Cyclooxygenase is responsible for many aspects of homeostatic maintenance in the body. Two isoforms of this enzyme, COX-1 and COX-2, have been characterized in many species, including humans and dogs.\(^1\) Constitutive expression of COX-1, especially in the gastrointestinal tract, vascular endothelium, brain, platelets, and kidneys, yields the basal concentrations of prostanoids needed for maintenance of homeostasis.\(^2\) Cyclooxygenase-2 is generally regarded as an inducible form of the enzyme and is expressed in many tissues (eg, monocytes, synovium, macrophages, and vascular endothelium) in the presence of inflammation.\(^3\) In dogs, COX-2 is also constitutively expressed in some tissues, including the kidneys and brain.\(^1\)

### ABBREVIATIONS

- **COX**: Cyclooxygenase
- **NSAID**: Nonsteroidal anti-inflammatory drug
- **TXA\(_2\)**: Thromboxane A\(_2\)
- **PGE\(_2\)**: Prostaglandin E\(_2\)
- **PGI\(_2\)**: Prostacyclin
- **PRP**: Platelet-rich plasma
- **PPP**: Platelet-poor plasma
- **TXB\(_2\)**: Thromboxane B\(_2\)
- **LPS**: Lipopolysaccharide

Nonsteroidal anti-inflammatory drugs are inhibitors of COX. Aspirin (acetylsalicylic acid) is an irreversible inhibitor of COX-1 and COX-2, with the latter...
isoform affected at higher doses. Other NSAIDs differentially and reversibly inhibit the 2 enzyme isoforms. The theoretic benefit of selective COX-2 inhibition is that the proinflammatory effects of COX-2 can be attenuated while the homeostatic effects of COX-1 are preserved. Profiles of COX inhibition by various NSAIDs are drug specific and, in some instances, species specific. In dogs, carprofen and meloxicam each has COX-1–sparing properties in vivo despite their different chemical classifications. The coxib class of NSAIDs inhibits COX-2 to a greater degree than COX-1 because of stronger binding affinity for COX-2 at enzyme binding sites.

Cyclooxygenase has an important function in the arachidonic acid pathway. This pathway mediates production of prostaglandins and TXA₂ from cell membrane–derived arachidonic acid. Prostaglandins help protect gastric mucosa from excessive gastric acidity, participate in regulation of gastric microcirculation, and modulate vascular tone in the renal and coronary arteries. In the presence of inflammation, COX–2–derived PGE₂ enhances nociception and other aspects of the inflammatory process. Production of TXA₂ in platelets is mediated exclusively by COX-1 and is a key step in platelet aggregation. In some dogs, TXA₂ induces platelet aggregation, whereas other dogs have an inherited insensitivity to thromboxane-induced platelet activation. The in vivo proaggregatory effects of TXA₂ are balanced in part by the vasodilatory and antiaggregatory effects of PGI₁ and nitric oxide derived from the vascular endothelium. Vascular endothelium–derived PGI₁ may be produced by either COX isoform.

The aims of the study reported here were to characterize changes in platelet aggregation, clot formation, and prostaglandin profiles in dogs treated with NSAIDs of various COX-isoform selectivities. We hypothesized that COX–2–specific drugs would preserve platelet function but result in hypercoagulability secondary to disturbances in the balance of pro- and anticoagulant prostaglandin concentrations.

Materials and Methods

Dogs with mild to moderate clinical signs of osteoarthritis were recruited from veterinary school students and staff. If available, radiographs were reviewed to confirm a diagnosis of osteoarthritis; otherwise, the diagnosis was made on the basis of clinical examination findings and history. Each dog was determined to be otherwise healthy on the basis of physical examination and results of routine blood tests (CBC and serum biochemical analyses) and urinalysis. Inclusion criteria were dogs that weighed > 10 kg and were not receiving any medications, including thyroid hormone supplementation or glucosamine. Dogs were maintained on commercial diets without additives during the study.

Once enrolled, each dog received 4 NSAIDs in a randomized crossover manner. Dogs received a drug for 10 consecutive days and had a minimum washout period of 14 days, after which administration of the next drug commenced. Drugs were assigned in a randomly assorted linear progression and administered at the following dosages: aspirin, 5 mg/kg, PO, every 12 hours; carprofen, 4 mg/kg, PO, every 24 hours; deracoxib, 2 mg/kg, PO, every 24 hours; and meloxicam, 0.1 mg/kg, PO, every 24 hours. For each drug, blood was collected prior to treatment and 4 to 6 hours after the last treatment at the end of each 10-day test period. Food was withheld for approximately 12 hours prior to each blood collection. At the beginning of the first and third study periods and at the end of the fourth study period, a CBC, serum biochemical analyses, and free-catch urine sample analysis were performed. On day 10 of each study period, blood was collected from a clinically normal, nontreated dog to serve as a control for platelet aggregation studies. Individuals who performed the platelet aggregation studies and the thrombelastography and prostaglandin assays were blinded to the drug administered during the test period; owners and 1 study administrator (BMB) were not blinded to the study drug. Owner compliance was assessed via collection of empty drug bottles and by use of a questionnaire. The study protocol was approved by the University of Pennsylvania Institutional Animal Care and Use Committee.

Platelet aggregometry—Platelet aggregation was assessed in PRP. The method for collection of PRP has been reported. Briefly, 20 mL of blood was collected via jugular venipuncture into a syringe containing adequate 3.8% citrate to yield a 9:1 blood-to-citrate ratio. This sample was centrifuged twice for 5 minutes at 600 × g. Between centrifugations the PRP was removed. The remaining blood was centrifuged a third time for 15 minutes at 1,400 × g, and the resultant PPP was collected. Platelet count in the PPP was determined with an automated analyzer, and the PRP was diluted with autologous PPP to obtain a platelet count between 300,000 and 350,000 platelets/mL. The PRP was maintained at approximately 21°C for at least 30 minutes but no longer than 90 minutes prior to assay. Five hundred microliters of diluted PRP was transferred to a cuvette containing a magnetic stir bar, and the sample was stirred at 1,000 revolutions/min and warmed to 37°C. Maximum aggregation was measured by use of an optical aggregometer. Agonists and concentrations evaluated were ADP (10 to 20µM) and collagen (10 to 20 µg/mL). The agonist concentration that resulted in sufficient (> 50%) aggregation in the baseline samples was the concentration that was tested after each course of medication. Aggregation was recorded as maximum percentage change in light transmittance, and the rate of aggregation, as calculated by the aggregometer, was represented by the slope of the aggregation tracing (increase in light transmittance/min).

Thrombelastography—Thrombelastography was performed on blood collected into 2-mL glass tubes containing 3.8% sodium citrate to yield a 9:1 blood-to-citrate ratio. The sample was kept at room temperature (approx 21°C) for 30 minutes prior to thrombelastography. Each analysis was performed in duplicate by use of a thrombelastograph. For each sample, 540 µL of citrated blood was added to 20 µL of 0.2M CaCl₂ in a thrombelastography cup warmed to 37°C that was continuously oscillated through an arc of 4° and 45° for 10 seconds. As a clot formed between the plastic pin and the side of the cup, the deflection in the pin’s posi-
tion was transferred via a transducer to a computer and recorded as a tracing (thrombelastogram). From this tracing, the computer reported the variables R and K in minutes, maximum amplitude in millimeters, α-angle in degrees, and the calculated coagulation index. The R value represents the reaction time, or time to the start of initial clot formation (ie, precoagulation), and K represents the time for the growing clot to achieve a standard firmness, defined by the instrument.α Maximum amplitude is a representation of maximum clot strength, and the α-angle is related to the speed with which the clot forms. The coagulation index is an integration of all components of the thrombelastographic tracing.α

During this phase of the study, blood was collected via direct venipuncture from 20 healthy dogs into tubes for a final 9:1 blood-to-citrate ratio. These samples were processed as described and were analyzed in duplicate via thrombelastography to verify reference ranges in healthy dogs.

Prostaglandin assays—Blood samples for the 6-keto-PGF-1α assay and free TXB assay were collected into tubes containing a final volume of 1.8 mL of K3 EDTA/mL. The sample was kept at approximately 21°C for 5 minutes, after which indomethacin was added to a final concentration of 10 µM. The tube was gently inverted and centrifuged at 5,000 × g for 10 minutes at 4°C. The supernatant was extracted in ethanol and stored at –80°C prior to analysis via ELISA.α The extraction procedure for the 6-keto-PGF-1α ELISA has been previously described.α For analysis of free TXB, the sample was evaporated under nitrogen and reconstituted in the ELISA buffer prior to analysis.α

Blood samples for analysis of platelet TXB production were collected into tubes containing no additive and allowed to clot for 1 hour at 37°C. After incubation, indomethacin was added to a final concentration of 30 µM and samples were centrifuged at 10,000 × g for 10 minutes at 4°C. Serum was removed and stored at –80°C prior to extraction. Samples were extracted as described and evaluated by use of an ELISA kit.α,β

Blood samples for the PGE2 assay, were collected into lithium heparin–coated tubes, and 500 µL of this blood was stimulated with LPS derived from Escherichia coli serotype 127:B8.β Samples were incubated for 24 hours at 37°C and extracted in methanol. Samples were stored at –80°C for ≤ 6 months prior to analysis by use of ELISA.α

Statistical analysis—Data were assessed for normality via visual inspection or by use of the Shapiro-Wilk test. Results are reported as mean ± SEM. Over all analyses to determine differences between drug treatment regimens and differences between pre- and posttreatment measurements for aggregation, thrombelastography, and prostaglandin variables were accomplished by use of ANOVA for repeated measures. Least-square means were used for all pairwise comparisons of drugs and to evaluate the differences between pre- and posttreatment measurements (aggregation, thrombelastography, and prostaglandins) within a drug group. Changes in values during the study period were also analyzed via ANOVA for repeated measures. Values of P < 0.05 were considered significant. All data were analyzed by use of dedicated statistical software.γ

Results

Eight dogs (3 castrated males and 5 spayed females ranging in age from 4 to 13 years [median, 9.8 years]) were included in the study. Breeds represented were Coonhound (n = 1), Rottweiler (1), Bernese Mountain Dog (1), and mixed (5). Weights ranged from 18 to 45 kg (median, 25.5 kg). All dogs completed the study for each drug, with the exception of 1 dog in which aspirin analysis was not completed because the dog developed signs of gastrointestinal intolerance. No other adverse effects were observed. Radiographs for review and confirmation of osteoarthritis were available for 6 of the 8 dogs.

After accounting for dogs’ individual weights, the mean administered dosages of drugs were aspirin, 5.6 ± 1.3 mg/kg, PO, every 12 hours; meloxicam, 0.1 ± 0.01 mg/kg, PO, every 24 hours; deracoxib, 2.0 ± 0.15 mg/kg, PO, every 24 hours; and carprofen, 3.8 ± 0.25 mg/kg, PO, every 24 hours.

Platelet aggregation studies—Pretreatment percentage aggregation and the slope of aggregation tracing were not significantly different among groups for any drug or agonist (Tables 1 and 2). Because of leucocytes at the time of testing or insufficient platelet aggregation for analysis, only 6 dogs were included in the ADP-stimulated aggregation analyses for carprofen, deracoxib, and aspirin. For collagen-stimulated aggregation, 3 dogs each were included in the meloxicam and deracoxib groups and 4 dogs each were included in the aspirin and carprofen groups.

Treatment with carprofen resulted in a 17% mean decrease in platelet aggregation in response to ADP (Table 1). Aggregation also decreased significantly from baseline values after treatment with aspirin and meloxicam (P = 0.038 and 0.046, respectively), but deracoxib had no effect on ADP-induced aggregation (P = 0.438).

Table 1—Median (range) percentage platelet aggregation in PRP before (pre) and after (post) treatment with 4 NSAIDs in dogs with mild or moderate signs of osteoarthritis. Adenosine diphosphate and collagen were used as aggregation reaction agonists; in each dog, the same concentration of agonist used to obtain the pretreatment sample was used to obtain the posttreatment sample.

<table>
<thead>
<tr>
<th>Agonist</th>
<th>Carprofen</th>
<th>Deracoxib</th>
<th>Meloxicam</th>
<th>Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>ADP†</td>
<td>68 (50–80)</td>
<td>56.5 (4–83)</td>
<td>67 (53–100)</td>
<td>58.5 (44–100)</td>
</tr>
<tr>
<td>Collagen</td>
<td>78 (59–100)</td>
<td>46 (2–100)</td>
<td>72 (51–85)</td>
<td>81 (2–100)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*For ADP-stimulated samples (ADP concentration, 10 to 12 µM), n = 8 for the meloxicam group and n = 6 for all other drugs. †For collagen-stimulated samples (collagen concentration, 20 to 40 µg/mL), n = 5 for the meloxicam and deracoxib groups and n = 4 for the carprofen and aspirin groups. **Values differ significantly (P = 0.007, P = 0.046, P = 0.038, P = 0.01, respectively) from pretreatment values.
With regard to collagen-induced platelet aggregation, a significant difference was noticed only in the aspirin-treated group, in which there was a mean decrease of 97% in light transmittance (Table 1). No differences in platelet aggregation were detected in any other treatment group. The slope of aggregation tracings (change in light transmission/min) for both ADP- and collagen-induced platelet aggregation was unchanged within and between drug treatment groups (Table 2).

Thrombelastography studies—Thrombelastography in the 20 clinically normal dogs was performed to verify existing reference ranges for various thrombelastography variables in a 95% confidence interval. Reference ranges for dogs were as follows: R time, 5.0 to 7.4 minutes; K time, 2.7 to 4.3 minutes; α-angle, 44.1° to 55.8°; maximum amplitude, 53.7 to 61.3 mm; and coagulation index, 1.3 to 2.4.

Treatment with neither aspirin nor meloxicam resulted in significant changes from baseline in any measured thrombelastography variable; however, the small number of dogs and biological variation limited the power of the analysis. Compared with reference values, baseline thrombelastograms as well as those obtained after both drug treatments (aspirin and meloxicam) contained values consistent with hypercoagulability, but the differences were not significant (Table 3).

Treatment with carprofen resulted in significant prolongation of the K time. Consistent with the prolonged K time, the α-angle decreased by 7.5 ± 3.4° (P = 0.043). The maximum amplitude after carprofen treatment also decreased by 5.7 ± 2.5 mm (P = 0.032). Treatment with deracoxib did not significantly change R, K, or α-angle values in thrombelastography tracings. The maximum amplitude, however, increased significantly after treatment by 7.7 ± 2.5 mm. Consistent with those data, the coagulation index also increased by 1.3 ± 0.4.

Changes in prostaglandin expression—No baseline prostaglandin concentrations were significantly different among dogs or drugs. Mean expression of PGE₂ by LPS-stimulated macrophages decreased significantly from baseline after treatment with carprofen and deracoxib, but not after treatment with aspirin (P = 0.129) or meloxicam (P = 0.052). Mean baseline expression prior to each treatment was 17,314 ± 12,034 pg/mL (Table 4).

Expression of PGI₂, as estimated from plasma 6-keto-PGF-1α concentrations, was not significantly changed in any group. Mean baseline concentrations of 6-keto-PGF-1α were 247.3 ± 89 pg/mL.

Platelet production of TXA₂, measured as TXB₂ in serum after blood clotted, was unchanged from baseline after treatment with deracoxib, carprofen, and meloxicam. There was, however, a significant (P < 0.001) decrease in platelet TXB₂ production after treatment with aspirin. Baseline production of TXB₂ by platelets was 1,326.3 ± 753.2 ng/mL.

Because of wide variation among dogs in production of circulating prostanooids, the ratio of circulating TXB₂ to circulating 6-keto-PGF-1α was evaluated for each treatment regimen. Mean circulating concentration of TXB₂ was 158.35 ± 29.9 pg/mL, and significant differences were not detected after treatment with any drug. After treatment with aspirin and carprofen, the TXB₂:6-keto-PGF-1α ratio decreased in any group.

Table 2—Median (range) percentage slope of platelet aggregation tracing (in percentage/min) in PRP before (pre) and after (post) treatment with 4 NSAIDs in the same dogs as in Table 1.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Agonist</th>
<th>Pre</th>
<th>Post</th>
<th>Pre</th>
<th>Post</th>
<th>Pre</th>
<th>Post</th>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carprofen</td>
<td>ADP</td>
<td>105.5 (79–147)</td>
<td>67 (38–93)</td>
<td>103.5 (60–150)</td>
<td>76 (58–187)</td>
<td>94.5 (71–176)</td>
<td>76 (34–178)</td>
<td>83 (66–106)</td>
<td>87 (55–104)</td>
</tr>
<tr>
<td>Deracoxib</td>
<td>Collagen</td>
<td>80 (51–139)</td>
<td>56.5 (20–121)</td>
<td>60 (47–125)</td>
<td>49 (20–128)</td>
<td>71 (62–108)</td>
<td>49 (20–121)</td>
<td>80.5 (55–126)</td>
<td>54 (49–60)</td>
</tr>
</tbody>
</table>

See Table 1 for key.

Table 3—Median (range) values for thrombelastography variables in citrated whole blood before (pre) and after (post) treatment with 4 NSAIDs in the same dogs as in Table 1.

<table>
<thead>
<tr>
<th>Drug</th>
<th>R (min)</th>
<th>K (min)</th>
<th>MA (mm)</th>
<th>Angle (°)</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carprofen (n = 6)</td>
<td>5.35 (4.4–5.75)</td>
<td>2.025 (1.8–2.35)</td>
<td>68 (58–70.75)</td>
<td>60.875 (43.75–69.75)</td>
<td>52.75 (34.75–67.75)</td>
</tr>
<tr>
<td>Deracoxib (8)</td>
<td>5.68 (2.5–7.2)</td>
<td>2.3 (1.45–3.85)</td>
<td>60.25 (53.7–71)</td>
<td>69.5 (59–84)</td>
<td>60.625 (46.25–69.25)</td>
</tr>
<tr>
<td>Meloxicam (8)</td>
<td>5.28 (3.6–7.65)</td>
<td>2.2 (1.5–3.4)</td>
<td>62.5 (55.4–74.25)</td>
<td>65.35 (59–70.5)</td>
<td>61.05 (45.5–68.5)</td>
</tr>
<tr>
<td>Aspirin (7)</td>
<td>5.95 (3.35–6.55)</td>
<td>2.05 (1.4–3.55)</td>
<td>61.35 (53.25–71.5)</td>
<td>62.4 (58.75–72.5)</td>
<td>57.85 (42.25–69.75)</td>
</tr>
</tbody>
</table>

R = Reaction time (time to initial clot formation), K = Time required for clot to reach a standard firmness, MA = Maximum amplitude (a representation of maximum clot strength), Angle = α-angle (a determinant of speed of clot formation), CI = Coagulation index (a calculated value that integrates all components of the thrombelastogram tracing).

* Values differ significantly (P = 0.01; P = 0.032; P = 0.043; P = 0.005; P = 0.007, respectively) from pretreatment values.
Dogs were evaluated for COX-2, TXB₂, 6-keto-PGF-1α, and freeTXB₂ concentrations, and 6-keto-PGF-1α:TXB₂ ratios in the same dogs with mild or moderate signs of osteoarthritis.

Dogs were evaluated for COX-2, TXB₂, 6-keto-PGF-1α, and freeTXB₂ concentrations, and 6-keto-PGF-1α:TXB₂ ratios in the same dogs with mild or moderate signs of osteoarthritis.

Treatment with selective COX-2 inhibitor deracoxib did not significantly alter platelet function. Treatment with carprofen, which is less COX-2 selective, resulted in decreased clot strength and decreased aggregation in response to ADP. Administration of aspirin, a COX-1 inhibitor, caused significant decreases in platelet aggregation and platelet thromboxane production.

At the doses of drugs tested, COX-2 inhibition (as measured by PGE₂ production) in blood after LPS stimulation was evident for deracoxib and carprofen. There was a high degree of biological variability among dogs with regard to results of the prostaglandin assays, which may have been the result of individual variation or variable sampling times. The ELISAs have been validated experimentally in dogs, and future studies in client-owned animals should aim to further standardize the phlebotomy protocol.

A mild inhibitory effect on platelet aggregation for carprofen has been reported, although the changes were not thought to be clinically relevant on the basis of results of buccal mucosal bleeding time as a measure of primary hemostasis. Significant decreases in platelet aggregation after carprofen treatment were confirmed in the present study, and analysis of the thrombelastography tracings revealed significant decreases in clot strength and speed of clot formation. Given the evidence for adverse effects on primary hemostasis and clot formation, we recommend caution in administration of carprofen to dogs that are receiving anticoagulant medications or that have primary hemostatic disorders (eg, von Willebrand disease), which may increase the risk for developing bleeding complications. Meloxicam also caused a slight decrease in ADP-stimulated aggregation; however, that finding was not duplicated in the thrombelastography tracing, possibly because the effect was too subtle to be detected via thrombelastography.

Evaluation of deracoxib-treated dogs via thrombelastography revealed changes that were compatible with hypercoagulability, characterized by increased clot strength (maximum amplitude) and a high coagulation index. Interestingly, although some dogs had minimal thrombelastography changes after treatment with deracoxib, others had dramatic changes that were indicative of hypercoagulability. Interindividual differences with regard to thrombelastography performance after NSAID treatment have been reported in humans, and some individuals are more prone to hypercoagulability than others. The same may have been true in the dogs in the present study.

We hypothesized that hypercoagulability after treatment with selective COX-2-inhibiting drugs would be secondary to changes in the ratio of circulating thromboxane to prostacyclin caused by COX-2 inhibition. Circulating PGI₂ concentration decreases in healthy humans.
after treatment with celecoxib, a highly selective COX-2 inhibitor.13 In the present study, a modest shift in the 6-keto-PGF-1α:TXB₂ ratio was seen in the deracoxib-treated group, but the change was not significant. That shift in the ratio may correspond with the minor increase in coagulability; however, further studies evaluating the 6-keto-PGF-1α:TXB₂ ratio and relation to coagulation after NSAID treatment in dogs are indicated.

The impairment of ADP-induced aggregation in NSAID-treated dogs was unexpected. Although platelet aggregation induced by collagen requires COX and thromboxane production, initial ADP-induced aggregation in dogs is not considered to require thromboxane production.14 The secondary aggregation response may be thromboxane dependent, although dog platelets may be able to release other proaggregatory substances that do not require active COX.15 Similar impairments in ADP-induced aggregation in dogs receiving either aspirin or carprofen have been reported,16,17 however, and may represent variation among dogs or breeds in the contribution of thromboxane to ADP-induced platelet aggregation. Conversely, results of other studies18,19 in dogs have not supported impairment of ADP-induced platelet aggregation after administration of aspirin or phenylbutazone.

Many variables compose the thrombelastogram, some of which may be more indicative of hypercoagulability than others. In humans, maximum amplitude is correlated to hypercoagulability.20 Consistent changes in multiple thrombelastography variables have been detected21 in dogs with hypercoagulable diseases such as immune-mediated hemolytic anemia and glomerulonephritis. In the present study, the most important changes were observed in maximum amplitude, which corresponds to clot strength. Thromboelastographic evaluation of 12 dogs with immune-mediated hemolytic anemia revealed maximum amplitude values of 75 ± 11 mm with steep values for the α-angle of 74 ± 8°.22

One variable that may affect thrombelastography tracings, especially variables that are indicators of clot strength, is total platelet count. Although a whole-blood platelet count was not performed prior to each thrombelastography analysis, the platelet count from the PRP was determined and was moderately reflective of total platelet count. The PRP platelet count differed among dogs, but no significant changes were seen in individual dogs in response to drug treatments. It is likely that changes detected in the thrombelastography variables were caused by drug treatment alone.

To the authors’ knowledge, the present study is the first in which canine platelet function was evaluated by use of both optical aggregometry and thrombelastography. Analyses did not reveal significant correlations between elements of the assays. None of the changes in clinical laboratory values were considered to be clinically important, and no dogs had evidence of hepato- or nephrotoxicosis or anemia.

Because client-owned dogs were evaluated, we were limited in testing and flexibility of sample collection. Owner compliance with dosing was good for most dogs. Ideally, serum drug concentrations would have been measured and the timing of blood collection after administration of final drug doses would have been more stringent. It would also have been useful to include a more clinical measure of bleeding time such as buccal mucosal bleeding time; however, this was not appropriate given our study population and the duration of the study. Additionally, buccal mucosal bleeding time has been evaluated in dogs for all NSAIDs evaluated in the present study with the exception of deracoxib.16,23 We also evaluated only 2 time periods, days 0 and 10. It is possible that early changes in platelet function may normalize with chronic treatment. Incorporation of additional time points for blood sampling would have further elucidated temporal changes that occur in platelet function with NSAID use in dogs.

In dogs in the present study, baseline thrombelastograms were consistent with mild hypercoagulability, compared with the reference range. This may be a reflection of subtle effects of the inflammatory process of osteoarthritis on hemostatic variables in dogs and may have masked drug effects that would be apparent in a more controlled population. Although the study dogs constituted a clinically relevant population, the use of healthy research dogs and a strict experimental protocol may have yielded more conclusive data on this point.

Prostacyclin is produced and quickly degraded in the circulation and, consequently, must be measured as its stable metabolite, 6-keto-PGF-1α. Prostacyclin may also be released with stimulation or endothelial injury, such as may occur during venipuncture.24 We used a standardized protocol for venipuncture for every dog at all times to minimize variation. Thromboxane may also be released during venipuncture. The values for circulating thromboxane obtained in the present study were slightly higher than those reported in humans,25 but were similar to values previously reported in dogs.26,27

Many NSAIDs affect both platelet function and overall coagulability in dogs. Some may increase clot formation. It is important to assess the suitability of NSAIDs for individual dogs prior to administration of these compounds. Coxib class drugs do not affect platelet function and may therefore be appropriate for perioperative use; however, they should be avoided in dogs with conditions that may predispose them to hypercoagulability. Some COX-1–sparing drugs may cause decreased platelet aggregation, and their use in dogs with known primary hemostatic defects should be avoided.

a. Aspirin, buffered, not enteric coated, LNK Int, Hauppauge, NY.
   c. Deramaxx, Novartis Animal Health, Greensboro, NC.
   d. Metacam suspension (0.5%), Boehringer Ingelheim Vetmedica, St Joseph, Mo.
   e. Sodium citrate, Sigma-Aldrich Co, St Louis, Mo.
   f. 1-Stat 1, Heska Corp, Waukesha, Wis.
   g. Chrono-log Corp, Havertown, Pa.
   h. ADP, Chrono-log Corp, Havertown, Pa.
   i. Collagen, Chrono-log Corp, Havertown, Pa.
   j. TEG 5000, Haemoscope, Chicago, Ill.
   k. Calcium chloride, Sigma-Aldrich Co, St Louis, Mo.
   l. BD Microtainer, Becton-Dickinson, Franklin Lakes, NJ.
   m. Indomethacin, Sigma-Aldrich Co, St Louis, Mo.
   n. 6-keto-PGF-1α enzyme-linked immunooassay kit, Cayman Chemical, Ann Arbor, Mich.
   o. TXB₂, enzyme-linked immunooassay kit, Cayman Chemical, Ann Arbor, Mich.
   p. Lipopolysaccharide (Escherichia coli), Sigma-Aldrich Co, St Louis, Mo.

Unauthenticated | Downloaded 10/08/23 03:24 PM UTC
q. PGE, enzyme–linked immunosassay kit, Cayman Chemical, Ann Arbor, Mich.

r. SAS, version 9.1, SAS Institute Inc, Cary, NC.


References


