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

Jeff C. H. Ko, DVM, MS, DACVA; Takayoshi Miyabiyashi, BVS, PhD, DACVR; Ronald E. Mandsager, DVM, DACVA; Terrell G. Heaton-Jones, DVM; Daniel F. Mauragis

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 nor- mal cardiorespiratory function is maintained. (J Am Vet Med Assoc 2000;217:346–349)

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.1,2 In humans, concerns have been raised regarding the effects of NSAID administered during the perioperative period on the renal and coagulation systems.3 Renal prostaglandins play a protective role in the kidney by functioning as local vasodilators to maintain renal perfusion,4 and because of their ability to inhibit renal prostaglandin synthetase, all NSAID can adversely affect renal function.5 Some authors have advised withholding NSAID prior to surgery in humans because of the risk of acute renal failure.6 Despite this warning, there has been widespread perioperative use of NSAID with few cases of acute renal failure reported in humans.7

The safety of administering NSAID in combination with agents that induce general anesthesia in small animals has not been extensively evaluated. A combination of methoxyflurane8 or halothane9 and flunixin10 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.11 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.12 Recently, determination of the urine γ-glutamyltransferase-to-creatinine concentration (urine GGT:creatinine) ratio has been used as a sensitive early indicator of nephrotoxicity.13,14 In addition, measurement of glomerular filtration rate (GFR) provides accurate assessment of renal function regarding the severity of disease.15 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.16 This method was used previously to evaluate the effects of different sedative protocols on GFR in healthy dogs.17 The purpose of the study reported here was to evaluate the potential interactions between carprofen, propofol, and isoflurane on renal function in healthy dogs.

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...
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/h], 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 CO$_2$ 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 CO$_2$ 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. 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. 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 1.97 ± 0.33 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 CO$_2$ 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 hemorrhage$^{16}$ 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.$^{22,24}$ Lonigro et al.$^{22}$ demonstrated that indomethacin, a non-selective 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 approxi-
mately 100-fold more sensitive to the inhibitory actions of carprofen than COX-1.21 Black et al22 suc-
cessfully 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 isoflu-
rane 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 main-
tained >60 mm Hg.23 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).21 General anesthesia itself activates the
angiotensin-renin system.21 Activation of this system
causes constriction of renal afferent and efferent arteri-
oles, hence modulating renal blood flow and decreas-
ing GFR.23

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.24 Results of a recent study25 indicate that plasma
centrations 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 admin-
istration. Synovial concentrations of carprofen peaked
3 hours after oral administration of 2 mg of carpro-
fen/kg every 12 hours, and the drug remained effective
for 6 hours following administration at modulating
responses to force-plate analyses in dogs.2 The mean
biological half-life of carprofen in dogs is 8 hours
(range, 4.5 to 9.8 hours) after a single oral administra-
tion 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 com-
monly measured to evaluate renal function in
dogs. It has been suggested that changes in these vari-
ables over time are more useful than a single measure-
ment.26 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 mini-
mal and nonsignificant changes we observed in GFR.

The manufacturer of carprofen reports that oral admin-
istration 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.28

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 treat-
ment 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.

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plasma renin activity during hypotensive hemorrhage in the dog. J


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**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 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)

<table>
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<th>Variable</th>
<th>Mean</th>
<th>SE</th>
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<tbody>
<tr>
<td></td>
<td>Ivermectin group</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control group</td>
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<tr>
<td>Final weight (kg)</td>
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<tr>
<td>Live</td>
<td>536.5*</td>
<td>527.2</td>
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<td>Carcass</td>
<td>546.8*</td>
<td>540.1</td>
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<td>Weight gain (kg)</td>
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<tr>
<td>Live</td>
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<td>233.0</td>
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<tr>
<td>Carcass</td>
<td>253.7*</td>
<td>245.5</td>
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<tr>
<td>Days on feed</td>
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<td>182.7</td>
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<td>Daily dry matter intake (kg/d)</td>
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<td>Average daily gain (kg/d)</td>
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</tr>
<tr>
<td>Live</td>
<td>1.33*</td>
<td>1.28</td>
</tr>
<tr>
<td>Carcass</td>
<td>1.39*</td>
<td>1.35</td>
</tr>
<tr>
<td>Dry matter intake-to-gain ratio</td>
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<td>6.54</td>
</tr>
<tr>
<td>Live</td>
<td>6.54*</td>
<td>6.21</td>
</tr>
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</table>

*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.