Effects of preoperative administration of carprofen on renal function and hemostasis in dogs undergoing surgery for fracture repair

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Objective—To evaluate effects of preoperative administration of carprofen on renal function and hemostasis in dogs undergoing general anesthesia for fracture repair.

Animals—26 client-owned dogs.

Procedure—Anesthesia was induced with levomethadone, diazepam, and propofol and maintained by administration of isoflurane in oxygen-nitrous oxide. Carprofen (4 mg/kg, SC) was administered 1 hour before induction to 13 dogs (group 1) and after extubation to the other 13 dogs (group 2). All dogs also received carprofen (4 mg/kg, SC, q 24 h) for the first 4 days after surgery. Renal function (glomerular filtration rate [GFR], urinary protein-to-urinary creatinine ratio [UP:UC], and results of urinalysis and biochemical analysis of plasma), hemostatic variables (bleeding time, platelet aggregation, prothrombin time [PT], activated partial thromboplastin time [APTT], and platelet count), and Hct were assessed before and at various time points after surgery.

Results—Analysis of results for renal function tests, most of the hemostatic and plasma biochemical variables, and Hct did not reveal significant differences between treatment groups. Values for GFR, UP:UC, PT, APTT, and platelet aggregation were outside reference ranges in many dogs before surgery and during the first 6 hours after surgery. In most dogs, these trauma-induced pathologic changes returned to within reference ranges during the 4-day period after surgery.

Conclusions and Clinical Relevance—Carprofen did not cause clinically relevant adverse effects in dogs anesthetized for fracture repair after 5 days of treatment, even when it was administered before surgery or given to patients with trauma-induced alterations in renal function or hemostasis. (*Am J Vet Res* 2005;66:1356–1363)

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been used successfully to control postoperative pain in dogs.[1] The anti-inflammatory, antipyretic, and analgesic effects of these drugs are attributed to inhibition of the enzyme **cyclooxygenase (COX)**.[2] When administered before surgery, NSAIDs can prevent peripheral and central sensitization and thereby improve postoperative analgesia.[3,4]

Carprofen is a potent analgesic with few adverse effects classically associated with NSAIDs.[5,6] Perioperative use of carprofen provides substantial pain relief and decreases the need for additional postoperative analgesia in animals subjected to various surgeries.[7-10] However, the administration of carprofen during the perioperative period remains a controversial issue.[9,11]

Any condition that causes renal vasoconstriction induces the synthesis of renal prostaglandins, which induce compensatory vasodilation to maintain renal perfusion.[12] By inhibiting prostaglandin synthetase in the kidneys, NSAIDs can adversely affect renal function when used during the perioperative period.[13] However, carprofen did not cause clinically important adverse effects on renal function in healthy anesthetized dogs, even in dogs with low blood pressure during anesthesia.[14-16]

Furthermore, NSAIDs prevent formation of thromboxane A2 in platelets, which leads to impaired platelet adhesion and increases the propensity for hemorrhage.[17] Preoperative use of NSAIDs may increase the incidence of hemorrhage during the perioperative period.[18] However, carprofen does not influence buccal mucosal bleeding time, clotting time, or thromboxane generation by platelets,[9,19] nor does it cause clinically important alterations in hemostatic variables when administered for 5 days.[20]

Patients with fractures are considered to have moderate to severe pain. Studies[7-10,21] have documented efficacy for the preoperative use of NSAIDs in patients with a fracture. However, trauma patients are susceptible to renal insufficiency, especially after a prolonged duration of anesthesia and surgery.[22-24] Furthermore, there are substantial alterations in the coagulation and fibrinolytic systems in patients with acute trauma.[25-27] Therefore, the purpose of the study reported here was to investigate whether preoperative administration of carprofen would increase negative effects on renal function and hemostasis, compared with a control treatment, in dogs undergoing fracture repair.

Materials and Methods

Animals—Twenty-six client-owned dogs (20 males and 6 females) between 3 months and 13.5 years (median, 3.2 years) of age and weighing between 5.5 and 45 kg (median, 13.8 kg) that were undergoing surgery to repair a fracture (humerus, 5 dogs; femur, 8; and pelvis, 13) were included in the study. The dogs were examined at our facility and treated during a period of 12 months. All procedures were performed

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after we had obtained written consent of the owners; procedures were approved by the Municipal Government of Hannover in accordance with section 8 of the *German Law for the Protection of Animals* (BGBl. I S.1105). Dogs with an increase in plasma concentrations of urea or creatinine, prolonged capillary bleeding time, or prior treatment with NSAIDs or corticosteroids were excluded from the study.

Study design—Dogs were randomly assigned to 1 of 2 groups. Carprofen[a] (4 mg/kg, SC) was administered 1 hour before surgical fracture repair to 13 dogs (group 1) and after extubation following fracture repair in the remaining 13 dogs (group 2). Day of the surgery was designated as day 0. All dogs received carprofen (4 mg/kg, SC, q 24 h) for the first 4 days after surgery (ie, days 1 to 4).

A **visual analogue scale (VAS)** was used to assess pain of the dogs. The VAS was a 100-mm line with no pain at 0 and worst pain possible at 100; investigators placed a mark on the line that corresponded to their assessment of each dog's signs of pain. The VAS score was obtained by measuring the distance from 0 to the investigator's mark. When the VAS score was > 30, fentanyl[b] (0.05 mg/kg, IV, for the first 6 hours after extubation) or levomethadone[c] (0.3 mg/kg, SC, for days 1 through 4) was administered as a rescue analgesic.

Anesthesia and surgical procedure—All dogs were medicated with diazepam[d] (1 mg/kg, IV [maximum dose, 25 mg]) and levomethadone (0.6 mg/kg, IV [maximum dose, 25 mg]). Anesthesia was induced by administration of an amount of propofol[e] sufficient to allow endotracheal intubation; anesthesia was maintained by administration of isoflurane[f] delivered in oxygen-nitrous oxide (ratio, 1:2). Dogs were ventilated mechanically,[g] and a balanced electrolyte solution[h] was administered IV during anesthesia. Durations of anesthesia and surgery were recorded. Heart and respiratory rates, ECG variables, fraction of inspired oxygen, end-tidal carbon dioxide concentration, end-tidal isoflurane concentration, and arterial oxygen saturation of hemoglobin were monitored continuously throughout anesthesia.[i] Mean arterial pressure was measured in triplicate at 5-minute intervals by use of an oscillometric blood pressure device,[j] and mean values were recorded.

Collection of blood and urine samples—A 19-gauge needle was used for venipuncture of a lateral saphenous vein and collection of 9 mL of blood into a plastic tube containing sodium citrate (1 part of sodium citrate:9 parts of blood). Samples were obtained before surgery and on days 1 and 4 after surgery and used for measurement of platelet aggregation. Samples were centrifuged (150 × *g* at 15°C for 30 minutes) immediately after collection to obtain **platelet-rich plasma (PRP)**. Then, 1 mL of PRP was centrifuged (10,000 × *g* at 15°C for 10 minutes) to obtain **platelet-poor plasma (PPP)**. Measurement of platelet aggregation was initiated within 2 hours after blood collection.

A second preparation of PPP was generated as described elsewhere.[28,29] A 19-gauge needle was used to collect 1 mL of blood from a lateral saphenous vein. Samples were obtained before surgery, 0.5 and 6 hours after extubation, and daily on days 1 through 4 and used for measurement of **prothrombin time (PT)** and **activated partial thromboplastin time (APTT)**. Blood was placed into a sodium citrate tube (1 part of sodium citrate:9 parts of blood) and centrifuged (2,000 × *g* at 4°C for 20 minutes) immediately to yield PPP. The PPP was stored frozen (–28°C) in small aliquots for a maximum of 30 days before it was thawed at 37°C for further analysis.[30]

To measure Hct and platelet count, a 20-gauge needle was used to collect 1 mL of blood from a lateral saphenous vein. Samples were placed into an EDTA-containing tube. Samples were collected before and on day 4 after surgery.

A sample (1 mL) of blood was collected and placed into a heparin-containing tube to enable us to measure plasma concentrations of creatinine, inorganic phosphorus, and potassium (before surgery, 0.5 and 6 hours after extubation, and daily on days 1 through 4). Blood samples were also obtained to enable us to measure plasma concentrations of urea, bilirubin, and total protein and activities of **alanine transaminase (ALT)**, **glutamate dehydrogenase (GMD)**, and **alkaline phosphatase (ALP)** before and on day 4 after surgery.

Glomerular filtration rate (GFR) was measured before and 1 and 4 days after surgery. For each GFR measurement, a blood sample (10 mL) was collected from a jugular vein into a 10-mL plastic tube that contained lithium and heparin; the sample was immediately centrifuged (3,000 × *g* for 30 minutes).

Urine samples were collected aseptically via cystocentesis by use of a 23-gauge needle and 10-mL syringe. Urine samples were collected for analysis by use of a strip test, specific-gravity measurement, and microscopic evaluation before surgery, before extubation, 0.5 and 6 hours after extubation, and daily on days 1 through 4 to determine the **urinary protein-to-urinary creatinine ratio (UP:UC)**.

Biochemical analysis of plasma—Plasma concentrations of urea, creatinine, total protein, and bilirubin and activities of ALT, GMD, and ALP were determined by use of an automated analyzer.[k] Plasma concentrations of potassium were determined by use of an ion-selective analyzer.[l]

Hematologic variables—Platelet count and Hct were determined by use of an automated hematologic analyzer.[m] The APTT and PT were measured as described elsewhere[28,29] by use of a semiautomatic crochet coagulometer[n] and standard clinicopathologic techniques. To measure APTT, 100 µL of PPP was incubated with 100 µL of APTT reagent[o] (diluted with diethylbarbiturate acetate buffer[p]) at 37°C for 2 minutes. This was followed by the addition of 100 µL of calcium chloride[q] (25 mmol/L) and simultaneous starting of the stopwatch integrated in the coagulometer. To measure PT, 100 µL of PPP was incubated with 100 µL of fibrinogen[r] at 37°C for 1 minute. Then, 100 µL of human thromboplastin[s] was added, and time until coagulation was measured. Measurement of APTT and PT was performed in duplicate, and the mean values were calculated.

Determination of bleeding time—Bleeding time was determined before surgery, 0.5 and 6 hours after extubation, and daily on days 1 through 4 by use of a method described elsewhere.[31] Briefly, each dog was positioned in lateral recumbency. Hair was clipped from the lateral surface of the fifth toe of a forelimb, and the cuff of a sphygmometer was placed proximal to the radius and ulna on that limb. Hyperemic ointment[t] was applied to the clipped area and removed after 1 minute. Pressure (60 mm Hg) was applied by the sphygmometer. After 1 additional minute, a spring-loaded device was used to make 2 concurrent parallel incisions of standardized length and depth. Gauze was used at 15-second intervals to blot away blood, with investigators being careful not to touch the wound edges. A stopwatch was used to measure the time from triggering the spring-loaded device until clotting was recorded for each incision, and the mean value was recorded as the final bleeding time.

Platelet aggregation—Platelet aggregation was measured as described elsewhere[32] by use of an automated platelet-aggregation system.[u] The aggregometer was calibrated by use of 200 µL of PPP and 10 µL of isotonic saline (0.9% NaCl) solution[v] as 100% aggregation and 200 µL of PRP and 10 µL of isotonic saline as 0% aggregation. An aliquot (200 µL) of PRP was placed in the aggregometer cuvette and stirred constantly (1,000 rounds/min). After equilibration at 37°C for 2

minutes, aggregation was induced with 10 µL of ADP[w] (25 mmol/L) in 1 canal and 10 µL of collagen[x] (10 µg/mL) in the other canal. After 12 minutes, aggregation was considered to be complete. Maximal aggregation was measured automatically by the aggregometer.

Urinalysis—Urinary concentrations of creatinine and protein were determined by use of an automated system,[k] and the UP:UC was calculated. A urine test strip[y] was used, and urine specific gravity was estimated by use of a refractometer.[z] Microscopic evaluation of the urine was accomplished after the sediment was stained.[aa]

GFR—To measure GFR, iohexol[bb] (70 mg/kg, IV) was injected through a catheter inserted in a cephalic vein. Blood was collected 2.5 and 4 hours after injection and prepared as described previously. During measurement of GFR, a balanced electrolyte solution[h] was infused in each dog (10 mL/kg/h). The iohexol concentration was measured via a radiographic-fluorescent technique,[cc] and clearance was calculated by applying a 1-compartment mode.[33-36]

Statistical analysis—Values for Hct, platelet count, ALP activity, and plasma concentrations of urea and potassium were analyzed by use of parametric statistical methods. An ANOVA was used to compare differences between the treatment groups at each test point. When the ANOVA yielded a value of $P < 0.05$, the Scheffe test was performed. For each treatment group, paired *t* tests were used to compare values obtained at each time point after the start of surgery with values obtained before surgery. Multiple analyses of variance were performed to compare differences between treatment groups over time. For all parametric analyses, values of $P < 0.05$ were considered to be significant.

Values for GFR, UP:UC, PT, APTT, and platelet aggregation; activities of ALT and GMD; and plasma concentrations of creatinine, phosphorus, total protein, and bilirubin were analyzed by use of nonparametric statistical methods. The Kruskal-Wallis test was used to compare differences between treatment groups at each time point. When the test yielded a value of $P < 0.05$, the Mann-Whitney test (Bonferroni as post hoc test) was performed. For each treatment group, the Wilcoxon test was used to compare values obtained at each time point after the start of surgery with values obtained before surgery. For all nonparametric analyses, values of $P < 0.05$ were considered to be significant. All analyses were performed by use of computer software.[dd]

Results

Twenty-six dogs admitted to our hospital for fracture repair met the inclusion criteria for the study reported here. We did not detect significant differences between treatment groups over time.

We did not detect significant differences between treatment groups with regard to age, body weight, duration of anesthesia, or duration of surgery. Dogs of group 1 ranged from 0.4 to 13.5 years of age (median, 3.4 years), whereas dogs of group 2 ranged from 0.3 to 13.1 years of age (median, 2.3 years). Dogs of group 1 ranged from 8.0 to 42.0 kg (median, 15.5 kg), whereas dogs of group 2 ranged from 5.5 to 45 kg (median, 9.0 kg). Duration of anesthesia for dogs of group 1 ranged from 113 to 252 minutes (median, 192.0 minutes), whereas duration of anesthesia for group 2 dogs ranged from 55 to 430 minutes (median, 172.2 minutes). Duration of surgery ranged from 105 to 241 minutes (median, 183.0 minutes) for dogs of group 1 and from 46 to 422 minutes (median, 125.0 minutes) for dogs of group 2.

Mean arterial pressure during anesthesia ranged from 73 to 163 mm Hg (median, 83 mm Hg) for dogs of group 1 and from 66 to 160 mm Hg (median, 89 mm Hg) for dogs of group 2. There were no significant differences between treatment groups or within groups over time. Values determined for heart and respiratory rates, fraction of inspired oxygen, end-tidal carbon dioxide concentration, end-tidal isoflurane concentration, and arterial oxygen saturation of hemoglobin did not differ significantly between treatment groups or within groups over time.

Before surgery, 3 dogs of group 1 and 4 dogs of group 2 had a GFR less than the reference range (3.0 to

Table 1—Values for renal variables and results of urinalysis before and after surgery to repair a fracture in 26 dogs (13 dogs/group) that received carprofen before surgery or at the time of extubation after completion of surgery.

			Hours after extubation		Day after surgery			
Variable	**Group***	**Before surgery**	**0.5**	**6**	**1**	**2**	**3**	**4**
Creatinine (mg/dL)†	1	0.59 (0.28–0.82)	0.52 (0.26–0.78)‡	0.41 (0.24–0.76)‡	0.56 (0.26–0.74)	0.56 (0.28–0.74)	0.52 (0.36–0.77)	0.57 (0.38–0.87)
	2	0.52 (0.40–0.83)	0.50 (0.27–1.11)	0.43 (0.26–0.86)‡	0.55 (0.25–1.43)	0.58 (0.25–1.46)	0.53 (0.31–0.90)	0.57 (0.29–0.85)
Urea (mg/dL)§	1	26 ± 8.6	ND	ND	ND	ND	ND	28 ± 8.8
	2	26 ± 7.1	ND	ND	ND	ND	ND	27 ± 6.1
Potassium (mmol/L)§	1	4.0 ± 0.36	ND	ND	ND	ND	ND	4.2 ± 0.49
	2	3.7 ± 0.42	ND	ND	ND	ND	ND	4.1 ± 0.26‡
Phosphorus (mmol/L)†	1	1.36 (0.35–2.41)	1.93 (1.42–2.71)‡	1.53 (0.95–2.36)	1.40 (0.83–2.34)	1.41 (1.14–2.41)	1.42 (1.20–2.56)	1.35 (1.11–2.46)
	2	1.35 (0.94–2.84)	1.52 (1.50–3.21)‡	1.52 (1.06–2.51)	1.34 (0.89–2.59)	1.37 (1.15–2.40)	1.52 (1.15–2.45)	1.49 (0.77–2.71)
GFR (mL/kg/h)†	1	4.1 (2.4–10.1)	ND	ND	4.8 (3.1–11.2)‡	ND	ND	4.4 (3.0–11.6)
	2	4.1 (2.2–10.8)	ND	ND	5.2 (3.5–16.8)	ND	ND	4.1 (3.2–14.2)
UP:UC†	1	0.26 (0.00–1.17)	0.28 (0.06–0.44)	0.28 (0.07–0.73)	0.34 (0.01–1.26)	0.21 (0.01–0.37)	0.20 (0.07–0.71)‡	0.21 (0.08–0.75)
	2	0.32 (0.07–1.39)	0.22 (0.03–0.69)	0.33 (0.11–1.36)	0.24 (0.08–0.53)	0.19 (0.00–2.23)	0.12 (0.00–0.91)‡	0.13 (0.03–0.52)‡

*Dogs were administered carprofen (4 mg/kg, SC) 1 hour prior to induction of anesthesia (group 1) or at the time of extubation at the conclusion of anesthesia (group 2). Both groups of dogs were administered carprofen (4 mg/kg, SC, q 24 h) for the first 4 days after surgery (day of surgery was designated as day 0). †Values reported are median (range). ‡Within a row, value differs significantly ($P < 0.05$), compared with value obtained before surgery. §Values reported are mean ± SE.

GFR = Glomerular filtration rate. UP:UC = Urinary protein-to-urinary creatinine ratio. ND = Not determined.

Table 2—Median (range) values for bleeding time (BT), activated partial thromboplastin time (APTT), and prothrombin time (PT) before and after surgery to repair a fracture in 26 dogs (13 dogs/group) that received carprofen before surgery or at the time of extubation after completion of surgery.

			Hours after extubation		Days after surgery			
Variable	**Group***	**Before surgery**	**0.5**	**6**	**1**	**2**	**3**	**4**
BT (s)	1	70 (40–145)	75 (45–120)	80 (40–150)	80 (55–120)	62.5 (45–105)	60 (45–100)†	60 (40–100)
	2	65 (50–120)	100 (53–130)†	85 (45–105)	70 (22–150)	65 (22–110)	60 (40–143)	60 (45–90)†
APTT (s)	1	17 (14–30)	20 (17–29)	20 (18–27)†	21 (13–23)	19 (17–25)	18 (15–20)	17 (15–26)
	2	17 (14–20)	20 (18–32)†	20 (17–36)†	20 (16–23)†	19 (16–23)†	18 (16–24)†	18 (15–22)†
PT (%)	1	76 (38–136)	72 (32–91)†‡	70 (31–96)	76 (41–96)	96 (70–125)†	108 (70–136)†	112 (67–136)†
	2	87 (58–136)	79 (73–136)	79 (43–115)	87 (43–115)	83 (70–125)	102 (76–162)†	98 (76–136)†

†Within a row, value differs significantly ($P < 0.05$), compared with value obtained before surgery. ‡Within a time point within a variable, value differs significantly ($P < 0.05$) from the value for group 2.
See Table 1 for remainder of key.

Table 3—Median (range) values for platelet aggregation before and after surgery to repair a fracture in 26 dogs (13 dogs/group) that received carprofen before surgery or at the time of extubation after completion of surgery.

			Day after surgery	
Platelet aggregation agent (concentration)	**Group***	**Before surgery**	**2**	**4**
ADP (25 mmol/L)	1	78.2 (0.0–89.2)	64.8 (1.2–88.9)[a]	81.0 (60.1–100.8)[b]
	2	65.9 (30.2–98.5)	85.8 (10.2–93.9)	86.0 (59.2–97.0)†
Collagen (10 mg/mL)	1	54.8 (0.0–90.5)	74.4 (0.0–90.8)	86.1 (11.3–105.4)
	2	54.7 (0.0–94.2)	62.4 (0.0–96.9)	75.4 (8.5–100.0)†

†Within a row, value differs significantly ($P < 0.05$), compared with value obtained before surgery.
[a,b]Within a row, values with different superscript letters differ significantly ($P < 0.05$).
See Table 1 for remainder of key.

6.5 mL/min/kg) provided by the laboratory. On days 1 and 4, no dogs had a GFR < 3.0 mL/min/kg (**Table 1**).

Plasma concentrations of urea and creatinine were within reference range values (urea, 20 to 50 mg/dL; creatinine, 0.4 to 1.2 mg/dL) at all time points. Plasma concentrations of urea did not vary significantly between treatments over time (Table 1).

Ten dogs (5 dogs from each group) had plasma phosphorus concentrations that were greater than the reference range (1.0 to 1.9 mmol/L) 0.5 hours after extubation. However, only 3 dogs of group 1 and 2 dogs of group 2 had plasma phosphorous concentrations greater than the reference range on day 4 (Table 1).

Plasma potassium concentrations did not differ significantly between the treatment groups or within groups over time (Table 1).

A significant decrease in urine pH was detected for dogs of group 2 on day 4 (range, 5.0 to 8.0; median, 6.3), compared with the pretreatment values. Urine pH did not differ significantly between treatment groups. The number of epithelial cells, cylinders, leukocytes, and RBCs and urine specific gravity did not differ significantly between treatment groups or within groups over time.

One dog of group 1 had UP:UC values greater than the reference range (0 to 1.0) before surgery. However, 1 dog of group 2 had UP:UC values greater than the reference range before surgery, 6 hours after extubation, and on day 2 (Table 1).

Bleeding time was within the reference range (< 150 seconds) in all dogs at all time points (**Table 2**). Before surgery, 5 dogs of group 1 and 1 dog of group 2 had APTT values greater than the reference range (14.5 to 19.0 seconds). In both groups, the number of dogs with pathologically increased APTT values increased 0.5 hours after extubation and decreased continuously thereafter.

Before surgery, 3 dogs of group 1 and 1 dog of group 2 had PT values less than the reference range (70% to 130%). The number of dogs with pathologically decreased PT values increased in both groups during the first 6 hours after extubation and decreased continuously thereafter; thus, all dogs had PT values within the reference range on days 2, 3, and 4 (Table 2).

Table 4—Values for hematologic variables before and after surgery to repair a fracture in 26 dogs (13 dogs/group) that received carprofen before surgery or at the time of extubation after completion of surgery.

Variable	**Group***	**Before surgery**	**4 days after surgery**
Hct (%)†	1	45 ± 3.5	34 ± 5.6‡
	2	45 ± 3.8	35 ± 3.2‡
Total protein (g/dL)§	1	5.8 (4.8–8.0)	6.2 (4.5–6.8)
	2	6.5 (4.9–7.0)	6.0 (5.3–6.4)
Platelet count ($\times 10^3$ platelets/L)†	1	205 ± 49.7‖	314 ± 72.5§‡
	2	283 ± 93.8	344 ± 139.4

†Values reported are mean ± SE. ‡Within a row, value differs significantly ($P < 0.05$), compared with value obtained before surgery. §Values reported are median (range). ‖Within a time point within a variable, value differs significantly ($P < 0.05$) from the value for group 2.
See Table 1 for remainder of key.

Platelet aggregation in response to ADP or collagen did not differ significantly between treatment groups. Although most dogs of each group had values less than the reference range (ADP, 80 to 98%; collagen, 80% to 96%) before surgery, the number of dogs with pathologically reduced maximal aggregation decreased in both groups over time (**Table 3**).

Before surgery, 2 dogs of group 1 and 1 dog of group 2 had pathologically reduced platelet counts (reference range, 150 × 10^3 platelets/μL to 500 × 10^3 platelets/μL), whereas on day 4 after surgery, all dogs had platelet counts within the reference range. Platelet count did not differ significantly between treatments over time (**Table 4**).

Before surgery, 6 dogs of group 1 and 4 dogs of group 2 had an Hct less than the reference range (44% to 52%). However, a significant decrease of Hct was detected in both groups over the treatment period so that Hct was less than the reference range in all dogs on day 4 after surgery. Values for Hct did not differ significantly among treatments over time (Table 4).

Before surgery, most dogs in both groups had ALT (group 1: range, 16 to 1,524 U/L [median, 79 U/L]; group 2: range, 16 to 548 U/L [median, 59 U/L]) and GDM (group 1: range, 2.2 to 98.9 U/L [median, 7.9 U/L]; group 2: range, 1.5 to 133.0 [median, 6.8 U/L]) activities greater than the reference range (ALT, < 55 U/L; GDM, < 6 U/L). Whereas a significant increase of ALT activity was detected on day 4 (group 1: range, 12 to 591 U/L [median, 128 U/L]; group 2: range, 11 to 103 U/L [median, 47 U/L]), compared with values before surgery, GMD activity was significantly decreased in both groups on day 4 (group 1: range, 1 to 72 U/L [median, 2.6 U/L]; group 2: range, 1 to 3 U/L [median, 2.3 U/L]), compared with values before surgery. The ALP activity did not differ significantly between treatments at each time point, within treatments over time, or between treatments over time.

Plasma bilirubin concentration was significantly higher in dogs of group 1 (range, 0.12 to 1.00 mg/dL [median, 0.22 mg/dL]) than in dogs of group 2 (range, 0 to 0.21 mg/dL [median, 0.15 mg/dL]) on day 4. However, bilirubin concentration did not differ significantly among time points within both groups.

Discussion

Dogs with increased plasma concentrations of urea and creatinine were not included in the study reported here. These 2 variables remained within the respective reference ranges during the observation period. Plasma concentrations of urea and creatinine are commonly measured to enable clinicians to evaluate renal function in dogs. However, they are insensitive markers of renal dysfunction and increase only when renal damage is severe; they are not sufficiently sensitive to enable early discovery of posttraumatic or postoperative renal damage.[37,38]

Glomerular filtration rate provides a more accurate assessment of renal function.[35] It is a reliable marker to record the progress of renal insufficiency and to enable clinicians to recognize compensated, clinically inapparent nephropathies at an early stage.[33] In the study reported here, one third of the dogs had GFR values below the reference range before surgery. These findings may have been attributable to trauma or hypovolemic shock.[22,39,40] The GFR values of all dogs were within the reference range on days 1 and 4, with no significant differences evident between the treatment groups. Thus, analysis of these results confirms that carprofen administered before surgery does not increase the risk of renal failure beyond those risks already associated with trauma, surgery, and anesthesia. However, the dogs used in our study did not have any preexisting renal disease. Furthermore, they were provided replacement fluids during surgery, and mean arterial pressure was maintained during surgery.

Furthermore, determination of the UP:UC, urine specific gravity, and urine pH; analysis by use of a test strip; urine sediment analysis; and measurement of plasma potassium concentration did not reveal negative effects of carprofen on renal function. However, a significant increase in plasma phosphorus concentration was evident in both groups 0.5 hours after extubation. Surgery-related soft tissue trauma may have caused this effect.[41]

Renal blood flow and GFR remain constant when mean arterial blood pressure is between 60 and 150 mm Hg.[42] In the study reported here, the dogs received a crystalloid solution during the perioperative period and mean arterial pressure was maintained at > 60 mm Hg. Therefore, the vasodilator function of local renal prostaglandins had no major effects on renal function. Another possible explanation for the lack of clinically important renal effects of carprofen may have been that carprofen did not exert an inhibitory effect on COX in the kidneys and therefore preserved the protective function of local prostaglandins during general anesthesia. Our results are similar to those of studies[14-16] in which renal function was evaluated after administration of carprofen to healthy anesthetized dogs with or without concomitant surgery or to healthy dogs with low blood pressure that were anesthetized. Our study differs in that carprofen was administered to dogs with traumatic injuries that had plasma concentrations of urea or creatinine (or both) within reference ranges but had GFRs or UP:UC (or both) that often were not within the respective reference ranges before surgery.

Apart from adverse renal effects, NSAIDs reduce platelet aggregation and primary hemostasis because they inhibit thromboxane synthetase in thrombocytes.[17,43] Analysis of the results of our study indicated that carprofen does not appear to aggravate the risk of hemostatic impairment in dogs undergoing surgery to repair a fracture beyond those risks already associated with trauma, surgery, and anesthesia.

Platelet aggregation in response to ADP and collagen was less than the reference range in most dogs in either group before surgery. Additionally, values for APTT and PT were not within the respective reference ranges in many dogs after surgery. Activation of the fibrinolytic system in response to initial trauma is a possible explanation for this result.[44,45] The lack of consistent inhibition of platelet aggregation after carprofen

administration is most likely attributable to a predominant inhibition of COX-2.[19] Because it spares COX-1 activity, carprofen administration appears to have little or no effect on platelet function. Because no significant differences were found between the 2 groups in the study reported here, it is unlikely that platelet function and hemostasis were compromised by preoperative administration of carprofen.

The number of dogs with PT and APTT values that were not within the respective reference ranges before surgery increased by 0.5 and 6 hours after extubation. Trauma because of surgery,[46] hemodilution because of infusions,[47] administration of antimicrobials,[48] and administration of anesthetics[49] are likely to be the reasons for transient worsening in hemostasis. The APTT is a commonly used screening test for evaluating the endogenous coagulation system of dogs and humans,[28] whereas PT is used as a global screening test for evaluating the extrinsic coagulation system for diagnosis and follow-up evaluation of coagulopathies caused by vitamin K deficiency, hepatopathy, and disseminated intravascular coagulation.[29] However, PT and APTT do not predict the amount or complexity of hemostatic alterations.[50] Measurement of concentrations of fibrin degradation products, fibrinogen, or antithrombin III would have yielded more information about the ongoing hemostatic alterations.

Bleeding time is the best in vivo test for evaluation of primary hemostasis.[17] It can be used to determine thrombopathia in animals with typical platelet counts and can alert clinicians to a potential risk of hemorrhage during surgery.[31,51] In the study reported here, bleeding time did not differ significantly between the 2 groups and was within the reference range at all time points. This implies that primary hemostatic function remained normal. These results are consistent with those of another study.[9] This is supported by the fact that no increase in intraoperative bleeding was detected in dogs after preoperative administration of carprofen, which is also in conformity with results of other studies.[5,19]

Carprofen does not affect Hct or platelet count when administered to healthy dogs.[9,20] Possible explanations for a reduction of Hct for a specific time point in both groups of dogs in our study included blood loss as a consequence of the initial trauma or surgery, hemodilution caused by infusions, or blood loss as a result of excessive collection of blood samples.[16,26]

In the study reported here, an increase in hepatic enzyme activities in many dogs before surgery may have been caused by blunt abdominal trauma.[52] Carprofen is unlikely to cause liver failure because hepatic enzyme activities decreased in most of the dogs within the treatment period. The reasons for significant increases of median ALT activity in dogs of group 1 during the treatment period remain unclear. In other studies,[16,19] carprofen also did not have a hepatotoxic effect when used for a short period.

The dosage of carprofen used in our study was selected on the basis of recommendations made by investigators who have used this drug for analgesia after surgery.[1,7] For ethical reasons, we refrained from including a control group that would not have received analgesics. Opioids were used as rescue analgesics in the study reported here. No significant differences were found between the 2 groups with respect to the need for administration of opioids; therefore, a reliable assessment of the adverse effects of carprofen on renal function and hemostasis was provided.

Analysis of results of our study suggested that preoperative administration of carprofen does not increase adverse effects on renal function and hemostasis, compared with a control treatment, in dogs with traumatic injuries that undergo surgery for fracture repair. Significant differences between the 2 treatment groups may have existed but were not identified by the statistical tests because of the small sample size and low power of nonparametric tests. However, none of the dogs in the study reported here had clinically relevant alterations of renal function and hemostasis within the observation period of 5 days.

Most dogs in our study were young and relatively healthy with no major metabolic abnormalities before the injury (ie, trauma resulting in a fracture). The ability to use carprofen in this group of dogs and the fact that the dogs did well during and after surgery may differ substantially from results in older dogs or those with other metabolic abnormalities.

Furthermore, there is little information on the use of carprofen in cats. A single injection of carprofen may be safe in cats.[53,54] However, studies are necessary to evaluate the perioperative use of carprofen in cats with traumatic injuries.

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a. Rimadyl, Pfizer Laboratories Germany, Karlsruhe, Germany.
b. Fentanyl-Janssen, Janssen-Cilag, Neuss, Germany.
c. L-Polamivet, Intervet, Unterschleißheim, Germany.
d. Diazepam-ratiopharm, Merckle, Blaubeuren, Germany.
e. Rapinovet, Essex Pharma GmbH, Munich, Germany.
f. Isoflurane-Pharmacia, Pharmacia & Upjohn, Erlangen, Germany.
g. Anesthesia ventilator Cato, Dräger, Lübeck, Germany.
h. Tutofusin, Baxter, Unterschleißheim, Germany.
i. Anesthesia monitor Cato, Dräger, Lübeck, Germany.
j. Memoprint, S+B medVET, Babenhausen, Germany.
k. Hitachi 704 autoanalyzer, Roche Diagnostics, Mannheim, Germany.
l. Blood gas analyzer 248 Ciba, Bayer Diagnostics, Munich, Germany.
m. Technikon H 1E, Bayer Diagnostics, Munich, Germany.
n. Coagulometer, Schnitger & Gross, Amelung, Lemgo, Germany.
o. Pathromtin, Dade Behring Inc, Marburg, Germany.
p. Diethylbarbiturate acetate buffer solution, Dade Behring, Marburg, Germany.
q. Calcium chloride, 0.025M, Diagnostica Stago, Roche Diagnostics, Mannheim, Germany.
r. Human fibrinogen, Haemochrom Diagnostics, Essen, Germany.
s. Thromborel S, Dade Behring Inc, Marburg, Germany.
t. Finalgon, Essex Pharma, Munich, Germany.
u. APACT, Labor, Hamburg, Germany.
v. Isotonic saline solution, Fresenius Kabi, Bad Homburg, Germany.
w. ADP, Sigma-Aldrich, Taufkirchen, Germany.
x. Collagen, Horm with SKF Horm-Puffer, Nycomed, Ismaning, Germany.
y. Combur^9-Test, Roche Diagnostics, Mannheim, Germany.
z. Krüss-Handrefraktometer HRM 18, Krüss, Hamburg, Germany.
aa. Testsimplets, Roche Diagnostics, Mannheim, Germany.
bb. Omnipaque-350, Schering, Berlin, Germany.
cc. Renalyzer PRX 90, Diatron AM, Svedala, Sweden.

dd. Statistical packages for the social sciences, version 11.0, SPSS Science Software, Erkrath, Germany.

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