutamyl transpeptidase /creatinine ratio (UGGT/C), and iohexol[b] plasma clearance[c] (IPC) to estimate GFR were also performed to further evaluate the kidney and to rule out concurrent diseases. Stable CKD was documented by evaluating SrCr, IPC, UP/C, UGGT/C, and systolic blood pressure twice (between -14 and -7 days and again at day 0) prior to treatment. Exclusion criteria included unstable azotemia (SrCr and/or IPC that varied by > 20% at the first two evaluations), positive bacterial urine culture, evidence of obstructive uropathy, fractious nature, or evidence of concurrent disease (e.g., hyperadrenocorticism, diabetes mellitus, neoplasia). Gastrointestinal protectants (e.g., H_2 receptor blockers and proton pump blockers) were not

routinely administered as part of this study, nor were they exclusionary criteria. If a dog with CKD was receiving any GI protectants prior to enrollment, the treatment was continued during NSAID administration.

Study Protocol

Tepoxalin[d] was administered orally to each dog (10 mg/kg/day) for 4 weeks in the acute phase. Tepoxalin prescriptions were refilled on a weekly basis and owners were asked to bring their prescription vials to each recheck. Pills were counted, and owners were asked about their ability to administer the pills in order to document compliance. Each dog was re-examined weekly; diagnostics included physical examination and body weight, CBC, serum biochemistry profile, urinalysis, UP/C, UGGT/C, and indirect systolic blood pressure. Plasma clearance of iohexol was measured at week 2 and 4 of tepoxalin treatment. Owners completed the mobility/activity questionnaire again at the end of 4 weeks of treatment.

After completion of the acute phase, owners were given the option to enroll in the chronic phase (an additional 6 months). Dogs in the chronic phase received tepoxalin at 10 mg/kg/day and were rechecked at 1, 3, and 6 months. History (owner compliance with the tepoxalin), physical examination and body weight, CBC, serum biochemistry profile, urinalysis, UP/C, UGGT/C, IPC, and indirect systolic blood pressure were performed at each of the recheck evaluations in the chronic phase. Owners also filled out mobility/activity questionnaires at the end of the chronic phase.

Statistical Analysis

The data for each parameter were analyzed by a repeated measures ANOVA[e] accounting for animal and repeated measures on each animal over treatment time. Treatment time was entered as a factor variable accounting for each animal visit over the course of the trial. Significance of the effect of treatment time was tested based on Box's conservative correction factor to adjust for the non-independence of the repeated measurements.

Results

Sixteen dogs were included in the acute phase of the study, and 10 of these dogs were enrolled in the chronic phase. Dogs ranged in age from 4-15 years, with a median age of 12

years. Of the sixteen dogs, 12 were spayed females and 4 were males; one male was intact. A wide range of breeds/mixed breeds were represented. Labrador retrievers (n=2) and border collies (n=3) were the only breeds with multiple dogs.

Adverse drug events that resulted in discontinuing tepoxalin included: increased SrCr in one dog (week 1), collapse in one dog (week 1), increased liver enzymes in one dog (week 4), and vomiting, hematochezia, and gastrointestinal (GI) ulceration/perforation, respectively in three dogs (weeks 8, 24, and 26, respectively). None of the dogs with GI ADE were receiving GI protectants. Discontinuation of the tepoxalin treatment resulted in stabilized renal function in the first dog and resolution of 4 of the 5 adverse events.

Acute deterioration in renal excretory function occurred in one dog in our study. This dog's baseline renal function was 74.5% less than the mean GFR for the canine population tested at Michigan State University based on the average of two IPC pretreatment values. This dog had also been diagnosed with systemic hypertension prior to inclusion in the study; his systolic blood pressure did not change (170 mmHg) with tepoxalin therapy. However, his SrCr increased from 1.6 mg/dl to 2.5 mg/dl within the first week of treatment, and his UP/C increased from 0.4 to 0.6. Other serum biochemical values, UGGT/C, USG, and urine sediment were unchanged from baseline at the 1 week recheck.

Collapse occurred in one dog during the first week of tepoxalin treatment. This dog was mildly hyperkalemic (6.2 mmol/L) and moderately hypertensive (160 mmHg systolic) at one baseline time point prior to inclusion. During the 7th day of tepoxalin treatment, he collapsed in the hospital during his recheck. Supportive care consisting of intubation and IV fluids was provided. The dog made a full recovery within minutes. No change in potassium or blood pressure was observed with tepoxalin treatment, although he gained 1.1 kg during the week of tepoxalin treatment. His SrCr had also increased from 1.7 mg/dl at baseline to 2.4 mg/dl. On the following day, his SrCr returned to pretreatment values.

One dog developed increased liver enzymes with hyperbilirubinemia at the end of the acute phase of the study. Baseline ALT, ALP, and total bilirubin (TB) were 62 U/L, 82 U/L, and 0.1 mg/dl, respectively. No elevation in liver enzymes occurred until the 4th week of tepoxalin treatment. At week 4, the ALT, ALP, and TB were 874 U/L, 290 U/L, and 1.1 mg/dl, respectively. The dog remained clinically normal. Eleven days after tepoxalin treatment was discontinued, the ALT, ALP, and TB were 181 U/L, 200 U/L, and 0.1 mg/dl, respectively.

Three dogs experienced gastrointestinal signs during the chronic phase of the study resulting in discontinuation of the tepoxalin treatment. One dog had vomiting and diarrhea at week 8. Retrospectively, the referring veterinarian's records indicated that a steroid responsive enteropathy was suspected but had not been definitively diagnosed, and the dog was being treated with prednisone. The second dog experienced hematochezia at 24 weeks. Discontinuation of the tepoxalin treatment resolved the GI signs in both of these dogs. The third dog with GI complications developed vomiting and anorexia at 26 weeks of tepoxalin administration. Hypertension (170 mmHg systolic) was documented for the first time during the second month of tepoxalin administration. On presentation to KSU-VMTH, this dog was laterally recumbent; supportive care consisting of intravenous fluids, GI protectants, and anti-emetics was initiated. Melena and hematemesis developed the following day. Segmental thickening of the greater curvature of the body of the stomach, a corrugated duodenum, and hyperechoic mesentery were visualized by abdominal ultrasound examination along with free peritoneal fluid. Cytology of the fluid was consistent with septic inflammation. The owner declined laparotomy and elected euthanasia. Gastric perforation and a right-sided pheochromocytoma were diagnosed at necropsy. Chronic kidney disease was also confirmed at necropsy; both kidneys had marked interstitial fibrosis along with degeneration, necrosis, and loss of tubules. Many of the remaining tubules were dilated and contained proteinaceous eosinophilic material. There was also multifocal infiltration of moderate numbers of lymphocytes and plasma cells in the interstitium and in the pelvis. The glomerular tufts were relatively small, and glomeruli had dilatation of Bowman's space.

Eighty-seven percent of dogs completed the acute phase of the study, and 70% of dogs that entered the chronic phase completed it. No significant change in any of the renal function parameters occurred in either the acute or chronic phase of the study in dogs that completed the study (Table 2.1). Review of owner questionnaires showed that mobility and activity scores either improved or remained unchanged throughout both phases of the study.

Table 2.1 Renal Function Parameters (mean ± SD) in Dogs with OA and CKD receiving tepoxalin (10 mg/kg/day)

	Baseline*	4 weeks (n = 14)	7 months (n = 7)
BUN (mg/dl)	33 $\pm$ 13	31 $\pm$ 18	31 $\pm$ 8
SrCr (mg/dl)	1.9 $\pm$ 0.3	1.8 $\pm$ 0.3	2.0 $\pm$ 0.4
PCI (mL/min/kg)	1.14 $\pm$ 0.35	1.06 $\pm$ 0.24	1.01 $\pm$ 0.19
UP/C	0.87 $\pm$ 1.3	0.80 $\pm$ 1.3	1.11 $\pm$ 1.5
UGGT/C	0.30 $\pm$ 0.21	0.24 $\pm$ 0.12	0.17 $\pm$ 0.06
SBP (mm Hg)	148 $\pm$ 16	156 $\pm$ 16	154 $\pm$ 19
Na (mmol/L)	149 $\pm$ 2.3	148 $\pm$ 2.2	148 $\pm$ 1.0
K (mmol/L)	4.9 $\pm$ 0.5	5.0 $\pm$ 0.4	4.7 $\pm$ 0.3

*Average of two baseline (pretreatment) values.

Discussion

Nonsteroidal anti-inflammatory drugs are widely used to treat OA, but few long-term studies of their safety exist. Adverse drug events observed in this study included increased SrCr (n=1), increased liver enzymes (n=1), collapse (n=1), and gastrointestinal problems (n=3). Although specific retrospective data on ADE with NSAIDs in dogs is scant, NSAID-related ADE tend to occur within the first 14-30 days of treatment, with a range of 3-90 days.[1] Dogs in the 10-15 year age range were most likely to be affected, followed by dogs ages 6-10.[1] In our study, ADE occurred anywhere from 7-182 days of treatment with tepoxalin. Four of the five dogs that were withdrawn from our study due to ADE were in the 10-15 year age range, while the remaining dog was 8 years old.

In addition to the paucity of long-term studies assessing NSAID-associated ADE, no studies have assessed the effects of NSAIDS on renal function in dogs with spontaneous CKD. Previous studies have assessed the effects of coxibs on renal function in aged cats with degenerative joint disease (some with spontaneous CKD) and cats with surgically-induced remnant kidneys.[35,45] Older cats with CKD and degenerative joint disease that received low dose (0.02 mg/kg/day) meloxicam for 6 months had no difference in USG or SrCr compared to cats that did not have CKD.[35] Administration of meloxicam or aspirin did not decrease GFR in a

study of cats with surgically reduced renal mass with the equivalent of IRIS Stage 2 or 3 CKD, prompting the authors to conclude that these cats were not dependent on COX-derived prostanoids for maintenance of renal function.[45]

Dehydration is a common complication of CKD that can predispose a patient to the nephrotoxic effects of NSAIDs. When dehydration occurs, the auto-regulatory vasodilatory mechanisms involving increased production of prostaglandins that would normally protect the kidney from transient decreases in RBF can make the kidney more susceptible to the effects of NSAIDs.[7] Two recent studies investigated the renal effects of ibuprofen, carprofen, and etodolac in euvolemic and volume-depleted dogs.[26,25] In both studies, no change in GFR occurred in euvolemic healthy beagles receiving either NSAID alone, but co-administration of furosemide produced a statistically significant increase in SrCr and decrease in GFR which was reversible when treatment with NSAIDs was discontinued. There was no advantage of one NSAID over another regarding the effect on renal hemodynamics, suggesting that both nonselective and selective COX inhibitors can produce renal excretory impairment in volume contracted dogs.

In the current study, tepoxalin treatment was discontinued in one dog at 1 week due to an increase in SrCr. This dog was receiving both enalapril and amlodipine for hypertension at the time of inclusion in the study. The effect of an ACE inhibitor and a calcium channel blocker concurrently with tepoxalin may have decreased renal perfusion. No change in GFR or RBF was observed in healthy beagles treated with enalapril and tepoxalin,[24] but the concurrent use of amlodipine, enalapril, and tepoxalin have not been evaluated in dogs with CKD. In our study the dog with increased SrCr progressed from IRIS Stage 2 to 3 CKD during the first week of tepoxalin treatment. Repeated injections of iohexol in dogs have been recently associated with a mild form of contrast-induced nephrotoxicity.[46] It is possible that the two baseline iohexol injections in this dog contributed to the increase in SrCr at the end of week one, although we did not observe this adverse effect in any of the other study dogs. After tepoxalin treatment was discontinued, this dog remained in IRIS Stage 3 CKD for 2 months before progressing to IRIS Stage 4 CKD. Seven months later (9 months after being removed from the study), this dog was euthanized because of progressive CKD. Two events that may have contributed to progressive renal dysfunction were 1) persistent systemic hypertension and 2) inadvertent ingestion of raisin bread three months after he was removed from the study, which was associated with an increase in his SrCr. Hypertension has been associated with progression of CKD.[47] Half of the dogs in

our study were moderately hypertensive (systolic blood pressure $\geq$ 160 mmHg based on the average of two pre-treatment measurements after acclimation to the KSU-VMTH), and 4/5 of the dogs that were withdrawn from the study for adverse events had moderate hypertension. Proteinuria has also been associated with progression of CKD,[48] however only 31% of the dogs in our study were proteinuric (UP/C $\geq$ 0.5). Two of the five dogs that were removed from the study for adverse events were proteinuric, although one of the dogs had concurrent hypertension as well.

Another ADE included one dog that developed increased liver enzymes and hyperbilirubinemia at the end of the fourth week of the acute phase of the study. Hepatocellular toxicity has previously been reported as an idiosyncratic reaction secondary to carprofen administration,[49] and hepatoxicity has been reported associated with all veterinary-approved NSAIDs.[1] Although further work-up to confirm hepatic necrosis was not performed, liver enzymes decreased substantially within 11 days of discontinuing the tepoxalin administration, suggesting that a reversible NSAID-related idiosyncratic reaction had occurred.

Collapse has been reported to the FDA-CVM as an adverse effect of tepoxalin.[50] In the dog that collapsed in our study, the owner mentioned that trembling of the back legs was intermittently present prior to starting tepoxalin. This dog also gained 1.1 kg while under treatment with tepoxalin, which could have been associated with fluid retention/subclinical edema. Inhibition of COX-2 by NSAIDs can result in impaired natriuresis resulting in sodium retention in human beings.[7] In another study, antinatriuresis was more significant in dogs than monkeys despite lower plasma levels of naproxen suggesting that dogs have an increased reliance on COX-2 mediated prostanoids for sodium excretion.[15] In the dog in our study, no further adverse events occurred following discontinuation of the tepoxalin treatment, and his body weight returned to normal.

A multi-center tepoxalin field study included 107 dogs that received 20 mg/kg/day of tepoxalin on day 1 followed by 10 mg/kg/day for 27 days. Gastrointestinal side effects including diarrhea, vomiting, loss of appetite, soft feces, and/or enteritis were observed in 21% of the study population.[51] While GI side effects were not noted in any dog during the acute phase in our study, the rate of GI adverse drug events including both phases of our study was 19%. Three dogs experienced GI side effects (vomiting, hematochezia, GI ulceration/perforation) during the chronic phase of the study. One of these dogs had an enteropathy suspected by the referring

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veterinarian which was being treated with prednisone, and the dog with GI ulceration/perforation was diagnosed with a pheochromocytoma at necropsy. It is possible that both of these underlying conditions as well as the prednisone treatment could have contributed to gastrointestinal signs. It is also possible that routine use of GI protectants in these CKD dogs receiving tepoxalin would have decreased the number of GI ADE observed in this study.

Limitations of this study include a small sample size. In addition, since all of the dogs were client-owned and remained under their owner's care at home, we could not confirm that the correct dosage of tepoxalin was administered daily. Plasma tepoxalin/metabolite concentrations were not measured in this study. Although a medical history was part of each visit, it is possible that other medications were being given concurrently that were not mentioned by the owner. Specifically, prednisone and tepoxalin were likely given concurrently in one dog, which may have been, at least in part, responsible for the observed adverse gastrointestinal effects. Finally, the etiology of the underlying CKD was unknown, so different rates of progression would be expected to occur for each dog.

This is the first study to assess renal function in dogs with CKD receiving NSAIDs. Renal function parameters were unchanged compared with baseline values after the acute (4 weeks) and chronic (an additional 6 months) phases of tepoxalin treatment. The results of this study suggest that with appropriate monitoring tepoxalin may be used for treatment of OA pain in dogs with IRIS Stage 2 or 3 CKD. Use of GI protectants should be considered in dogs with CKD receiving tepoxalin. Additional caution is warranted in dogs that are hypertensive and/or receiving concurrent medications such as ACE inhibitors.

Footnotes

a. Doppler Ultrasonic Flow Detector, Parks Medical Electronics Inc., Aloha, OR

b. Iohexol (Omnipaque®), GE Healthcare Inc., Princeton, NJ

c. Michigan State University, Diagnostic Center for population & Animal Health, Lansing, MI

d. Tepozalin (Zubrin®), Schering Corp., Kenilworth, NJ

e. STATA 11, STATA Corp LP, College Station, TX

Addendum

Use of NSAIDs in dogs with chronic kidney disease should always be approached with caution. Although the results of our study suggest that tepoxalin may be used safely in dogs with IRIS Stage 2 – 3 CKD with appropriate monitoring, additional considerations may be warranted. The addition of H_2 blockers such as famotidine may have prevented or lessened the adverse gastrointestinal side effects (vomiting, hematochezia, soft stools) observed in our study. Hypergastrinemia and gastric hyperacidity can both occur in azotemic CKD.[52] Even without NSAIDs, the symptomatic treatment of dogs with IRIS Stage 2 and 3 CKD often involves administration of H_2 receptor antagonists to minimize gastrointestinal effects of uremia that may accompany CKD.[21]

Administration of an ACEi has been shown to increase GFR while decreasing the urine protein to creatinine ratio in dogs with CKD.[53] The effects of combining antihypertensive/antiproteinuric medications with NSAIDs were not evaluated in our study. Several of our dogs were treated with an ACE inhibitor concurrently while receiving tepoxalin. Further hemodynamic effects (i.e. decreased perfusion) to the kidneys may have been due in part to co-administration of these two drug classes.[54]

Four out of five dogs that were withdrawn for adverse events had concurrent moderate systemic hypertension. Hypertensive dogs with CKD likely have increased risk of adverse effects from NSAIDs since the kidney loses its ability to autoregulate blood flow and intraglomerular pressures when the systemic mean blood pressure is greater than 170 mmHg.[55] Calcium channel blockers would be expected to lower systemic blood pressure by decreasing peripheral resistance but could increase glomerular hypertension by causing vasodilation at the afferent arteriole. The one dog that experienced worsening of his azotemia had preexisting hypertension and was being treated with enalapril and amlodipine prior to initiating the tepoxalin treatment.

Subclinical edema from sodium retention has not been previously reported in animals receiving NSAIDs to the author's knowledge. One dog in our study gained weight during the first week of tepoxalin administration and subsequently experienced apparent cardiovascular collapse. This may have been due to decreased expression of COX-2 metabolites secondary to NSAID administration. Activation of the RAAS may have a negative feedback on COX-2

expression since administration of captopril to dogs resulted in upregulation of COX-2 in the medulla.[56]

Monitoring standards for dogs with CKD receiving an NSAID have not been established. After establishing that no changes have occurred in renal parameters over the first few weeks of administration, reevaluation of the patient should be considered every 3 months unless any changes in clinical condition occur.

Measurement of renal function by assessing GFR, though accurate and reliable for determining excretory function, may not be a very sensitive early indicator for renal tubular cell damage. To monitor for early signs of damage to the proximal tubule, further studies could evaluate trends in N-acetyl-β-D-glucosaminidase (uNAG) and/or urinary retinol binding protein (uRBP) in comparison to urinary creatinine.[57] Increased concentrations of uNAG, a lysosomal enzyme, reflect tubular damage while uRBP, which appears in the urine due to decreased absorption, indicates decreased tubular cell function. Urinary retinol binding protein could be a better choice in dogs with CKD since it would be less likely to be altered by proteinuria.[58]

In conclusion, close monitoring of dogs with CKD treated with NSAIDs is justified, but patient selection may be even more critical to try to prevent NSAID-related adverse events in dogs with CKD. The results of our study suggest that hypertensive CKD dogs are at increased risk for adverse effects associated with NSAID administration. Alternative pain management such as opioids would likely be a better choice for dogs with moderate to severe hypertension or that are receiving concurrent medications which could decrease perfusion to the kidneys.

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Appendix A - Abbreviations

ADE	Adverse drug event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANOVA	Analysis of variance
CBC	Complete blood count
CKD	Chronic kidney disease
COX	Cyclooxygenase
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
FDA-CVM	Food and Drug Administration Center for Veterinary Medicine
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transpeptidase
GI	Gastrointestinal
IPC	Iohexol plasma clearance
IRIS	International Renal Interest Society
KSU	Kansas State University
KSU-VMTH	Kansas State University Veterinary Medical Teaching Hospital
LOX	Lipoxygenase
$LT\beta_4$	Leukotriene β_4
MmHg	Millimeters of mercury
NSAID	Nonsteroidal anti-inflammatory drug
OA	Osteoarthritis
PGE_2	Prostaglandin E_2
$PGF_{2\alpha}$	Prostaglandin $F_{2\alpha}$
PGI_2	Prostacyclin
RAAS	Renin angiotensin aldosterone system
RBF	Renal blood flow
RPF	Renal plasma flow
SrCr	Serum creatinine

TB	Total bilirubin
TxA$_2$	Thromboxane A$_2$
UGGT/C	Urine gamma glutamyl transpeptidase ratio
UP/C	Urine protein to creatinine ratio
USG	Urine specific gravity