Effect of meloxicam and carprofen on renal function when administered to healthy dogs prior to anesthesia and painful stimulation

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Objective—To determine whether administration of the nonsteroidal anti-inflammatory drugs meloxicam or carprofen to healthy dogs that were subsequently anesthetized and subjected to painful electrical stimulation has adverse effects on renal function as measured by glomerular filtration rate (GFR) and evaluation of serum concentrations of urea and creatinine.

Animals—6 male and 6 female healthy young-adult Beagles.

Procedure—A study was conducted in accordance with a randomized crossover Latin-square design. One of 3 treatments (saline [0.9% NaCl] solution, 0.2 mg of meloxicam/kg, or 4.0 mg of carprofen/kg) was administered IV 1 hour before anesthesia was induced by use of drugs with a standard anesthetic protocol (butorphanol tartrate and acepromazine maleate preanesthetic medications, ketamine hydrochloride and diazepam for induction, and maintenance with isoflurane). Anesthetized dogs were subjected to intermittent electrical stimulation for 30 minutes. Direct, mean arterial blood pressure; heart rate; and respiratory rate were monitored. Endtidal isoflurane concentration was maintained at 1.5 times the minimum alveolar concentration. The GFR, as measured by plasma clearance of 99mTc-diethyleneetriaminepentaacetic acid, and serum concentrations of serum and creatinine were determined 24 hours after induction of anesthesia.

Results—Neither meloxicam nor carprofen significantly affected GFR or serum concentrations of urea and creatinine, compared with values for the saline treatment.

Conclusions and Clinical Relevance—When administered 1 hour before onset of anesthesia and painful electrical stimulation, meloxicam or carprofen did not cause clinically important alterations of renal function in young healthy dogs. (Am J Vet Res 2004;65:1384–1390)

Meloxicam and carprofen are nonsteroidal anti-inflammatory drugs (NSAIDs) considered to be effective analgesics for the management of pain in dogs after soft tissue or orthopedic surgery.15 Meloxicam and carprofen are approved for use in dogs in Canada, Europe, South America, Australia, and the United States. In addition to their use for postoperative analgesia, they are also used for dogs with chronic osteoarthritis. The NSAIDs are an important part of multimodal analgesia and are commonly used in conjunction with opioids. They do not cause sedation, which facilitates faster return to typical behavior, shortens hospital stays, and reduces associated costs for owners. The long dosing intervals allow provision of analgesia overnight as well as convenient once-daily dosing for ongoing analgesia after patient discharge.

The NSAIDs provide analgesia by suppressing generation of prostaglandins via inhibition of cyclooxygenase (COX)-1 and COX-2 enzymes. Prostanoids generated by COX-2 are important players in the inflammatory and pain response to surgical tissue injury.6,7 The NSAIDs provide analgesia by acting peripherally and at the level of the spinal cord.5 Preoperative administration of NSAIDs may help prevent wind-up,7 the phenomenon of central sensitization to painful stimuli caused by persistent stimulation of the neurons in the dorsal horn of the spinal cord. In addition to reducing central sensitization, preemptive provision of analgesia provides more compassionate care than waiting to intervene until after signs of pain have been perceived. Although administration of NSAIDs before anesthesia may be desirable for analgesic purposes, their use in this manner has been tempered by concerns of possible deleterious adverse effects on renal function. Hypotension and increased sympathetic tone, which are common effects of surgery and anesthesia, cause renal blood flow to become a prostaglandin-dependent event10-12; subsequent inhibition of prostaglandin production by NSAIDs can adversely affect glomerular filtration rate (GFR) and renal hemodynamics.13-17 Because the renal-protective prostaglandins are believed to be derived primarily from the actions of COX-1, it has been proposed that NSAIDs such as meloxicam and carprofen, which preferentially target COX-2, will cause less perturbation of renal blood flow when the kidneys are in a prostaglandin-dependent state, compared with the hemodynamic effects for the nonpreferential NSAIDs. However, evaluation of accumulated evidence reveals that COX-2 also has a constitutive role in the kidneys.18 Although intricacies of the role of COX-2 in the kidneys have yet to be elucidated, the assumption that selective COX-2 inhibitors have a renal-protective function has been called into question.19,20

The degree of selectivity of meloxicam and carprofen for COX-2 over COX-1 is debatable; however, there is general agreement that both preferentially inhibit COX-2. Neither targets COX-2 exclusively because both retain some activity against COX-1,20,21 which
warrants even more caution when administering these drugs to animals that are in a renal prostaglandin-dependent state.

The purpose of the study reported here was to mimic a typical, short, surgical procedure and determine whether the administration of meloxicam or carprofen before anesthesia and painful stimulation without fluid support would deleteriously affect renal function, compared with results after administration of saline solution (0.9% NaCl solution). Glomerular filtration rate and serum concentrations of urea and creatinine were used as measures of renal function.

Materials and Methods

Animals—Twelve Beagles (6 females and 6 males) between 1 and 5 years of age and ranging from 6.0 to 15.5 kg were used in the study. Baseline health was determined on the basis of results of a physical examination, CBC count, and serum biochemical analysis. Dogs were housed separately in kennels, walked daily, and fed a standard commercial food twice daily. Dogs had ad libitum access to water. Body weights were monitored weekly, and feeding was adjusted as needed to maintain a constant body weight. This project met the guidelines of the Canadian Council on Animal Care and was approved by the Animal Care Committee of the University of Guelph.

Experimental design—The study was a crossover design randomized on 2 factors (dog order and treatment order) in accordance with a Latin-square design to account for period and carryover effects.2 The investigators were not aware of the treatments administered to each dog at each time point until all data were collected and GFR calculations were performed. Each dog was anesthetized 3 times. Each episode of anesthesia was preceded by 1 of 3 treatments (saline solution, IV; 0.2 mg of meloxicam/kg, IV; or 4 mg of carprofen/kg, IV). A minimum 14-day washout period was allowed to elapse between subsequent anesthetic episodes. Each dog was medicated, anesthetized, and allowed to recover. The GFR and serum concentrations of urea and creatinine were assessed 24 hours after each anesthetic episode.

Anesthesia—One hour before induction of anesthesia, each dog was administered the appropriate treatment. Thirty minutes before anesthetic induction, each dog was administered preanesthetic medications (0.05 mg of acepromazine maleate/kg, IM; and 0.2 mg of butorphanol tartrate/kg, IM). A catheter was inserted in a cephalic or lateral saphenous vein. Anesthesia was induced by IV administration of a combination of ketamine hydrochloride1 (100 mg/mL) and diazepam2 (5 mg/mL); equal volumes of each were mixed in 1 syringe, and an amount of the combination was injected to provide an anesthetic plane sufficient to allow endotracheal intubation (maximum, 5 mg of ketamine/kg and 0.25 mg of diazepam/kg). Following intubation, each dog was maintained on isoflurane in oxygen (200 mL/kg/min) delivered via a Bain circuit. Isoflurane3 was delivered to achieve a concentration of 1.8% (ie, 1.5 times the minimum alveolar concentration [MAC]), as determined by measurement of end-tidal concentrations.3 A catheter4 was inserted in the dorsal pedal artery of each dog; however, this was not possible in a few dogs, and the catheter was inserted in a pinnal or lingual artery as alternative sites. After arterial catheters were in place, baseline values for mean arterial blood pressure (MAP), heart rate (HR), and respiratory rate (RR) were recorded. After baseline values were recorded, a 30-minute stimulation period was begun. A 23-gauge needle was inserted into the interdigital tissues. Stimulation consisted of 60-second bursts of electrical stimulation applied to the needle and repeated at 5-minute intervals to mimic a painful surgical stimulus. The electrical stimulator5 was set at a frequency of 50 cycles/s for a duration of 10 milliseconds at 50 V, which has been used for evaluation of MAC.2 The MAP, HR, and RR were monitored and documented at 5-minute intervals during the stimulation period. Also during the stimulation period, a catheter6 was inserted in a jugular vein of each dog, flushed with heparinized saline solution (10 IU of heparin/mL), and protectively handaged for atraumatic collection of blood samples the following day. No fluids were administered during the anesthetic episodes, other than the minimum amount required to maintain catheter patency. After completion of the stimulation period, catheters were removed (except for the bandaged catheter in the jugular vein). The dogs were observed during recovery from anesthesia.

Measurement of GFR—Plasma clearance tests for measurement of GFR were performed 24 hours after induction of anesthesia. A catheter7 with an injection cap was inserted in a cephalic or lateral saphenous vein of each dog for administration of 99mTc-diethylenetriaminepentaacetic acid (99mTc-DTPA). A reference blood sample was collected via the jugular catheter into an evacuated serum-collection tube. A dose of 15 to 30 MBq of 99mTc-DTPA8 was placed in a 3-mL syringe. The dose was diluted to a final volume of 2 to 3 mL by the addition of sterile saline solution. Radioactivity in the syringe was measured in a dose calibrator and recorded. The 99mTc-DTPA was immediately injected via the catheter into the cephalic or lateral vein during a period of approximately 3 seconds. Time zero was recorded at the midpoint of the injection. The catheter and injection cap were flushed with 2 or 3 mL of heparinized saline solution. The catheter used for administration of 99mTc-DTPA was removed within 10 minutes after injection of the radiopharmaceutical. Residual activity of the injection syringe and needle was measured in the dose calibrator within 5 minutes after completion of the injection. The injected dose was calculated as the difference between activity measured before and after injection.

Blood samples (1 to 2 mL) were collected from the catheter in the jugular vein by use of a standard 3-syringe technique (ie, collection of 1.5 mL of blood into a syringe containing 1.5 mL of heparinized saline solution, collection of 1 to 2 mL of blood into a second syringe, injection of the initial 1.5 mL of blood-heparinized saline solution, and flushing of the catheter with 2 mL of heparinized saline solution contained in a third syringe). Blood samples were transferred from the syringe to evacuated serum-collection tubes. Blood samples were collected 2, 4, 10, 30, 60, 90, 150, and 240 minutes after injection of 99mTc-DTPA. In a few cases, technical difficulties in collection of blood samples altered the time of sample collection; these were indicated in the records, and the actual time of sample collection was recorded. In 3 dogs, the catheter in the jugular vein became occluded during the course of the study. In these dogs, a catheter was inserted in the contralateral cephalic or lateral saphenous vein to allow collection of blood samples.

All blood samples were centrifuged (1,500 X g for 10 minutes). For each sample, a pipette was used to transfer 0.5 mL of serum to a 5-mL evacuated serum-collection tube marked with the time of sample collection and identification of the dog.

Samples were counted in a gamma counter7 within 2 to 3 hours after collection of the last blood sample. A standard solution of 99mTc-DTPA was used as a calibration standard to determine the counting efficiency of the gamma counter. Upper and lower discriminators of the gamma counter were set to capture emissions between 120 and 190 KeV. Counting was set to terminate at 5 minutes or when a minimum of 10,000 counts...
had been achieved; thus, the SD of counts was 1%. Correction of data for radioactive decay was performed by use of computer calculations at the time of calculation of the GFR. Gamma counter software was programmed to subtract background counts, which were measured during calibration for each assay.

**Calculation of the GFR**—Sample counts were adjusted on the basis of the time of injection by use of a half-life (t1/2) of 6.02 hours. The net dose injected was converted into an expected count on the basis of the calculated counting efficiency of the gamma counter. A time-activity curve was plotted on a semilogarithmic graph. A 2-compartment model was used. By use of computer software, the curve was fitted to the following biexponential logarithmic equation:

\[ y = a^{t} + c^{d} \]

where y is radioactivity; x is time; and a, b, c, and d are constants.

**Area under the curve (AUC)** was calculated by use of the following equation:

\[ \text{AUC} = (a/b) + (c/d) \]

The AUC was derived from the integration of the equation between 0 and infinity. The GFR was then calculated as the area under the curve divided by the time of injection by use of a general linear mixed model with dog as a random blocking factor. A Shapiro-Wilk test was conducted on the residuals to confirm that the data were normally distributed. Significance was set at \( P < 0.05 \).

**Results**

Mean ± SD time from administration of meloxicam, carprofen, or saline solution to induction of anesthesia was 61 ± 13 minutes. Mean ± SD duration of anesthesia (from induction of anesthesia to extubation) was 91 ± 11 minutes.

We did not detect significant differences among treatments for MAP, HR, and RR values recorded at baseline or during electrical stimulation. Mean ± SD lowest HR in each dog during the entire anesthesia period was 85 ± 10 beats/min. Mean baseline HR was 95 ± 20 beats/min. Increases above baseline values were evident immediately after onset of electrical stimulation. Mean HR during electrical stimulation was 160 ± 29 beats/min, which was a mean increase of 71 ± 38 beats/min over baseline values. Mean lowest MAP was 55 ± 12 mm Hg. Mean baseline MAP was 57 ± 12 mm Hg. Mean highest MAP during electrical stimulation was 108 ± 23 mm Hg, which was a mean increase of 53 ± 24 mm Hg over baseline values. Mean lowest RR was 14 ± 4 breaths/min. Mean baseline RR was 19 ± 9 breaths/min. Mean highest RR during electrical stimulation was 48 ± 33 breaths/min, which was a mean increase of 30 ± 31 breaths/min over baseline values.

Analysis by use of an ANOVA revealed that carryover effects (ie, sequence of drug administration) were not significant, whereas effects of period (ie, order in the study) and dog were significant. Thus, the carryover factor was removed from the model to refine the analysis. Power of the study to detect a difference of 0.5 mL/kg/min for the GFR among treatments by use of the estimated variance from the ANOVA output was 0.90.

Mean (95% confidence interval) for GFR was 4.28 mL/kg/min (4.06 to 4.50 mL/kg/min), 4.08 mL/kg/min (3.87 to 4.29 mL/kg/min), and 3.32 mL/kg/min (4.10 to 4.53 mL/kg/min) for carprofen, meloxicam, and saline solution, respectively. Mean (95% confidence interval) serum concentration of creatinine was 64.94 µmol/L (60.69 to 69.20 µmol/L), 68.77 µmol/L (64.68 to 72.87 µmol/L), and 63.03 µmol/L (57.35 to 68.71 µmol/L) for carprofen, meloxicam, and saline solution, respectively. Mean (95% confidence interval) for serum concentration of urea were 5.0 mmol/L (4.4 to 5.6 mmol/L), 6.0 mmol/L (5.4 to 6.6 mmol/L), and 5.1 mmol/L (4.3 to 5.9 mmol/L) for carprofen, meloxicam, and saline solution, respectively. There was no significant difference in GFR or serum concentration of urea or creatinine for the carprofen or meloxicam treatments, compared with values for treatment with saline solution.

**Discussion**

In the study reported here, we did not detect significant differences in GFR or serum concentrations of creatinine or urea between dogs when they were administered carprofen or saline solution. Our results are consistent with those of 3 other studies in which investigators examined the use of carprofen before anesthesia, with or without surgery, and did not detect adverse renal effects. However, another study conducted in dogs revealed a significant decrease in GFR (as measured by endogenous clearance of creatinine) 24 hours after castration when comparisons were made between groups of dogs administered carprofen or saline solution. In comparison to our study, the investigators in that study used drugs in accordance with an anesthesia protocol that differed slightly (acepromazine, atropine, and morphine before induction; induction with thiopentone; and maintenance with halothane), and those dogs then underwent a surgical procedure. Either of those differences may have had an impact on renal function. Duration of anesthesia and surgery in that study was reportedly 44 to 65 minutes, which is less than the value reported in our study.

Studies evaluating renal effects for the use of meloxicam before anesthesia and surgery in dogs are sparse in the veterinary literature. In 1 study, investigators primarily evaluated the analgesic efficacy of meloxicam when used before various abdominal surgical procedures with intraoperative IV administration of fluids. Those investigators also assessed urea and creatinine concentrations in the 12 dogs 24 and 48 hours after surgery, but they did not detect significant changes from baseline values. Analysis of results for the study reported here did not reveal significant differences between dogs when administered the meloxicam and saline solution treatments.

The study design had sufficient power to detect a difference in GFR of 0.5 mL/kg/min among treatments.
A decrease in GFR of < 0.5 mL/kg/min may not have been detected; however, more subtle changes in GFR are likely to be clinically unimportant. The study design also allowed comparisons among treatments, rather than comparison with baseline values or a reference range. Regardless, it is worthwhile mentioning that regardless of treatment administered, none of the dogs had values that exceeded the reference range established for our laboratory for serum concentrations of urea (3.5 to 9.0 mmol/L) or creatinine (20 to 150 μmol/L). Mean ± SD GFR for this group of 12 dogs, as measured by the authors in the month prior to onset of this study, was 3.90 ± 0.74 mL/min/kg (data not shown). Timing of collection of blood samples for this study was altered slightly from the schedule that was used to establish the reference range for our laboratory, which precluded direct comparison of values; however, the GFR for each treatment was still within the established range.

Studies on the safety of NSAIDs often focus on their use in association with anesthesia and surgery. Hypotension and increased sympathetic tone, which are common effects of surgery and anesthesia, cause renal blood flow to become a prostaglandin-dependent event.8,9,10 Subsequent inhibition of prostaglandin production by NSAIDs can adversely affect GFR and renal hemodynamics.11,12 Loss of effective circulating volume caused by fluid loss, blood loss, sodium deprivation, congestive heart failure, or various causes of hypotension will invoke increased release of the vasoconstrictors angiotensin II and norepinephrine.3 This physiologic response is an attempt to preserve adequate blood pressure in the face of an effective decrease in circulating volume, thus supporting continued perfusion of the cerebral and coronary circulation. In the face of such vasoconstrictive influences, prostaglandins act as vasodilators in the kidneys, moderating vasoconstriction of the renal vessels and thereby preserving GFR and renal blood flow.24

In the study reported here, we intentionally attempted to mimic a clinical setting in which NSAIDs would be most commonly used before anesthesia and routine surgical procedures of short duration in young, healthy dogs. Preanesthetic medications and anesthetic agents were typical of those commonly used in veterinary practices. Acepromazine is commonly used for its sedative effects, whereas butorphanol is selected for its analgesic effects. Ketamine and diazepam were selected as typical induction agents; they both impair neurocirculatory control mechanisms but only for a short time.25 Thus, they would have had minimal impact on the renin-angiotensin system and sympathetic response to hypotension during most of the study.

Hypotension (mean baseline MAP, 57 mm Hg) was evident in most dogs after insertion of a catheter into an artery and subsequent institution of direct monitoring of blood pressure. This hypotension was probably attributable to the hypotensive effects of acepromazine, an α₁-receptor antagonist,26 and the vasodilation and minor reduction in cardiac output associated with isoflurane. We observed that the target of 1.5 MAC induced a deeper plane of anesthesia than is generally necessary for surgical procedures. To ensure consistency in the study, we maintained the deep plane of anesthesia despite the accompanying hypotension. Administration of supportive fluids, which often are provided to alleviate hypotension, is frequently not used in clinical practice. It was intentionally withheld in this study, not to serve as an endorsement of withholding fluid treatment but in an attempt to mimic a clinical situation in which the kidneys may be under maximal hypotensive stress and thus most affected by prostaglandin-dependent mechanisms. The phenomenon of renal autoregulation (ie, reduction of renal vascular resistance during reduction of renal perfusion pressure) is highly dependent on prostaglandin production for MAP in the range of 77 to 95 mm Hg. This dependency becomes greater as blood pressure decreases further,27 until autoregulation fails and renal blood flow is compromised, which is at approximately 65 mm Hg.28 The low pressures achieved in the test subjects suggested that they were in the range at which renal autoregulation would have been prostaglandin-dependent.

It has been proposed29 that acepromazine may provide a protective effect on renal function by blockade of the peripheral action of catecholamines, thus preventing renal vasoconstriction. Acepromazine may have provided some renal protection by maintaining vasodilatation of renal vessels, thus obviating otherwise deleterious effects of NSAIDs on renal function. However, after electric stimulation, the dogs had increases in MAP, HR, and RR indicative of severe sympathetic stimulation, suggesting that a potential blockade action on peripherally acting catecholamines provided by acepromazine was overcome.

In addition to being central for protection of renal blood flow during hypotensive and low-flow states, prostaglandins are also necessary for preservation of GFR and renal blood flow in dogs with increases in MAP caused by increased sympathetic tone.30 Such sympathetic influence in surgical settings is typically induced by pain-inducing tissue manipulation. Arguably, findings for the study reported here may have been more representative of clinical practice had we actually performed surgery on the dogs. Electrical stimulation is frequently used as a means of assessing analgesia or depth of anesthesia in dogs and is an accepted and recognized means of providing a painful stimulus.27,30-41 A stimulus of the same intensity and duration was applied to all dogs, which decreased the variability. Electrical stimulation also avoided the confounding effects and humane issues related with repeated surgical interventions. Use of electrical stimulation allowed us to assess variation within each dog, which is statistically more powerful than analysis of variation among dogs, and provide more meaningful results with fewer experimental subjects.

Depth of anesthesia, as assessed by physical examination, was at a plane typically achieved in clinical settings or possibly deeper, considering blood pressure determinations. The duration of anesthesia was as long as or longer than that required for most routine veterinary surgical procedures. In addition, the physiologic responses of increases in HR, MAP, and RR detected
after electrical stimulation indicated a profound sympa
thetic influence, despite the apparent depth of anes
thesia that, in the authors’ experience, was as great or
greater than that which typically results from most sur
gical stimulations. As a result, we believe this study
method posed a greater challenge to the prostaglandin
dependent kidneys than most routine surgical proce
dures (eg, ovariohysterectomy or castration) per
formed by experienced veterinarians.

Potential NSAID-mediated harm to the kidneys
during anesthesia and surgery is caused by interference
with the renal response to decreases in perfusion.
Decreased renal perfusion, which is mediated by vaso
constrictive influences, hypotension, or hypovolemia,
results in reduced delivery of chloride to the tubular
lumen in the region of the macula densa, which in turn
stimulates increased secretion of renin. Because COX
-2–expressing epithelial cells are a likely source of
prostaglandins in the signaling pathway between the
macula densa and renin-producing granular cells,42 we
postulate that COX-2 inhibitors could minimize the
release of renin in situations of hypotension, which in
turn may reduce the vasoconstrictive effects of
angiotensin II and thus provide a sparing effect on
vasoconstriction of renal vasculature. However, the
baroreceptor mechanism for renin release, although
probably mediated by prostaglandin release,43 has not
been definitively established and may not be depen
dent on COX-2.44 Additionally, vasoconstrictive in
fluences are also provided by norepinephrine inde
pendent of those attributable to prostaglandins.45 Any
decrease in renin release secondary to inhibition of
COX-2 may be overshadowed by other vasoconstric
tive mechanisms.

Glomerular filtration rate, as measured by clear
ance of 99mTc-DTPA, and serum concentrations of
urea and creatinine were used as markers of renal func
tion in the study reported here. Total renal GFR is
equal to the sum of the filtration rate in each of the
functioning nephrons and thus is an index of the func
tioning renal mass.46 Reduction of GFR is a recognized
marker of postrenal ischemia and has been attributed to
persistent vasoconstriction.47 Serum concentrations of
urea and creatinine are technically simple to deter
mine and are commonly used estimates of GFR, but
they can be influenced by extrarenal factors48; there
fore, they are considered less sensitive than clearance
techniques.47–49 We used them in our study for thor
oughness, for comparison to GFR determined by use of
the clearance technique, and in case of failure of the
more technically demanding clearance technique. Two
compartment models of plasma clearance after a single
injection of 99mTc-DTPA are widely accepted as a reli
able measure of GFR in dogs, as determined on the
basis of studies46,48,50,51 conducted in dogs and extrap
olation of findings in humans.48 Reference ranges must
be established by each laboratory because variation in
the clearance technique may alter results considerab
ly.

Accuracy and precision of the dose calibrator,
gamma counter, pipette, and pipetting technique ac
count for most of the sources of error when assessing
GFR with the technique used here. Another source of
experimental error is the accuracy of timing for collec
tion of blood samples. A computerized software pro
gram was used to generate the best-fit constants for the
biexponential equation used for calculating AUC, thus
removing researcher bias and error. Variation in the fit
of the data points to the biexponential equation ac
counts for another source of experimental error.

Ischemic injury to the kidneys causes a reduction in
GFR. Damage to the proximal tubular cells leads to
increased solute delivery to the distal nephrons; this in
turn stimulates tubuloglomerular feedback, which re
sults in vasoconstrictive influences that reduce GFR.
Damage to endothelial cells and subsequent activation
of leukocytes contribute to impaired GFR by physically
impeding blood flow and through generation of fac
tors that are locally vasoconstrictive.50 Consequently,
any reduction in GFR resulting from renal ischemia
would be evident shortly after the onset of the ischemic
insult. We chose to measure renal variables 24 hours
after induction of anesthesia on the basis of informa
tion documented in another study.51 In that study, some
dogs developed increased serum concentrations of cre
atinine and urea, compared with presurgical values, by
24 hours after anesthesia; however, all values had
returned to within the reference range by 48 hours
after anesthesia. Studies of renal ischemia have docu
mented that decreased renal blood flow is sustained for
at least 24 hours after an acute, ischemic injury52,53 and
that GFR returns to the reference range within a week
after such an injury.54 Therefore, it was expected that
potential alterations in GFR and serum concentrations
of creatinine and urea would be detected at an earlier
(24 hours after anesthesia) rather than later (48 hours
after anesthesia) period.

The \( t_{1/2} \) of carprofen in dogs is 8 hours,55 whereas
the \( t_{1/2} \) of meloxicam is 24 hours.56 A 14-day washout
period was chosen to allow at least 5 half-lives between
subsequent treatments. The drug administered would
have been in the serum at the time of measurement of
GFR and serum concentrations of urea and creatinine.
Because prostaglandin-dependent mechanisms are not
involved in typical physiologic situations, it is unlikely
whether their continued effects would have altered the
GFR or serum concentrations of urea or creatinine.

Any changes in these variables among the carprofen or
meloxicam treatments, compared with values for the
saline solution treatment, would have been a reflection
of the action of the NSAID at the time of anesthesia and
electrical stimulation.

The respective roles of COX-1 and -2 in the kid
neys of dogs are increasingly being clarified. This
knowledge may enable clinicians and investigators
to more reliably predict the effects of COX-2
inhibitors on renal hemodynamics in various physi
ologic situations. Contrary to earlier assumptions,
results of studies are pointing toward an important
constitutive role of COX-2 in renal hemodynamics.
Thus, a renal-sparing effect of NSAIDs that are pre
ferential for COX-2 is being challenged. We suggest
that clinicians adhere to considered and cautious
use of these drugs with respect to renal function. As
is true of all pharmacologic agents, safety may be
confirmed only after widespread clinical use of these
agents, which could bring to light problems not evi
dent during experimentally controlled studies. Thus, we urge continued caution in the perioperative use of these drugs by veterinary practitioners. Analysis of our study revealed that administration of meloxicam or carprofen before anesthesia and painful electrical stimulation in young, healthy dogs that did not receive supportive fluids did not cause discernible alterations in renal function 24 hours after anesthesia, compared with results for administration of saline solution.

References

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