

# Evaluation of the Renal Effects of Ibuprofen and Carprofen in Euvolemic and Volume-depleted Dogs

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## KEY WORDS:

### ABSTRACT

The goals of this study were to determine the effects of cyclooxygenase (COX) inhibition with nonsteroidal anti-inflammatory agents (NSAIDs) that were either COX-nonspecific (ibuprofen) or a preferential inhibitor of COX-2 (carprofen) on renal function in euvolemic female beagle dogs and in those same dogs following induction of extracellular fluid volume depletion. Plasma and urine biochemistries and urinary clearances of creatinine and para-aminohippuric acid were used to assess glomerular filtration rate (GFR) and renal plasma flow (RPF), respectively, in dogs with and without chronic administration of 4 mg furosemide/kg body weight orally twice daily for 8 days. In this setting, the effects of oral administration of ibuprofen (10 mg/kg once daily) and carprofen (2.2 mg/kg twice daily) were compared utilizing a randomized crossover design. Compared to placebo treatment, dogs receiving furosemide plus either NSAID experienced a quantitatively similar, statistically significant

increase in plasma creatinine and decrease in GFR. These changes resolved when treatment was discontinued. The renal effects of the COX-nonspecific and the preferential COX-2 inhibitor were comparable and not significantly different. These results suggest that the use of either NSAID in dogs with extracellular fluid volume depletion or in dogs receiving furosemide is deleterious to renal function during treatment.

### INTRODUCTION

The formation of prostanoids is largely mediated by isoforms of cyclooxygenase (COX). The COX-1 isoenzyme was traditionally considered to be the constitutive isoform that preserved renal functions, such as renal plasma flow (RPF) and glomerular filtration rate (GFR) in certain states, such as extracellular fluid volume depletion<sup>1-3</sup> Inhibition of COX-2 produces some of the therapeutic effects of NSAIDs, which include anti-inflammatory, analgesic, and antipyretic properties.<sup>4-6</sup> The COX-2 was originally viewed as an inducible form, being expressed primarily in the presence of inflammation.<sup>2,7-9</sup> By this simple paradigm, the therapeutic effects of NSAIDs (eg, an-

algnesia) are mediated by COX-2 inhibition and the toxic effects (eg, gastric ulceration and reduced renal function) are mediated through COX-1 inhibition. To the extent this simple scheme is valid, differential inhibitory effects of NSAIDs on the various isoforms of cyclooxygenase may provide therapeutic advantages and COX-2 selective agents have been advocated as safer alternatives to non-selective agents. The physiologic and pathologic roles of blockade of COX-2 in the kidney are not completely understood,<sup>5,10</sup> particularly in canine patients.

Carprofen and ibuprofen are non-steroidal anti-inflammatory drugs (NSAIDs) that may be prescribed for dogs for the symptomatic treatment of acutely and chronically painful conditions, with analgesic effects mediated through inhibition of prostaglandin synthesis.<sup>6,11,12</sup> Ibuprofen, a propionic acid derivative that has been used in dogs, is classified as a nonselective COX inhibitor. Accordingly, ibuprofen has been associated with gastrointestinal erosions<sup>13-15</sup> and nephrotoxicity<sup>13</sup> in clinical patients. While controversial,<sup>16,17</sup> there is evidence that the propionic-acid derivative, carprofen, is a preferential COX-2 inhibitor.<sup>18-20</sup>

Gastrointestinal toxicity associated with vomiting is a common complication of NSAIDs. Vomiting animals may suffer from volume-depletion alkalosis,<sup>21</sup> particularly if vomiting is protracted and severe, and this might enhance the renal effects of NSAIDs. Diuretic administration, particularly loop diuretics, induce a similar volume-depletion alkalosis.<sup>21,22</sup>

The purpose of the study reported here was to test the hypothesis that:

- The renal effects of NSAIDs would be enhanced by the presence of volume-depletion
- A nonselective NSAID (ibuprofen), but not a preferential COX-2 inhibitor (carprofen), would adversely affect renal function in this setting
- If a decrement in renal function occurred in this setting with either NSAID, determine its reversibility.

## MATERIALS AND METHODS

### Animals

Twelve female beagle dogs between 6 months and 2 years of age weighing  $9.7 \pm 0.2$  kg were used in the study. Results of physical examination, complete blood count, and serum biochemical analysis were normal. The dogs were housed individually in an indoor, temperature-controlled environment, fed 132 kcal/kg<sup>0.75</sup> of a maintenance canine food<sup>a23</sup> (Purina Pro-Plan Chicken and Rice diet, Nestle Purina PetCare Company, St. Louis, MO) once daily (which contained 26% protein, 16% fat, 3% fiber, 12% moisture, 1.3% salt, 1.0% calcium, and 0.8% phosphorus on a dry matter basis), and allowed free access to water. One month prior to the start of the study, the dogs were given vaccines against distemper, parvovirus, canine hepatitis, and leptospirosis. Fecal examinations were performed at that time, and appropriate antiparasitic drugs were administered if needed. This project complied with the Animal Welfare Act, the U S Public Health Service Policy on the Humane Care, Use of Laboratory Animals, the NRC Guide for the Care, Use of Laboratory Animals, and the University of Georgia Animal Care and Use Committee.

### Experimental design

The dogs were paired and randomized to a Latin-square crossover design. There were six treatment pairs and six treatment periods (A-F, Table 1), each of approximately 20 days in duration. Drug(s) and/or placebo were administered during the first 8 days of each treatment period, which was followed by 10 - 13 days of drug withdrawal before the treatment pair was randomly assigned to a new treatment. Day 1 for each of the treatment periods was defined as the day on which that animal was first treated with placebo, furosemide, or NSAID.

Between 0700-1220 hrs of day, one for each treatment period, renal clearance studies as defined in this article, were conducted. Starting between 1,400-1,700 hrs on day 1, placebo, ibuprofen, carprofen, and/or furosemide (Gelatin capsules, Eli Lilly,

Indianapolis, IN, Advil, Wyeth Consumer Healthcare, Richmond, VA, Rimadyl, Pfizer Animal Health, Exton, PA, and Salix, Intervet Inc, Millsboro, DE, respectively) were administered daily to the 12 animals. The treatment dosages were determined using the body weight determined on day 1 of each treatment period. The target dosage for carprofen was 2.2 mg/kg orally twice daily, for ibuprofen was 10 mg/kg orally once daily,<sup>24</sup> and for furosemide, 4 mg/kg orally twice daily. The carprofen dosage was based on canine dosages recommended in package inserts for the medication. The last dosage was administered at 0700 rsh on day 8 of each treatment period, and renal clearance studies were repeated, beginning 75-90 minutes after administration of medication. Following the clearance studies, medication was discontinued for 10-13 days until the beginning of the next treatment period.

Approximately 1 month following the end of the 6th treatment period, as an estimate of the effects of furosemide on plasma volume, inulin concentration after IV injection was determined.

### **Plasma Biochemistries**

Blood was obtained by venipuncture and collected into tubes containing approximately 5 U of heparin/ml of blood for measurement of plasma concentrations of BUN, creatinine, and electrolytes, immediately prior to renal clearance studies on days 1 and 8.

### **Renal Clearance Studies**

Three months prior to the start of the study, the dogs were acclimated to collection stands once weekly for 2-hour intervals. Before clearance studies, dogs were fasted but allowed ad lib access to water for 12-20 hours.

Glomerular filtration rate (GFR) and renal plasma flow (RPF) were determined for all dogs by measuring the urinary clearance of creatinine (fCreatinine, Sigma Chemical Co, St. Louis, MO) and para-aminohippuric acid (PAH, Sigma Chemical Co, St Louis, MO), respectively. For determination of GFR and RPF, urinary catheters were aseptically placed in all dogs. The dogs were

given water equal to 3% body weight (wt/vol) by gavage. Immediately after completing the gavage, 2ml/kg of a solution containing 25 mg creatinine and 3.75 mg of PAH was administered SQ to each dog. A second injection of 0.6ml/kg of the creatinine/PAH solution was given to each dog 25 minutes later. The bladder was emptied and rinsed with sterile distilled water. Three consecutive timed urine collections were then obtained approximately 50 minutes after administration of creatinine and PAH. A venous blood sample was obtained at the beginning of the first period and the end of all 3 periods.

Use of Plasma Inulin Concentration to Estimate Plasma Volume Changes Following the six treatment periods, blood was obtained in all 12 dogs by venipuncture and collected into tubes containing approximately 5 IU of heparin/ml of blood for measurement of plasma concentration of inulin 5.0 minutes post-infusion of 1.0 gm of inulin (Sigma Chemical Co, St Louis, Mo.) prepared as a 5% inulin solution in 0.9% saline solution, prior to and at the end of 8 days of administration of furosemide (4 mg/kg orally twice daily).

### **Analyses and Calculations**

Plasma biochemistries and creatinine concentrations in plasma and urine were determined by automated analyzer (iAutomated Analyzer, Abbott Diagnostics, Irving, TX). The PAH concentrations in plasma and urine were measured by a standard chemical method.<sup>1</sup> The urinary clearance of creatinine and PAH, calculated by standard clearance formula, was taken to indicate GFR and RPF, respectively.<sup>1</sup> Inulin concentration in plasma was determined as previously reported<sup>25</sup> and the ratio of plasma inulin concentration prior to furosemide administration and after 8 days of furosemide administration (4 mg/kg twice daily orally) was calculated as an index of the decrement in plasma volume.

### **Statistical Analyses**

Statistical analyses were performed with the aid of a commercial software package

**Table 1** – Values for urine and plasma analyses on day 8 of treatment

Treatment	Medication(s)	PCr	BUN	Na+	Cl-	K+	HCO3-	USG
Day 1	None	0.97 ± 0.02	13.0 ± 0.3	150 ± 1	110 ± 1	4.4 ± 0.1	20.4 ± 0.4	1.038 ± 0.003
Day 8								
A	Placebo	0.94 ± 0.03 <sup>a</sup>	14.0 ± 1.1 <sup>a</sup>	152 ± 3 <sup>a</sup>	111 ± 1 <sup>a</sup>	4.4 ± 0.2 <sup>a</sup>	19.8 ± 0.4 <sup>a</sup>	1.039 ± 0.003 <sup>a</sup>
B	Ibuprofen	0.95 ± 0.03 <sup>a</sup>	13.4 ± 0.6 <sup>a</sup>	151 ± 2 <sup>a</sup>	111 ± 1 <sup>a</sup>	4.5 ± 0.1 <sup>a</sup>	20.7 ± 0.6 <sup>a</sup>	1.030 ± 0.003 <sup>b</sup>
C	Carprofen	1.00 ± 0.05 <sup>a,b</sup>	14.9 ± 1.2 <sup>a,b</sup>	150 ± 3 <sup>a</sup>	113 ± 2 <sup>a</sup>	4.6 ± 0.2 <sup>a</sup>	20.1 ± 0.7 <sup>a</sup>	1.031 ± 0.003 <sup>b</sup>
D	Furosemide	1.06 ± 0.06 <sup>a,b</sup>	17.8 ± 1.4 <sup>b,c</sup>	152 ± 3 <sup>a</sup>	107 ± 4 <sup>a</sup>	4.0 ± 0.2 <sup>a</sup>	24.4 ± 0.8 <sup>b</sup>	1.010 ± 0.002 <sup>c</sup>
E	Ibuprofen + Furosemide	1.14 ± 0.09 <sup>b</sup>	19.3 ± 1.2 <sup>c</sup>	153 ± 3 <sup>a</sup>	111 ± 4 <sup>a</sup>	4.3 ± 0.1 <sup>a</sup>	23.8 ± 0.8 <sup>b</sup>	1.012 ± 0.002 <sup>c</sup>
F	Carprofen + Furosemide	1.14 ± 0.08 <sup>b</sup>	19.6 ± 1.9 <sup>c</sup>	152 ± 2 <sup>a</sup>	109 ± 2 <sup>a</sup>	4.3 ± 0.2 <sup>a</sup>	22.8 ± 0.3 <sup>b</sup>	1.008 ± 0.001 <sup>c</sup>

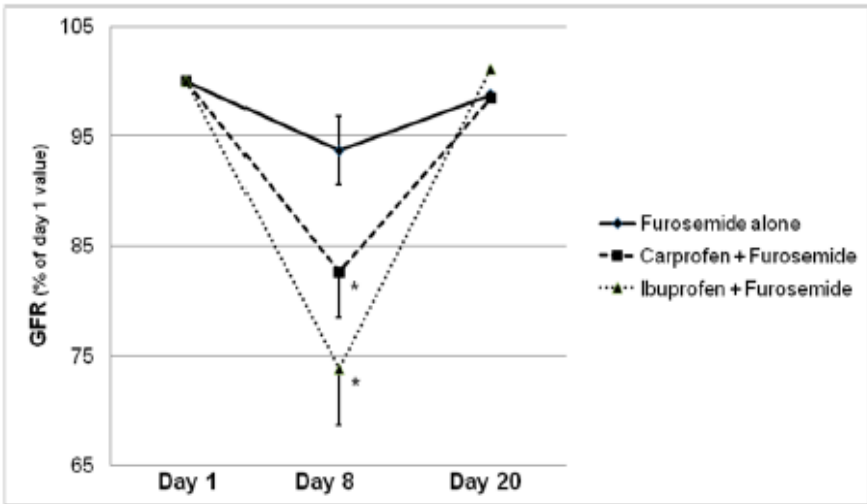
Abbreviations used are: PCr = plasma creatinine concentration; BUN = blood urea nitrogen concentration; Na+ = plasma sodium concentration; Cl- = plasma chloride concentration; K+ = plasma potassium concentration; HCO3- = plasma bicarbonate concentration; USG = urine specific gravity.  
a,b,c: Values in same column with no shared superscripts are different ( $P < 0.05$ ).

**Table 2** - Results of renal clearance studies

Treatment	GFR (ml/min/kg)		RPF (ml/min/kg)		FF	
	Pre (day 1)	Post (day 8)	Pre (day 1)	Post (day 8)	Pre (day 1)	Post (day 8)
A	3.12 ± 0.07a	3.08 ± 0.07a	11.4 ± 0.5a	12.2 ± 0.8a	0.28 ± 0.01a	0.26 ± 0.02a
B	3.06 ± 0.07a	3.02 ± 0.06a	11.2 ± 0.5a	11.1 ± 0.6a	0.28 ± 0.01a	0.27 ± 0.01a
C	3.04 ± 0.06a	3.03 ± 0.07a	11.5 ± 0.4a	11.7 ± 0.6a	0.26 ± 0.02a	0.25 ± 0.01a
D	3.07 ± 0.09a	2.87 ± 0.12a	11.5 ± 0.6a	12.4 ± 0.8a	0.27 ± 0.01a	0.23 ± 0.02a
E	3.11 ± 0.05a	2.29 ± 0.10b	10.9 ± 0.3a	10.4 ± 0.7a	0.29 ± 0.01a	0.23 ± 0.01b
F	3.10 ± 0.09a	2.54 ± 0.16b	11.6 ± 0.6a	10.7 ± 0.9a	0.27 ± 0.01a	0.24 ± 0.01b

Abbreviations used are: GFR = glomerular filtration rate; RPF = renal plasma flow; FF = filtration fraction.  
a,b: Values in same column with no shared superscripts are different ( $P < 0.05$ ).

**Figure 1:** Mean ( $\pm$ SEM) values for GFR, expressed as a % of day 1 values from the corresponding treatment period. Day 1 is the first day of treatment, day 8 is the last day of treatment, and day 20 is the first day of the next period, following approximately 12 days of drug withdrawal. \* $P < 0.05$  vs. corresponding day 8 value for furosemide alone.



(Statview 4.5, Abacus Concepts, Berkeley, CA). Numeric data were compared among groups by analysis of variance. Values were compared among and within groups by use of repeated measures ANOVA. Values are reported as a mean score  $\pm$  SEM. A  $P$  value  $< 0.05$  was considered indicative of statistically significant difference.

## RESULTS

### Medication Dosage

The mean administered dosage of furosemide for treatments D, E, and F was  $3.8 \pm 0.2$  mg/kg given orally twice daily, and was not significantly different among treatments or periods. The mean administered dosage of ibuprofen was  $10.4 \pm 0.4$  mg/kg given orally once daily, and was not significantly different between treatments B and E. The mean administered dosage of carprofen was  $2.2 \pm 0.2$  mg/kg given orally twice daily, and was not significantly different between treatments C and F.

### Pretreatment (day 1) Measurements

Significant differences were not detected in mean values obtained on day 1 for body weight, RPF, and GFR, or for plasma con-

centrations of electrolytes, BUN, and creatinine among the six treatment periods. Mean food intake was  $185.8 \pm 5.5$  g/kg/d during the treatment periods and did not vary significantly among treatments or periods.

### Effects of Furosemide

Compared to pretreatment values, inulin concentration in plasma 5 minutes after IV injection of 1.0 gm was increased ( $P < 0.05$ ) by  $13.0 \pm 3.2$  % after 8 days of furosemide administration. Following 8 days of treatment with furosemide alone (treatment D), the BUN was increased ( $P < 0.05$ ), and both the plasma bicarbonate concentration and urine specific gravity were decreased ( $P < 0.05$ ) compared to placebo treatment (Table 1). The mean values for GFR and RPF were not significantly different from the corresponding value for placebo treatment although there was a statistically insignificant trend for GFR to decline (Table 2).

### Effects of Ibuprofen

Following 8 days of treatment with ibuprofen alone (treatment B), the mean values for GFR and RPF were not significantly different from the corresponding value for pla-

cebo treatment (Table 2). Following 8 days of administration of ibuprofen plus furosemide (treatment D), there was a significant increase in plasma creatinine concentration, BUN, and bicarbonate, and a decrease in urine specific gravity compared to placebo treatment. For treatment D, there was a decrease in GFR but not RPF, compared to corresponding values for placebo (treatment A), ibuprofen alone (treatment B), carprofen alone (treatment C), and furosemide alone (treatment D). Compared to pre-treatment values, the mean reduction in GFR was  $0.83 \pm 0.12$  ml/min/kg. The GFR returned to pretreatment values after drug withdrawal (Figure 1).

### Effects of Carprofen

Following 8 days of treatment with carprofen alone (treatment C), the mean values for GFR and RPF were not significantly different from the corresponding value for placebo treatment (Table 2). Following 8 days of administration of carprofen plus furosemide (treatment E), there was a significant increase in plasma creatinine concentration, BUN, and bicarbonate, and a decrease in urine specific gravity compared to placebo treatment (Table 1). For treatment E, there was a significant decrease in GFR but not RPF, compared to corresponding values for placebo (treatment A), ibuprofen alone (treatment B), carprofen alone (treatment C), and furosemide alone (treatment D). Compared to pre-treatment values, the mean reduction in GFR was  $0.55 \pm 0.17$  ml/min/kg. The GFR returned to pretreatment values after drug withdrawal (Figure 1).

### DISCUSSION

In the kidney, prostaglandins have a variety of effects, including hemodynamic, hemostatic, and cytoprotective functions.<sup>5,6,10,20</sup> Prostaglandins also participate in the regulation of the renin-angiotensin-aldosterone system by promoting the release of renin from the kidney in response to extracellular fluid volume depletion.<sup>5,6,10</sup> Prostaglandins also play a role in tubular handling of water and electrolytes in animals.<sup>10</sup>

The therapeutic approach to analgesia in

dogs has been affected by the development of classes of potentially safer cyclooxygenase inhibitors that preferentially inhibit the COX-2 isoenzyme. Preferential COX-2 inhibitors appear to be less likely to result in gastrointestinal toxicity.<sup>26</sup> However, the effects of these newer NSAIDs on the kidney are incompletely understood. As a non-selective COX inhibitor, ibuprofen alone did not affect GFR and RPF in euvoletic beagle dogs. Similar results were seen with carprofen when administered alone. These results are consistent with the assertion that prostanoids are important in renal hemodynamics only in certain pathophysiological settings. Interestingly, both agents administered alone reduced urine specific gravity. We did not test maximal urinary concentration ability and these results merit further investigation to determine if urinary concentrating ability in dogs is compromised by NSAID administration.

The COX-1 isoenzyme is constitutively expressed in canine kidneys in collecting duct cells, medullary interstitial cells, endothelial cells, and smooth muscle cells of the pre- and postglomerular vessels, and appears to play a role in hemodynamic regulation.<sup>27-29</sup> Conventionally, COX-1 was held to be the important isoenzyme in the canine kidney in producing vasodilatory prostaglandins to maintain renal plasma flow GFR and RPF during conditions that otherwise favor renal vasoconstriction and depressed renal function, such as volume-depletion. As noted above, renal expression of COX-2 was once thought to be inducible and up-regulated only in the presence of inflammation. However, COX-2 is constitutively expressed in the canine macula densa, cortical thick ascending limb of the loop of Henle, and medullary interstitial cells.<sup>10,30-33</sup>

While it was reasonable to speculate that a preferential COX-2 inhibitor would have less impact on GFR and RPF than a non-selective NSAID, our results do not support this contention. While carprofen is classified as a preferential COX-2 inhibitor, in volume-depleted animals, the effects of car-



profen on plasma biochemistries (increased plasma creatinine concentration and BUN) were similar to, and not significantly different from those of the nonselective agent ibuprofen.<sup>18</sup> The decrement in GFR caused by NSAIDs in dogs receiving furosemide was not significantly different between ibuprofen and carprofen in our study. This effect occurred in a relatively short time-frame (8 days), and was rapidly reversible, suggesting the mechanism was hemodynamic rather than nephrotoxicity of these agents. The co-administration of either NSAID led to a reduction in GFR but not RPF. A decrease in GFR without a corresponding decrease in RPF suggests preglomerular constriction coupled with a comparable decrease in postglomerular vascular resistance. The preglomerular dilation was likely due to loss of vasodilatory prostanoids. As COX-2 plays an important role in regulation of local production of renin, it is plausible that the postglomerular effect was mediated by local effects of angiotensin II, which preferentially constricts the efferent arteriole in dogs. However, there are a myriad of factors that alter renal arteriolar tone and we did not investigate the mechanism of these effects in our study.

Diuretic administration, particularly at high dosages, can produce volume-depletion alkalosis.<sup>22</sup> Accordingly, furosemide administration led to a decrease in urine specific gravity and estimated plasma volume and an increase in plasma bicarbonate concentration. The alterations in plasma bicarbonate concentration are likely due to known effects of volume contraction on renal bicarbonate handling.<sup>22</sup> We chose this model of volume depletion because previous reports suggested that gastrointestinal and renal complications may coexist in animals with NSAID toxicity, suggesting there may be synergism. Gastrointestinal toxicity from NSAID administration is often associated with vomiting and volume depletion, a classic cause of volume-depletion alkalosis. In the present study, furosemide administration was utilized to test the effects of NSAIDs on kidney function in that setting. Volume-

depletion would appear to place dogs at risk for acute reduction in GFR from NSAID administration, with comparable effects observed with both agents tested in the present study. While the effects of the administration of furosemide could be mediated wholly by extracellular fluid volume depletion and metabolic alkalosis, there could also be drug-specific factors that impacted the results we observed. For example, furosemide is known to increase expression of mRNA for COX-2 and renin in the renal cortex,<sup>34</sup> an effect which could be mediated solely by volume-depletion<sup>22</sup> or by drug specific effects of this diuretic. Our studies do not permit us to separate the relative contributions of a drug-specific effect vs an effect common to all causes of volume-depletion or metabolic alkalosis. Nonetheless, volume depletion, metabolic alkalosis, and furosemide administration are common conditions in veterinary patients. In particular, volume-depletion alkalosis associated with gastrointestinal toxicity from NSAID administration would appear to place dogs at risk for acute reduction in GFR.

While adverse health effects were not observed in the present study, reductions in GFR were associated with increases in BUN and plasma creatinine concentration in young, otherwise healthy dogs with normal renal function prior to the study. Our study does not permit us to predict the effects of these NSAIDs in volume-depleted animals in which advancing age or pre-existing clinical abnormalities co-exist. Critically, our study does not support the hypothesis that renal effects are markedly different between a COX-nonselective agent and a preferential COX-2 inhibitor. In volume-depletion, the risk for renal complications from NSAID administration would appear to be similar for these 2 agents.

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