Renal effects of carprofen administered to healthy dogs anesthetized with propofol and isoflurane

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Objective—To evaluate renal effects of carprofen in healthy dogs following general anesthesia.

Design—Randomized clinical trial.

Animals—10 English hound dogs (6 females and 4 males).

Procedure—Dogs were randomly assigned to control (n = 5) or carprofen (5) groups. Anesthesia was induced with propofol (6 to 8 mg/kg [2.7 to 3.6 mg/lb] of body weight, IV) and maintained with isoflurane (end-tidal concentration, 2.0%). Each dog underwent two 60-minute anesthetic episodes with 1 week between episodes, and mean arterial blood pressure was maintained between 60 and 90 mm Hg during each episode. Dogs in the carprofen group received carprofen (2.2 mg/kg [1 mg/lb], PO) at 9:00 AM and 6:00 PM the day before and at 7:00 AM the day of the second anesthetic episode. Glomerular filtration rates (GFR) were determined during each anesthetic episode by use of renal scintigraphy. Serum creatinine and BUN concentrations and the urine γ-glutamyltransferase-to-creatinine concentration (urine GGT:creatinine) ratio were determined daily for 2 days before and 5 days after general anesthesia.

Results—Significant differences were not detected in BUN and serum creatinine concentrations, urine GGT:creatinine ratio, and GFR either between or within treatment groups over time.

Conclusions and Clinical Relevance—Carprofen did not significantly alter renal function in healthy dogs anesthetized with propofol and isoflurane. These results suggest that carprofen may be safe to use for preemptive perioperative analgesia, provided that normal cardiorespiratory function is maintained.

Materials and Methods

Animals—Ten healthy 2-year-old English hound dogs that weighed between 15.2 and 32.0 kg (33.4 to 70.4 lb) were used. Dogs were housed in university-approved facilities, fed a standard commercial diet, and given water ad libitum. Results of physical examinations, serum biochemical analyses, and CBC were within reference limits.

Study design and procedures—Dogs were randomly assigned to either control (n = 5) or carprofen (5) groups. Both groups underwent 2 anesthetic episodes, with 1 week elapsing between episodes. Prior to the second anesthetic episode, dogs in the carprofen group received carprofen (2.2 mg/kg [1 mg/lb] of body weight, PO) at 9:00 AM and 6:00 PM the day before anesthesia and at 7:00 AM the day of anesthesia.

For each anesthetic episode, anesthesia was induced of their ability to inhibit renal prostaglandin synthetase, all NSAID can adversely affect renal function. Some authors have advised withholding NSAID prior to surgery in humans because of the risk of acute renal failure. Despite this warning, there has been widespread perioperative use of NSAID with few cases of acute renal failure reported in humans.

The safety of administering NSAID in combination with agents that induce general anesthesia in small animals has not been extensively evaluated. A combination of methohexital or halothane and flunixin meglumine can result in nephrotoxicity in dogs. Renal toxicity has been reported as an adverse effect of carprofen administration in dogs with preexisting renal disease. It is not known whether there are any risks to the renal system associated with the short-term use of carprofen in dogs that undergo general anesthesia.

Multiple methods have been used to evaluate kidney function in veterinary medicine. Determination of serum creatinine and BUN concentrations is most commonly used because of the ease of measurement. Recently, determination of the urine γ-glutamyltransferase-to-creatinine concentration (urine GGT:creatinine) ratio has been used as a sensitive early indicator of nephrotoxicity. In addition, measurement of glomerular filtration rate (GFR) provides accurate assessment of renal function regarding the severity of disease. The use of nuclear scintigraphy after administration of technetium Tc 99m pentetate is a rapid method for determining renal function without the need for indwelling catheters or prolonged urine collection. This method was used previously to evaluate the effects of different sedative protocols on GFR in healthy dogs.

The use of nonsteroidal anti-inflammatory drugs (NSAID), including carprofen, prior to surgery has been proven to be an effective method of perioperative pain management in dogs. In humans, concerns have been raised regarding the effects of NSAID administered during the perioperative period on the renal and coagulation systems. Renal prostaglandins play a protective role in the kidney by functioning as local vasodilators to maintain renal perfusion, and because the use of nuclear scintigraphy after administration of technetium Tc 99m pentetate is a rapid method for determining renal function without the need for indwelling catheters or prolonged urine collection. This method was used previously to evaluate the effects of different sedative protocols on GFR in healthy dogs.
with propofol (6 to 8 mg/kg [2.7 to 3.6 mg/lb], IV) via a catheter placed in the cephalic vein. Dogs were then endotracheally intubated, and anesthesia was maintained with isoflurane (end-tidal concentration, 2%). Mean arterial blood pressure was maintained between 60 and 90 mm Hg. In addition, lactated Ringer's solution (10 to 20 ml/kg/h [4.5 to 9 ml/lb], IV) was administered to help maintain circulating blood volume and blood pressure.

During each anesthetic episode, heart rate, hemoglobin oxygen saturation, respiratory rate, end-tidal CO2 concentration, and blood pressure were measured. Blood pressure was measured, using an oscillometric device; hemoglobin oxygen saturation was measured by use of pulse oximetry; and end-tidal CO2 and isoflurane concentrations were measured, using a side-stream airway gas monitor. Blood pressure values were validated indirectly, using the heart rate obtained from the blood pressure monitor, pulse oximeter, and ECG; values were recorded only when the heart rate obtained from all 3 devices matched. If the heart rate measured from the blood pressure monitor did not match rates obtained from the pulse oximeter and ECG, the blood pressure measurement was repeated.13

Blood and urine samples for determination of BUN and serum creatinine concentrations and urine GGT:creatinine ratios were collected daily for 2 days prior to and 5 days after each anesthetic episode. After induction of anesthesia, anesthesia was maintained with an end-tidal isoflurane concentration of 2% for 30 minutes before determination of GFR by use of nuclear scintigraphy after IV administration of technetium 99m Tc pentetate.11 Serial 6-second data were acquired for 6 minutes. A composite image was made, and a region of interest was drawn by 1 investigator (DFM) over each kidney. The GFR was then calculated, using a dedicated computer program and incorporating the depth adjustment. Duration of each anesthetic episode was 60 minutes.

Statistical analyses—Data were compared between groups and across times within each group by use of ANOVA for repeated measures and Tukey multiple comparison tests. Significance was set at P < 0.05.

Results
We did not detect significant differences in GFR between or within the 2 groups (control vs carprofen) during either anesthetic episode. During the first episode, in which carprofen was not administered, mean (± SD) GFR in the control group was 1.94 ± 0.37 ml/kg/h and in the carprofen group was 1.94 ± 0.37 ml/kg/h. Glomerular filtration rate increased slightly but not significantly in the carprofen group after administration of carprofen during the second anesthetic episode (2.16 ± 0.45 ml/kg/h). The GFR in the control group during the second anesthetic episode changed minimally (1.98 ± 0.83 ml/kg/h).

Prior to the first anesthetic episode, values for BUN, serum creatinine concentration, and urine GGT:creatinine ratio were within reference ranges in the control and carprofen groups (BUN, 15.84 ± 4.86 mg/dl and 13.76 ± 2.59 mg/dl, respectively; serum creatinine concentration, 0.74 ± 0.09 mg/dl and 0.78 ± 0.19 mg/dl, respectively; urine GGT:creatinine ratio, 0.43 ± 0.10 and 0.35 ± 0.10, respectively). Values obtained before the second anesthetic episode did not differ significantly. Moreover, values were not significantly different between groups and did not change significantly over time before or after either anesthetic episode.

Values determined for heart rate, hemoglobin oxygen saturation, respiratory rate, end-tidal CO2 concentration, and blood pressure during the first anesthetic episode did not differ between groups, nor did they differ from values determined during the second anesthetic episode. During the first anesthetic episode, mean heart rate varied between 116.3 ± 10.5 and 93.2 ± 12.4 beats/min in the control group and 108.4 ± 9.8 and 87.9 ± 14.2 beats/min in the carprofen group. Hemoglobin oxygen saturation varied between 97.5 ± 2.0 and 93.8 ± 3.1% in the control group and 96.4 ± 2.8 and 97.1 ± 1.8% in the carprofen group. Respiratory rate varied between 20.4 ± 5.8 and 18.2 ± 3.4 breaths/min in the control group and 15.6 ± 4.7 and 16.2 ± 3.3 breaths/min in the carprofen group. Mean arterial blood pressure was maintained between 60 and 90 mm Hg in both groups during each episode. All dogs recovered without complications and did not develop clinical signs of nephrotoxicosis for at least 2 weeks after the study.

Discussion
Our results suggest that short-term carprofen use in conjunction with general anesthesia induced and maintained by administration of propofol and isoflurane does not result in significant changes in renal function in healthy dogs. There are several potential explanations why we did not detect significant differences in renal function between groups. Although inhibition of prostaglandin biosynthesis has profound effects on renal blood flow and GFR in dogs with hypotension resulting from hemorrhage16 or in dogs that are salt deprived,17 the dogs in our study were healthy. Moreover, mean arterial blood pressure was maintained >60 mm Hg during anesthesia, and lactated Ringer’s solution was administered IV to help maintain circulating blood volume. We did not attempt to induce abnormal renal function in these dogs. Small variations in blood pressure have a minimal effect on GFR because of renal autoregulation, a feedback mechanism whereby the glomerular afferent or efferent arterioles dilate or constrict as necessary to maintain a constant filtration rate.18,19 Renal blood flow and GFR remain constant at mean arterial blood pressures between 60 and 150 mm Hg.20 Because the dogs in our study were not subjected to any type of renal stress, it is possible that the vasodilator function of local renal prostaglandins did not play a major role in maintaining normal renal function in these dogs.

Another possibility is that carprofen did not exert an inhibitory effect on constitutive cyclooxygenase (COX) in the kidney of these dogs, thereby preserving the protective function of local renal prostaglandins during general anesthesia. The discovery that COX exists in a constitutive form (ie, COX-1) and a cytokine-inducible form (COX-2) has changed the traditional view of the role of COX in the kidney.21,22 Lonigo et al22 demonstrated that indomethacin, a nonselective COX inhibitor, significantly reduced renal blood flow in anesthetized dogs. Those results suggest
that the decrease in renal blood flow was attributable to indomethacin-induced inhibition of renal prostaglandin synthesis. However, in dogs, COX-2 is approximately 100-fold more sensitive to the inhibitory actions of carprofen than COX-1.25 Black et al26 successfully demonstrated that the effects of indomethacin on renal blood flow are the result of inhibition of COX-1 activity; short-term administration of a selective COX-2 inhibitor did not have deleterious effects on renal function. Results of our study also suggest that short-term administration of carprofen, a potent COX-2 inhibitor, in combination with propofol and isoflurane did not have a significant effect on renal function in healthy dogs.

Results of a previous study indicated that GFR did not differ significantly between awake and sedated dogs when mean arterial blood pressure was maintained >60 mm Hg.27 In the present study, although the mean arterial blood pressure was maintained >60 mm Hg, GFR (1.94 to 2.16 ml/kg/min) were slightly less than those in the previous study in which dogs were sedated and not anesthetized (2.80 to 3.13 ml/kg/min). General anesthesia itself activates the angiotensin-renin system.21 Activation of this system causes constriction of renal afferent and efferent arterioles, hence modulating renal blood flow and decreasing GFR.20

Short-term use (single IV or SC administration) of carprofen either immediately prior to or after elective surgery is effective at managing acute surgical pain in dogs.28 Results of a recent study29 indicate that plasma concentrations of carprofen were not directly related to analgesia. However, dogs given carprofen had lower pain scores than control dogs. Carprofen is available in the US in a tablet formulation designed for oral administration. Synovial concentrations of carprofen peaked 3 hours after oral administration of 2 mg of carprofen/kg every 12 hours, and the drug remained effective for 6 hours following administration at modulating responses to force-plate analyses in dogs.28 The mean biological half-life of carprofen in dogs is 8 hours (range: 4.5 to 9.8 hours) after a single oral administration of doses ranging from 1 to 35 mg/kg (2.2 to 77 mg/lb).27 On the basis of this information, we believe that the dose of carprofen used in the present study was a reasonable dose for assessing renal toxicity of carprofen in healthy dogs.

Serum creatinine and BUN concentrations are commonly measured to evaluate renal function in dogs. It has been suggested that changes in these variables over time are more useful than a single measurement.30 In the present study, serum creatinine and BUN concentrations did not change significantly between anesthetic episodes within each group or between treatment groups at any time during each anesthetic episode. These results were consistent with the minimal and nonsignificant changes we observed in GFR. The manufacturer of carprofen reports that oral administration of carprofen at a dose of 20 mg/kg (9 mg/lb) to rats given saline (0.9% NaCl) solution IV caused no deleterious effects on urine volume or electrolyte excretion.20

We did not detect any significant renal effects of short-term administration (3 doses over 2 days) of carprofen (2.2 mg/kg) to healthy dogs anesthetized with propofol and isoflurane. It is possible that our inability to detect differences between or within treatment groups reflected the small number of dogs used. However, further studies are necessary to evaluate effects of carprofen on renal function in dogs with hypotension or abnormal renal function.

References

**Correction:** Relative cost-effectiveness of treatment of feedlot calves with ivermectin versus treatment with a combination of fenbendazole, permethrin, and fenthion

In the Results section of "Relative cost-effectiveness of treatment of feedlot calves with ivermectin versus treatment with a combination of fenbendazole, permethrin, and fenthion" (JAVMA, 2000;216:1965-1969), Table 2 was published incorrectly. The correct table appears below:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ivermectin group</th>
<th>Control group</th>
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<tr>
<td><strong>Final weight (kg)</strong></td>
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<tr>
<td>Live</td>
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<td>Carcass</td>
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<td><strong>Weight gain (kg)</strong></td>
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<tr>
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<td>233.0</td>
<td>1.2</td>
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<tr>
<td>Carcass</td>
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<td>245.4</td>
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<td>8.34</td>
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<tr>
<td>Carcass</td>
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<tr>
<td>Live</td>
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<td>6.21</td>
<td>0.02</td>
</tr>
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*Significantly (P < 0.05) different from value for control group.
To convert to values in pounds, multiple values by 2.2.
See Appendix for calculation details.

Table 2—Growth performance of feedlot calves treated with ivermectin (7,094 animals; 15 pens) versus a combination of fenbendazole, permethrin, and fenthion (control group, 7,090 animals; 15 pens)