Evaluation of adverse effects of long-term oral administration of carprofen, etodolac, flunixin meglumine, ketoprofen, and meloxicam in dogs

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Objective—To evaluate adverse effects of long-term oral administration of carprofen, etodolac, flunixin meglumine, ketoprofen, and meloxicam in dogs.

Animals—36 adult dogs.

Procedures—Values for CBC, urinalysis, serum biochemical urinalyses, and occult blood in feces were investigated before and 7, 30, 60, and 90 days after daily oral administration (n = 6 dogs/group) of lactose (1 mg/kg, control treatment), etodolac (15 mg/kg), meloxicam (0.1 mg/kg), carprofen (4 mg/kg), and ketoprofen (2 mg/kg for 4 days, followed by 1 mg/kg daily thereafter) or flunixin (1 mg/kg for 3 days, with 4-day intervals). Gastroscopy was performed before and after the end of treatment.

Results—For serum γ-glutamyltransferase activity, values were significantly increased at day 30 in dogs treated with lactose, etodolac, and meloxicam within groups. Bleeding time was significantly increased in dogs treated with carprofen at 30 and 90 days, compared with baseline. At 7 days, bleeding time was significantly longer in dogs treated with meloxicam, ketoprofen, and flunixin, compared with control dogs. Clotting time increased significantly in all groups except those treated with etodolac. At day 90, clotting time was significantly shorter in flunixin-treated dogs, compared with lactose-treated dogs. Gastric lesions were detected in all dogs treated with etodolac, ketoprofen, and flunixin, and 1 of 6 treated with carprofen.

Conclusions and Clinical Relevance—Carprofen induced the lowest frequency of gastrointestinal adverse effects, followed by meloxicam. Monitoring for adverse effects should be considered when nonsteroidal anti-inflammatory drugs are used to treat dogs with chronic pain. (*Am J Vet Res* 2007;68:258–264)

Nonsteroidal anti-inflammatory drugs are one of the best classes of drug to prevent and treat postoperative pain. They induce potent analgesic and anti-inflammatory effects,[1] inhibit spinal nociceptive transmission,[2] and are indicated for situations of potential edema and inflammation, mainly in cases of musculoskeletal disorders.[3]

Results of several studies indicate that NSAIDs are sometimes more effective than opioids in treating postoperative pain in dogs[1,4-7] and cats.[8] These drugs are the World Health Organization's first choice for treating mild to moderate chronic pain.[9] Their prolonged use is preferable, compared with pure agonist opioids, because they are nonaddictive, have a long-lasting effect, do not cause sedation or respiratory depression, and have no narcotic control issues.[9,10] The NSAIDs reduce inflammation by inhibiting the action of cyclooxygenase, which converts arachdonic acid into prostanoids (PGG_2 and H_2 and prostacyclines). Prostaglandin H_2 is converted into various eicosanoids, such as PGD_2, PGE_2, $PGF_{2\alpha}$, PGI, and thromboxane A_2, which are inflammation mediators and amplify nociceptive input and transmission to the spinal cord.[2,3,11] Nonsteroidal anti-inflammatory drugs limit the formation of PGs and the effects on peripheral sensory receptors of inflammatory mediators such as histamine, bradykinin, and other kinins.[12] Central antinociceptive effects have also been suggested because NSAIDs may act on excitable membranes, on second messenger systems, or in the expression of inflammatory mediators.[13]

Abbreviations

NSAID	Nonsteroidal anti-inflammatory drug
PG	Prostaglandin

Results of several studies indicate that NSAIDs have good analgesic properties in dogs; however, there is concern about their adverse effects, particularly after long-term use. These include gastric ulcers; development of protein-losing enteropathy; nephrotoxicosis[11,14]; and coagulation disorders, such as inhibition of platelet cyclooxygenase, reduced formation of proaggregatory eicosanoid thromboxane A_2, and prevention of platelet aggregation.[3]

Advances in developing more specific drugs that reduce these adverse effects have been made. More recently developed drugs predominantly inhibit inductive cyclooxygenase-2 that is released by damaged or inflamed tis-

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sue, which is responsible for pain and hyperalgesia after injury, while at the same time maintaining as much of the constitutive cyclooxygenase-1 effect as possible, which modulates renal and gastrointestinal blood flow and coagulation. However, even more specific recent cyclooxygenase-2 inhibitor NSAIDS are not free of adverse effects, which are intensified when they are used for long periods to treat chronic pain.[15-17]

Flunixin is a potent anti-inflammatory and analgesic drug,[15] which preferentially inhibits cyclooxygenase-1 and is indicated for acute and surgical pain. However, acute renal failure,[18] increased serum alanine aminotransferase activity,[19] and gastroduodenal ulcers[15,16] have been reported in dogs treated with flunixin. Carprofen is classified as a preferential cyclooxygenase-2 inhibitor and is available as a racemic mixture.[20] Its mode of action is not fully understood, and the low prevalence of adverse effects caused by clinical doses may be attributed to its weak inhibition of cyclooxygenases.[14] Carprofen is an effective analgesic for dogs with induced acute synovitis, orthopedic problems, or osteoarthritis, and after soft tissue surgery.[6, 20-22]

Ketoprofen is an arylpropionic acid and potent cyclooxygenase inhibitor with no cyclooxygenase-2 selectivity in dogs. It is different from other NSAIDs in that it also inhibits lipoxygenase and the leukotriene inflammatory pathway and promotes proteoglycan synthesis, creating a double blockade of arachidonic acid metabolism.[2,23,24] Ketoprofen induces a 30% rate of adverse effects, including gastrointestinal changes, dizziness, headache, and nephritis in humans.[25]

Etodolac is a pyranocarboxylic acid and one of the most commonly used NSAIDs for treating arthritis. In vitro data suggest that it has low cyclooxygenase-2 selectivity.[13,26] It does not appear to interfere with PG synthesis in the gastrointestinal mucosa, as do other NSAIDs, and thus preserves the beneficial effects of local PGs.[2,9,27] It is well tolerated by dogs with minimal adverse effects when used for 8 days.[28] However, when used for 28 days in dogs, minor gastric lesions are observed, similar to carprofen.[29,30]

Meloxicam has been used in dogs for medium- to long-term treatment of musculoskeletal pain and inflammation. It has selectivity against cyclooxygenase-2 versus cyclooxygenase-1 and appears to be safe for the gastrointestinal tract in humans.[31]

Several studies have been performed to investigate acute adverse effects from NSAIDs, but only a few report long-term adverse effects. The purpose of the study reported here was to evaluate the safety of administration of carprofen, etodolac, meloxicam, flunixin, or ketoprofen for 90 days in dogs.

Materials and Methods

This study was approved by the Animal Research Ethics Committee of the School of Veterinary Medicine and Animal Science at São Paulo State University. Forty-two crossbreed adult female dogs, 1 to 5 years of age and weighing from 15 to 20 kg, underwent a clinical and preliminary laboratory investigation (urinalysis, CBC, and serum biochemical analyses) to ensure that they were healthy. The dogs were identified with numbered collars; treated against endoparasites and ectoparasites with selamectin[a] and praziquantel, febantel, and pyrantel[b]; and vaccinated against distemper, leptospirosis, parvovirus, infectious hepatitis, adenovirus type I, parainfluenza, and rabies.[c] All dogs were spayed and maintained in quarantine for 3 months prior to the study. During this period, they underwent adaptation to housing and feeding conditions and group socialization.

After a 30-day adaptation period, dogs were clinically inspected and a second complete urinalysis and CBC were performed. Urine samples were collected via cystocentesis; specific gravity was measured with a handheld refractometer[d]; pH and concentrations of proteins, glucose, ketones, and bilirubin, and fecal occult blood were determined by use of multiple-test reagent strips;[e] and urinary sediment was evaluated with a light microscope.[f] Blood (10 mL) was withdrawn from a jugular vein by venipuncture; part was put into a glass tube containing EDTA[g] for CBC and part into a tube without anticoagulant[h] for serum biochemical analyses.

The CBC and platelet count were determined by use of an automated cell counter[i] and Hct via the microhematocrit method.[32] Differential leukocyte counts were performed with blood on slides stained according to Leishman[32] and total plasma protein by refractometry.[d] Hemoparasites were also investigated.

Clinical biochemical analyses included serum urea and creatinine concentration and serum activity of alanine transaminase, alkaline phosphatase, and γ-glutamyltransferase. Total protein, albumin, and globulin concentrations were determined with standard kits[j] and a spectrophotometer.[k]

Bleeding time was measured by use of the Duke method. Each dog was restrained, and a puncture was performed on the internal surface of the ear with a trifaced lancet. Time until bleeding stopped was recorded by use of a filter paper and stopwatch. Clotting time was determined by the Lee-White method.[32]

Gross and occult blood in feces were determined from feces collected from the rectum with lubricated gloves. The feces were divided in 2 aliquots, and each was placed in an envelope window of the standard kit,[l] with 2 drops of reagent. When blood was present in the feces, a halo formed on the paper around the fecal sample. When results were positive, this test was repeated with fresh, naturally passed feces taken from the floor. Results were recorded as positive if blood was present and negative if blood was absent.

After premedication with acepromazine[m] (0.05 mg/kg, IM), a cephalic vein was aseptically catheterized with a 20-gauge catheter.[n] Anesthesia was induced approximately 20 minutes after premedication with thiopental sodium[o] (10 mg/kg, IV). After endotracheal intubation, anesthesia was maintained with halothane[p] in oxygen administered though a circular breathing circuit. Gastroscopy was performed in all dogs at least 8 days before the study to ensure gastric integrity. Lactated Ringer's solution was administered IV at a rate of 10 mL/kg/h throughout examination. Stomach lesions were graded according to Forsyth et al[33] as grade 0 (no visible hemorrhages, erosions, or ulcers), 1 (1 to 5 punctate erosions, hemorrhages, or both), 2 (6 to 15 punctate erosions, hemorrhages, or both), 3 (16 to

25 punctate erosions, hemorrhages, or both), 4 (> 25 punctate erosions, hemorrhages, or both; 1 to 5 invasive erosions; or both), 5 (> 6 invasive erosions), or 6 (ulcers of any size). All dogs had grade 0 scores before treatment. Erosion was defined as a discontinuation of the mucosa < 3 mm in diameter and an ulcer as > 3 mm with a craterous center. On the same occasion, 10-mL samples of urine were collected via urethral catheter and anesthesia. Urine was examined for density, protein concentration, and pH.

Thirty-six dogs that met the inclusion criteria (values of all measured variables within reference ranges) were equally allocated into 6 collective 4 × 3.5-m isolated boxes with natural ventilation. Dogs were fed commercial dry food, and water was provided ad libitum. On day 0, dogs were weighed and the boxes randomly assigned to the 6 treatment groups. The dogs were treated for a maximum of 90 days with single daily orally administered doses of one of the following: lactose (control treatment; 1 mg/kg), etodolac[q] (15 mg/kg), meloxicam[r] (0.1 mg/kg), ketoprofen[s] (2 mg/kg for 4 days, followed by 1 mg/kg/d thereafter), carprofen[t] (4 mg/kg), or flunixin meglumine[u] (1 mg/kg for 3 days with consecutive 4-day intervals). The FDA only licenses flunixin and ketoprofen for use in horses in the United States, flunixin is licensed for use in dogs in Europe,[11] and ketoprofen is licensed for use in dogs and cats in Canada. Carprofen, etodolac, and meloxicam are FDA-approved for dogs at the doses used in this study.

A veterinarian performed a general daily health examination for any evidence of diarrhea, signs of depression, inappetence, or signs of abdominal pain during the course of the study. When a dog had abnormal clinical findings, it underwent a complete clinical and laboratory examination, as described. When those findings were judged by an investigator (unaware of treatment assignment) to be related to a study drug, the dog was excluded from the study and treated appropriately and no further data were recorded for that dog. Regardless of daily examinations, a complete examination including clinical and laboratory tests was performed on all dogs 7, 30, 60, and 90 days after the beginning of treatments. The study terminated on day 90, when the last endoscopy was performed. The veterinarian performing gastroscopies was unaware of the treatments received by the dogs.

Statistical analysis—The number of dogs removed from the study because of drug-related adverse events was recorded. Statistical analysis was performed with software.[v] Data with a normal distribution were compared by use of ANOVA followed by the Dunnett test to investigate differences over time in each treatment, compared with baseline values, and the Student-Newman-Keuls test to investigate differences among treatments at each time. Nonparametric data were compared by use of ANOVA followed by the Friedman test to investigate differences over time in each treatment, compared with baseline values, and the Kruskal-Wallis test to investigate differences among treatments at each time. Significance was set at $P < 0.05$.

Results

Three dogs treated with ketoprofen were removed on days 39, 66, and 87, respectively, because of fighting and consequent lesions that could have interfered with results. There were no changes in values of the CBC, hemoglobin, Hct, total plasma protein, platelet count,

Table 1—Mean ± SD bleeding and clotting times (seconds) in dogs (n = 6/group) treated with lactose, etodolac, meloxicam, ketoprofen, carprofen, or flunixin for 90 days.

	Baseline		7 days	30 days		60 days		90 days	
Drug	Bleeding time	Clotting time	Bleeding time	Bleeding time	Clotting time	Bleeding time	Clotting time	Bleeding time	Clotting time
Lactose	40 ± 8	11 ± 1	40 ± 15	38 ± 8	11 ± 1	38 ± 21	11 ± 1	38 ± 31	11 ± 1
Etodolac	45 ± 13	9 ± 1†	45 ± 19	45 ± 12	10 ± 1	49 ± 28	11 ± 1	41 ± 23	11 ± 1
Meloxicam	60 ± 9	10 ± 1	73 ± 15†	43 ± 15	11 ± 1*	50 ± 15	13 ± 1*	40 ± 20	12 ± 1*
Ketoprofen	53 ± 21	10 ± 1	73 ± 28†	28 ± 20	12 ± 2	27 ± 13	13 ± 2*	55 ± 17	8 ± 3
Carprofen	35 ± 8	9 ± 1†	40 ± 18	60 ± 30*	11 ± 1	35 ± 12	12 ± 1*	60 ± 19*	10 ± 2
Flunixin	53 ± 8	9 ± 1†	75 ± 16†	53 ± 19	9 ± 1	45 ± 27	10 ± 1	60 ± 32	15 ± 3*†

*Significant ($P < 0.05$) difference from baseline value. †Significant ($P < 0.05$) differences between lactose and other treatments at each time.
Clotting time was not measured at 7 days.

Table 2—Proportions of dogs with positive results of fecal occult blood test before and during treatment with lactose, etodolac, meloxicam, ketoprofen, carprofen, or flunixin for 90 days.

Treatment	Before	7 days	30 days	60 days	90 days
Lactose	0/6	0/6	0/6	0/6	0/6
Etodolac*	0/6	4/6	3/4	2/4	4/4
Meloxicam	0/6	1/6	1/6	3/6	5/6
Ketoprofen†	0/6	1/6	0/6	3/5	3/3
Carprofen	0/6	0/6	1/6	1/6	3/6
Flunixin‡	0/6	3/6	0/4	4/4	4/4

*Two dogs were removed at day 25 because of melena. †Three dogs were removed at days 39, 66, and 87, respectively, because of fighting and consequent lesions that could have interfered with results. ‡Two dogs were removed at day 19 because of melena.

Table 3—Number of dogs removed from the study and distribution of gastric lesion grades in remaining dogs after 90 days of treatment with lactose, etodolac, meloxicam, ketoprofen, carprofen, or flunixin.

Treatment	No. of dogs removed	Grade						
		0	1	2	3	4	5	6
Lactose	0	6	0	0	0	0	0	0
Etodolac	2	0	0	1	0	2	0	1
Meloxicam	0	4	0	0	0	2	0	0
Ketoprofen	3	0	0	0	0	2	0	1
Carprofen	0	5	0	0	0	0	1	0
Flunixin	2	0	0	0	0	1	2	1

urea, creatinine, alanine transaminase, alkaline phosphatase, albumin, and globulin between basal values and other measurement times for each group or among groups at each time. Mean and individual values were within reference ranges for dogs.

Serum γ-glutamyltransferase activity was increased significantly at day 7 in dogs treated with lactose and meloxicam, compared with values obtained at baseline. At 30 and 90 days, bleeding time was significantly increased in dogs treated with carprofen, compared with baseline. At 7 days, bleeding time was significantly longer in dogs treated with meloxicam, ketoprofen, and flunixin, compared with dogs treated with lactose (**Table 1**). Clotting time increased significantly between 30 and 90 days after meloxicam administration, at 60 days after ketoprofen and carprofen administration, and at 90 days after flunixin administration, compared with baseline values. Dogs that received lactose had significantly longer clotting time before treatment, compared with dogs treated with etodolac, carprofen, and flunixin. At day 90, clotting time was significantly shorter in flunixin-treated dogs than those treated with lactose.

There was no difference within and among groups in urine density, pH, and proteins before treatment versus day 90 of treatment. At the end of the study, various numbers of dogs had positive results of a fecal occult blood test (**Table 2**). Two dogs treated with flunixin were removed at day 19 and 2 treated with etodolac were removed at day 25 because of melena.

There were no gastric lesions in lactose-treated dogs at 90 days. Gastric lesions of various grades were seen in dogs in the other groups (**Table 3**).

Discussion

The most common findings from NSAID-induced PG inhibition in the gastrointestinal tract are nausea, vomiting, gastric pain, diarrhea, and blood in feces.[2,12,16] Although endoscopy is considered a sensitive method for detecting early NSAID-induced gastric injury in dogs,[15] most studies that used gastroscopy did not find any correlation between clinical signs (eg, attitude, appetite, and signs of abdominal pain) and gastrointestinal injury.[15] Gatrointestinal biopsies were not performed in the study reported here, although gross endoscopic evaluation of gastric lesions correlates with gross lesions at necropsy and is therefore a reliable method of evaluating ulceration and gastric adverse effects.[1,15]

Although false-positive results for fecal occult blood may be found in dogs fed meat-based diets,[20] this test was apparently reliable in the present study because dogs from the control group yielded negative results even when fed commercial food. Dogs treated with carprofen had the lowest frequencies of occult blood in feces and gastric lesions, compared with the other NSAID-treated groups. These findings are similar to those of a previous study[20] in which carprofen induced a low frequency of adverse gastrointestinal effects when used for 2 weeks in dogs. Fecal alpha(1)-proteinase inhibitor, which is a noninvasive marker for protein-losing enteropathy and an indicator of NSAID-induced gastrointestinal damage, was not modified by daily meloxicam or carprofen administration for at least 30 days.[34] This was also confirmed in the present study in which only 1 of 6 dogs had fecal occult blood at day 30 of treatment with meloxicam and carprofen. However, at day 60, with the exception of carprofen, fecal occult blood was detected in at least 50% of dogs in all groups.

Gastric lesions were found in 3 of 6 ketoprofen-treated dogs in this study (grade 4 in 2 dogs; grade 6 in 1 dog). In a previous study,[33] endoscopy revealed hemorrhage or erosions in 5 of 6 dogs treated with ketoprofen for 28 days. No gastrointestinal or other adverse effects were observed when a lower ketoprofen dosage (0.25 mg/kg/d) was used for 30 days,[35] indicating that most adverse effects from administering ketoprofen are probably caused by higher doses. This may be of clinical relevance because a low (0.25 mg/kg) ketoprofen dose improves peak vertical force weight bearing and signs of joint pain in dogs, similar to 0.5 and 0.75 mg/kg doses.[35] The ketoprofen dosage used in the present study was recommended in pain management textbooks.[13,14] Further studies are necessary to confirm the analgesic effects of lower ketoprofen doses and the possible reduction in gastrointestinal adverse effects when low doses are used over a long period.

The potential adverse gastrointestinal effects of prolonged flunixin use have been reported[15]; however, most adverse effects were caused by incorrect doses and intervals or treatment being maintained despite signs of toxicosis.[16] Four dogs treated with flunixin in the present study had gastric lesions ranging from grade 4 to 6, and 2 dogs were removed at day 19 because of occult blood in feces and melena. The remaining flunixin-treated dogs had occult blood in feces after 90 days of treatment. Therefore, flunixin cannot be recommended for chronic use and should be restricted to the postoperative period only.[9,14]

At the end of treatment, 2 dogs treated with meloxicam had grade 4 gastric lesions and 5 of 6 dogs had occult blood in feces. To the authors' knowledge, this

is the first report of administration of meloxicam over such a long period. At day 30, only 1 of 6 dogs had occult blood in feces. Similar findings have been reported in which 12% of dogs treated with meloxicam for up to 39 days had mild transient clinical signs, such as diarrhea, vomiting, dullness, and loss of appetite and treatment was discontinued in 5%.[36] Also, a larger dose (0.2 mg/kg, PO) of meloxicam administered daily for 16 days caused vomiting and soft feces in 80% of dogs on day 5 of treatment, with hyperemia and gastroduodenal mucosal erosions in 80% and histopathologic signs of gastritis in 60% at necropsy.[17] These data suggest that the ideal dosage for meloxicam is 0.1 mg/kg, PO, once daily, as used in the present study.

Long-term use of carprofen and etodolac in this study caused grade 5 gastric lesions in 1 dog and grade 2 to 6 gastric lesions in 4 dogs, respectively. Two dogs treated with etodolac were removed at day 25, 1 because of occult blood in feces and the other because of melena, and the 4 remaining dogs had occult blood in feces after 90 days of treatment with etodolac. Although a previous study[37] in which dogs were treated with etodolac for 10 days did not reveal important gastric mucosal lesions during gastroscopy, in the present study, 4 of 6 dogs had occult blood in feces after 7 days of treatment, which indicated that etodolac is apparently not safe even for short-term treatment.

When just considering occult blood in feces, it seemed that the frequency was similar for carprofen, meloxicam, and ketoprofen when used for 30 days, as reported. However, frequency of occult blood was lower with carprofen after 60 and 90 days of treatment, which suggested that carprofen should be used for treatment periods exceeding 30 days. Evaluation of the mechanisms involved in NSAID-induced gastrointestinal tract injury was beyond the scope of this study and is reported elsewhere.[9,14,15]

Hepatotoxicosis has been associated with the use of carprofen and other NSAIDs in dogs[38] and is generally considered an idiosyncratic reaction. Creatinine clearance is significantly lower in dogs receiving a single dose of carprofen and ketoprofen, compared with dogs treated with saline (0.9% NaCl) solution.[39] Although clinical and laboratory findings of hepatic and renal lesions have been reported with administration of carprofen in dogs,[38] no significant changes were detected in the study reported here. The number of dogs used in this study was too low to draw a firm conclusion, but a retrospective study[40] involving a large number of dogs revealed that the frequency of liver dysfunction was < 0.06% in dogs treated with carprofen. Other studies have not detected hepatotoxic effects from the long-term use (60 days) of carprofen[41] or renal effects from carprofen in anesthetized dogs,[42] even with hypotension.[43] The same may be true for meloxicam because serum biochemical values, results of urinalysis, and glomerular filtration rate measured by use of scintigraphy[44] were not modified by administration of meloxicam in dogs with hypotension during anesthesia. Although ketoprofen did modify the serum biochemical profile in 1 study,[45] it induced transient azotemia in 2 of 10 clinically normal dogs undergoing general anesthesia and decreased urine specific gravity.

The potential risk of renal failure may be intensified when flunixin is combined with inhalation anesthesia because acute interstitial nephritis has been reported in a dog undergoing halothane anesthesia[46] and increased urea and creatinine concentrations and tubular necrosis have been reported after 24 hours of anesthesia with methoxiflurane.[19] As with the other drugs, flunixin and etodolac did not have any significant renal effects on the clinically normal dogs in the present study.

Although urea and creatinine concentrations may be used to evaluate renal function, they are not sensitive markers of renal failure because they increase only when renal damage is severe and are not reliable for early diagnosis of renal failure.[41] For a better assessment of renal function, glomerular filtration rate should be used because it is a good marker of the progress of renal insufficiency and nephropathies, even at early stages.[41] Urea and creatinine concentrations were measured in the present study because they are easy to measure under clinical conditions and because there is a possibility that long-term use of NSAIDs may induce alterations in serum biochemical variables associated with renal function.

Bleeding time is the best in vivo test for evaluating primary hemostasis, and several sites may be used for this examination. Skin bleeding time varies from 1 to 5 minutes in healthy dogs.[47] Most studies[1,7,48] use buccal mucosa bleeding time. In the present study, the internal surface of the ear was used to minimize physical restraint and stress to the dogs. Nonsteroidal anti-inflammatory drugs prevent or reduce the formation of thromboxane A_2 in platelets, impairing platelet functions such as adhesion.[41] Carprofen was the only NSAID in this study to increase bleeding time significantly, compared with baseline values, and with the exception of etodolac, all other NSAIDs increased clotting time significantly, compared with baseline values, although all values were within reference ranges for dogs. Except for 1 study[49] in which carprofen decreased and delayed the onset of platelet aggregation, most studies[22,24,41] have revealed that carprofen does not modify hemostatic variables. Also, mucosal bleeding time does not significantly change after a single dose of meloxicam[7,48] or ketoprofen in dogs.[48] Platelet aggregation is inhibited by preoperative administration of ketoprofen in dogs but not by a single dose of meloxicam.[7,22,50]

Our findings suggested that all NSAIDs studied induced only minor, clinically unimportant changes in hemostatic and serum biochemical variables in dogs, even after long-term use. Results suggested that carprofen induced the lowest frequency of gastrointestinal adverse effects, followed by meloxicam, etodolac, flunixin, and ketoprofen, when given to dogs for 90 days. Periodically, CBC, serum biochemical analysis, and endoscopy must be performed to monitor adverse effects.

a. Revolution 12%, Laboratórios Pfizer LTDA, Guarulhos, Brazil.
b. Drontal Plus, Bayer SA, São Paulo, Brazil.
c. Vanguard HTLP 5/CV-L, Laboratórios Pfizer LTDA, Guarulhos, Brazil.
d. SUR-NE, Atago Co Ltd, Tokyo, Japan.
e. Combur10testUX, Roche Diagnostics GmbH, Mannheim, Germany.

f. JENAMED 2, CARL ZEISS Inc, Jena, Germany.
g. EDTA, Vacutainer, Beckton-Dickinson, Franklin Lakes, NJ.
h. Vacutainer, Beckton-Dickinson, Franklin Lakes, NJ.
i. Cell-Dyn 3500R, Abbott Diagnostics, Abbott Park, Ill.
j. CELM, Cia Equipadora de Laboratórios Modernos, Barueri, Brazil.
k. SB190, Cia Equipadora de Laboratórios Modernos, Barueri, Brazil.
l. Propper Manufacturing Co, Long Island City, NY.
m. Acepran 0.2%, Lab Univet, São Paulo, Brazil.
n. Angyocath, Beckton-Dickinson, São Paulo, Brazil.
o. Thiopental, Lab Cristália, Itapira, Brazil.
p. Tanohalo, Lab Cristália, Itapira, SP, Brazil.
q. Etogesic tablets, Fort Dodge Animal Health, Madison, NJ.
r. Metacam suspensión oral, Boehringer Ingelheim Vetmedica, Guadalajara, México.
s. Ketofen tablets, Rhodia, São Paulo, Brazil.
t. Rimadyl comprimidos mastigáveis, Laboratórios Pfizer LTDA, Guarulhos, Brazil.
u. Banamine comprimidos, Schering Plough, São Paulo, Brazil.
v. GraphPad Prism, GraphPad Software Inc, San Diego, Calif.

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