Effects of meloxicam on hematologic and plasma biochemical analysis variables and results of histologic examination of tissue specimens of Japanese quail (Coturnix japonica)

Kristin M. Sinclair, DVM; Molly E. Church, VMD, MS; Thomas B. Farver, PhD; Linda J. Lowenstine, DVM, PhD; Sean D. Owens, DVM; Joanne Paul-Murphy, DVM

Objective—To determine the effects of meloxicam on values of hematologic and plasma biochemical analysis variables and results of histologic examination of tissue specimens of Japanese quail (Coturnix japonica).

Animals—30 adult Japanese quail.

Procedures—15 quail underwent laparoscopic examination of the left kidneys, and 15 quail underwent laparoscopic examination and biopsy of the left kidneys. Quail in each of these groups received meloxicam (2.0 mg/kg, IM, q 12 h; n = 10) or a saline (0.9% NaCl) solution (0.05 mL, IM, q 12 h; control birds; 5) for 14 days. A CBC and plasma biochemical analyses were performed at the start of the study and within 3 hours after the last treatment. Birds were euthanized and necropsies were performed.

Results—No adverse effects of treatments were observed, and no significant changes in values of hematologic variables were detected during the study. Plasma uric acid concentrations and creatine kinase or aspartate aminotransferase activities were significantly different before versus after treatment for some groups of birds. Gross lesions identified during necropsy included lesions at renal biopsy sites and adjacent air sacs (attributed to the biopsy procedure) and pectoral muscle hemorrhage and discoloration (at sites of injection). Substantial histopathologic lesions were limited to pectoral muscle necrosis, and severity was greater for meloxicam-treated versus control birds.

Conclusions and Clinical Relevance—Meloxicam (2.0 mg/kg, IM, q 12 h for 14 days) did not cause substantial alterations in function of or histopathologic findings for the kidneys of Japanese quail but did induce muscle necrosis; repeated IM administration of meloxicam to quail may be contraindicated. (Am J Vet Res 2012;73:1720–1727)

Nonsteroidal anti-inflammatory drugs have anti-inflammatory and analgesic effects. Such drugs are used to relieve acute visceral and musculoskeletal signs of pain (including signs of pain associated with trauma) and chronic signs of pain (from conditions such as arthritis) and to decrease inflammation and central nervous sensitization associated with surgery.1–3 Although NSAIDs are considered effective for treatment of signs of chronic pain in birds, few studies have been conducted to investigate this. Meloxicam is one of the most frequently prescribed NSAIDs for companion birds because of ease of administration; oral and injectable formulations of this drug are commercially available in concentrations appropriate for use in small patients. Meloxicam is an enolic acid derivative that is a COX-2–preferential NSAID.4,5 Cyclooxygenase-2 is an inducible enzyme expressed by cells in response to inflammatory mediators and is constitutively expressed in the kidneys.5,6 At high doses, meloxicam can also inhibit COX-1 in mammals, leading to decreased production of prostaglandins required for physiologic functions.4,5 Substantial differences may exist regarding relative COX-1 and COX-2 selectivities of certain NSAIDs among species of animals and differences in

**ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<td>CK</td>
<td>Creatine kinase</td>
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<td>COX</td>
<td>Cyclooxygenase</td>
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drug selectivity for these COX isoforms in vivo and in vitro. In birds, toxic effects of NSAIDs include renal effects leading to increased plasma uric acid concentrations and development of glomerular lesions.\textsuperscript{4-10} Renal function in animals of most species involves prostaglandin-mediated regulation of vascular tone and blood flow. Prostaglandins aid regulation of renal blood flow during conditions that decrease circulating blood volume or systemic blood pressure (eg, anesthesia); NSAIDs may interfere with such regulation, resulting in decreased renal blood flow during those conditions.\textsuperscript{3,11} In adult and embryonic chickens, COX-1 and COX-2 are expressed in higher than doses used in other studies\textsuperscript{8,19} in which analgesic effects of meloxicam are listed. In one study, administration of 1 mg/kg of meloxicam to 7 days, were not significantly different from those received a high dose (5.5 mg/kg) of flunixin meglumine. In pigeons, repeated IM injection of carprofen is associated with increased circulating AST and alanine aminotransferase enzyme activities, gross lesions in muscle injection sites and liver tissue, histopathologic lesions in liver and muscle tissue, and acute vascular congestion in renal tissue.\textsuperscript{20} Budgerigars (Melopsittacus undulatus) that received a high dose (3.5 mg/kg) of flunixin meglumine for 3 to 7 days develop renal lesions of greater severity than do budgerigars that receive low doses of flunixin meglumine.\textsuperscript{8} In that study, plasma uric acid concentrations in budgerigars receiving meloxicam at a dosage of 0.1 mg/kg, every 24 hours, for 3 to 7 days, were not significantly different from those in budgerigars receiving a control treatment. Histopathologic renal tubular degeneration lesions were detected in 1 of 16 budgerigars that received meloxicam, and glomerular congestion developed in 1 of 16 control-treated and 2 of 16 meloxicam-treated budgerigars.\textsuperscript{8} In another study,\textsuperscript{19} administration of meloxicam at a dosage of 0.5 mg/kg, twice daily for 14 days to African grey parrots (Amazona ventralis) that ingested diclofenac-treated carrion are associated with renal tubular necrosis and visceral gout.\textsuperscript{3,10,16,17} Results of another study\textsuperscript{18} indicate quail of one species (Colinus virginianus) develop glomerular lesions following 7 days of administration of various doses of flunixin meglumine. In pigeons, repeated IM injection of diclofenac is associated with increased circulating AST and alanine aminotransferase enzyme activities, gross lesions in muscle injection sites and liver tissue, histopathologic lesions in liver and muscle tissue, and acute vascular congestion in renal tissue.\textsuperscript{20} Budgerigars (Melopsittacus undulatus) that receive a high dose (3.5 mg/kg) of flunixin meglumine for 3 to 7 days develop renal lesions of greater severity than do budgerigars that receive low doses of flunixin meglumine.\textsuperscript{8} In that study, plasma uric acid concentrations in budgerigars receiving meloxicam at a dosage of 0.1 mg/kg, every 24 hours, for 3 to 7 days, were not significantly different from those in budgerigars receiving a control treatment. Histopathologic renal tubular degeneration lesions were detected in 1 of 16 budgerigars that received meloxicam, and glomerular congestion developed in 1 of 16 control-treated and 2 of 16 meloxicam-treated budgerigars.\textsuperscript{8} In another study,\textsuperscript{19} administration of meloxicam at a dosage of 0.5 mg/kg, twice daily for 14 days to African grey parrots (Psittacus erithacus) did not cause any abnormalities in the blood biochemical analysis variables evaluated, and histopathologic evaluation of renal biopsy specimens did not reveal any abnormalities for 9 of the 10 birds in the study. The analgesic effect of meloxicam in birds has been recently investigated. In 1 study,\textsuperscript{21} analgesic effects of IM-administered meloxicam in Hispaniolan Amazon parrots (Amazona ventralis) with experimentally induced arthritis were evaluated. The highest dose of meloxicam evaluated (1 mg/kg) in that study\textsuperscript{21} provided the most effective analgesia. That dose of meloxicam is higher than doses used in other studies\textsuperscript{8,15,18} in which adverse effects of meloxicam on renal function and histopathologic findings for psitacines were evaluated. The purpose of the study reported here was to determine the effect of a high dose of meloxicam (2 mg/kg, IM) on hematologic, plasma biochemical, and histologic findings for Japanese quail (Coturnix japonica).\section{Materials and Methods} \subsection*{Animals—}Thirty adult Japanese quail (body weight range, 110 to 135 g) were acquired from the University of California-Davis Avian Sciences breeding facilities and housed at the University of California-Davis School of Veterinary Medicine for the duration of this study. The University of California-Davis Institutional Animal Care and Use Committee approved the experimental protocol. The study included 2 cohorts of quail: 15 birds (6 female and 9 male) that were used in a veterinary student teaching laboratory (cohort 1) and 15 male birds that were not used in a teaching laboratory (cohort 2). Gender of birds was determined during laparoscopy. Female birds were excluded from cohort 2 to facilitate endoscopic examination of the birds because female reproductive tracts in birds with active ovarian follicles can interfere with that procedure. All of the birds were housed separately in battery cages (23 X 25 X 20 cm) in a temperature- (20° to 22°C) and photoperiod- (10 hours of light and 14 hours of darkness/d) controlled room. A commercially available diet\textsuperscript{e} and water were offered to the birds ad libitum. All of the birds were healthy as determined on the basis of unremarkable results of physical examinations, CBCs, and plasma biochemical analyses, which were performed within 1 week prior to the start of the study. A blood sample (0.8 to 1.0 mL) was collected from a jugular vein of each bird and placed in EDTA-containing tubes\textsuperscript{d} for performance of a CBC (including fibrinogen measurement) and lithium heparin-containing tubes\textsuperscript{b} for performance of plasma biochemical analyses (pretreatment blood samples). Blood samples from birds that were used in a teaching laboratory (cohort 1) were obtained by veterinary students during that laboratory; blood samples from birds that were not used in a teaching laboratory (cohort 2) were obtained by a veterinarian who was an experienced avian venipuncturist (KMS). Blood samples for CBCs were immediately prepared with a modified Natt and Herrick stain and evaluated by use of a hemocytometer by personnel at a hematology laboratory.\textsuperscript{4} Fibrinogen concentrations were measured via the heat precipitation method.\textsuperscript{22} Blood samples containing heparin were centrifuged within 30 minutes after collection, and plasma was harvested and stored in plastic tubes\textsuperscript{b} at –70°C until analysis. Plasma samples were analyzed for determination of AST and CK activities and uric acid, glucose, calcium, phosphorus, potassium, chloride, and sodium concentrations with an avian-reptile cartridge and a benchtop analyzer.\textsuperscript{7} \subsection*{Experimental design—}The 15 quail in each study cohort were weighed and assigned by use of a random integer generator program\textsuperscript{f} to 1 of 2 treatment groups; 10 birds in each cohort received meloxicam,\textsuperscript{8} and 5 birds (control birds) in each cohort received a volume of preservative-free saline (0.9% NaCl) solution\textsuperscript{8} that was similar to the volume of meloxicam administered to birds. For all quail, laparoscopic examination of the left kidney was performed prior to starting treatment; birds in cohort 1 (birds that were used in a teaching laboratory) also underwent laparoscopically guided renal biopsy. Therefore, 4 groups of birds were included: birds that underwent renal biopsy and received meloxicam,
cam (2 mg/kg, IM, q 12 h for 14 days; n = 10), birds that underwent renal biopsy and received saline solution (0.05 mL, IM, q 12 h for 14 days; 5), birds that did not undergo renal biopsy and received meloxicam (2 mg/kg, IM, q 12 h for 14 days; 10), and birds that did not undergo renal biopsy and received saline solution (0.05 mL, IM, q 12 h for 14 days; 5). All IM injections were performed in pectoral muscles.

Laparoscopy and biopsy procedures—Each bird received butorphanol tartrate1 (1 to 2 mg/kg, IM) 20 minutes prior to induction of anesthesia. Birds were anesthetized via mask induction with isoflurane.1 Endotracheal intubation was performed, and anesthesia was maintained with isoflurane (1% to 3%) in oxygen (1 L/min) with intermittent positive pressure ventilation. Heart rates of birds were monitored with a stethoscope and a Doppler ultrasonic device placed on the brachial artery, and respiratory rates were determined via visual observation. Following induction of anesthesia, quail were placed in right lateral recumbency with the left leg extended forward and secured to the neck with loosely applied self-adhesive bandaging material.3 Birds were in a surgical plane of anesthesia, bupivacaine1 (2 mg/kg, IM, q 12 h) or preservative-free saline solution (0.05 mL, SC) was administered, a blood sample (0.8 to 1.0 mL; posttreatment period) was obtained from each bird by Seldinger technique.3,20 Cardiovascular data were recorded, and the birds were allowed to recover. Lactated Ringer's solution (5.0 mL, SC) was administered to birds during anesthetic recovery. Meloxicam1 (0.05 mL, IM, q 12 h) administration was started immediately following the laparoscopy procedure.

Treatment period and necropsy—Treatments were administered for 14 days (28 doses/bird). During the treatment period, appetite, activity, fecal and urine output, and body weight of birds were monitored twice daily by a single veterinarian (KMS). Two to 3 hours after the last dose of meloxicam or saline solution was administered, a blood sample (0.8 to 1.0 mL; posttreatment blood sample) was obtained from each bird by one of the authors (KMS) via the same procedure used to obtain blood samples at the beginning of the study, and CBCs and plasma biochemical analyses were performed. The birds were euthanized via IV injection of sodium pentobarbital1 (300 to 350 mg/kg).

Carcasses of birds were placed in a cooler (4.0°C) immediately, and necropsies were performed within 5 hours after euthanasia. Tissue specimens were obtained and fixed in neutral-buffered 10% formalin, containers were labeled, and tissue specimens were submitted to a laboratory for histologic examination. For each quail, each tissue specimen was embedded in a separate paraffin block, cut in 5-µm sections, and stained with HE. Slides of tissue specimens were examined by 2 of the authors (LJL and MEC) who were unaware of the bird from which tissue specimens were obtained, and histologic findings were subjectively scored. For birds that underwent renal biopsy, tissue specimens of all viscera were evaluated histologically; for birds that did not undergo renal biopsy, only kidney, liver, and skeletal muscle tissue specimens were evaluated. Histologic scores (0 to 5) were assigned for tissues; scores were determined via examination of 5 randomly selected 200X fields, the number of 200X fields in which abnormalities were detected was recorded, and scores for extent and severity of abnormalities (0, absent; 1, minimal; 2, mild; 3, moderate; 4, moderate to severe; and 5, severe) were assigned. For kidney tissue specimens, scores for collecting duct ectasia, renal tubular casts, renal tubular epithelium anisocytosis and anisokaryosis, and interstitial nephritis were determined; these specimens were also evaluated to detect glomerulopathy, and scores were determined on the basis of severity of mesangial thickening. Histopathologic changes in injection site pectoral muscle tissue specimens (including myofiber necrosis and degeneration, hemorrhage, inflammation, and fibrosis) were scored. Liver tissue specimens were evaluated to detect hepatocellular necrosis, hepatic lipodosis, and multifocal random lymphohytic hepatitis. Inflammation and ulceration scores were determined for proventriculus and ventriculus tissue specimens.

Statistical analysis—Reference intervals for pretreatment serum biochemical analysis variables were determined via the nonparametric method.4,5 and the Tukey test was used to identify outlier values. Reference intervals, mean values, and 90% CIs of data for all 30 birds were calculated.23,24 Hematologic and plasma biochemical analysis data were initially analyzed via a 2-factor ANOVA with pretreatment versus posttreatment values, a repeated-measures factor, and treatment (an among-subject [grouping] factor) as factors. The interaction between treatment group and blood sample collection time (pretreatment vs posttreatment values) was not significant for Hct values (P = 0.208) and heterophil counts (P = 0.213) and was significant for plasma AST (P < 0.001), CK (P < 0.001), calcium (P = 0.041), urea (P = 0.024), and concentrations. Results of an initial analysis of CBC data via the same statistical method indicated the interaction between treatment group and blood sample collection time (pretreatment vs posttreatment values) was not significant for RBC (P = 0.101), WBC (P = 0.157), lymphocyte (P = 0.129), monocyte (P = 0.090), eosinophil (P = 0.166), or basophil (P = 0.117) counts. Significant interactions indicated that differences between pre- and posttreatment & posttreatment values differed among the 4 treatment groups, and the nature of the difference in response (the treatment effect) was not the same among the 4 treatment groups. Because interactions for some of the variables were close to being significant, a paired t test was used to compare pretreatment vs posttreatment data for each treatment group. Treatment effects were evaluated separately for birds for pretreatment and posttreatment periods via a 1-factor ANOVA. Data that
were significantly different were further evaluated via a Tukey honestly significant difference multiple pairwise comparison of means procedure with a level of significance of 1% for all comparisons.

A Kruskal-Wallis test was used to compare kidney, pectoral muscle, and liver specimen histologic scores between birds that received meloxicam and those that received saline solution. 

Values of $P < 0.05$ were considered significant. Statistical software was used for analysis of clinicopathologic data and histologic scores.

Results

Birds—All quail maintained or gained weight, remained active, and continued to vocalize throughout the treatment period. Feed intake of birds was considered normal for all quail except for 1 bird that underwent renal biopsy and received saline solution. That bird was anorexic for the first 12 hours after renal biopsy; the bird received 1 feeding via gavage, was eating within 24 hours after renal biopsy, and was consuming adequate amounts of food by 48 hours after the biopsy.

Hematologic evaluation—Values of CBC variables were not significantly different among groups of birds and were within published reference intervals for Japanese quail (Table 1). No significant differences were detected between values of hematologic variables before and after the treatment period for each group of birds or among the 4 groups of birds after the treatment period.

Plasma biochemical analyses—Reference intervals were calculated for pretreatment values of plasma biochemical analysis variables for which data among the 4 groups of birds were not significantly different (Table 2). Plasma total protein, albumin, bile acids, and potassium concentrations were determined, but values of those variables were not evaluated because multiple analyzer errors occurred or concentrations were lower than the lower limit of quantitation of the analyzer.

Posttreatment plasma biochemical analysis data for 1 bird that underwent renal biopsy and received meloxicam were excluded from analysis because of severe lypem mia in the posttreatment blood sample. Mean pretreatment plasma CK activity was significantly ($P < 0.005$) higher for cohort 1 birds ($757 \pm 164$ U/L) than it was for cohort 2 birds ($612 \pm 117$ U/L); therefore, plasma CK activity reference intervals were calculated separately for these cohorts. The pretreatment plasma uric acid concentration was $> 7$ mg/dL in 2 of the birds that did not undergo renal biopsy and received meloxicam; although these values were within the published reference interval for Japanese quail, inclusion of these values caused the mean pretreatment plasma uric acid concentration value for that group of birds to be significantly ($P = 0.003$) higher than the value for the other groups of birds. Those values were identified as outliers and removed from calculation of the pretreatment reference interval for plasma uric acid concentration. Posttreatment plasma uric acid concentrations for those 2 birds were lower than pretreatment values, and posttreatment values for those birds were similar to posttreatment values for the other birds in that same treatment group.

For the group of birds that underwent renal biopsy and received meloxicam, posttreatment plasma uric acid concentration was significantly ($P = 0.003$) higher than the pretreatment value (Table 3). Mean posttreatment plasma CK activity values were higher than pretreatment values for all groups of birds except that the group that underwent renal biopsy and received saline solution, but differences were only significant ($P < 0.001$) for the group of birds that did not undergo renal biopsy and received meloxicam. Likewise, posttreatment plasma AST activity values were higher than pretreatment values for all 4 groups of birds, although differences were not significant and values remained within published reference intervals for Japanese quail.

Histologic evaluation of renal biopsy specimens—Results of histologic evaluation of renal biopsy

Table 1—Hematologic data for Japanese quail (Coturnix japonica) before and after 14 days of treatment with meloxicam or saline (0.9% NaCl) solution administered IM.

<table>
<thead>
<tr>
<th>Variable</th>
<th>RBCs (x 10^12/L)</th>
<th>Hct (%)</th>
<th>WBCs (x 10^9/L)</th>
<th>Heterophils (x 10^9/L)</th>
<th>Lymphocytes (x 10^9/L)</th>
<th>Monocytes (x 10^9/L)</th>
<th>Eosinophils (x 10^9/L)</th>
<th>Basophils (x 10^9/L)</th>
<th>Fibrinogen (mg/dL)</th>
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<tr>
<td>Group 1 (n = 10)</td>
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<tr>
<td>Pretreatment</td>
<td>3.68 (3.02–3.96)</td>
<td>46.3 (44.6–48.0)</td>
<td>19.2 (15.3–23.1)</td>
<td>2.7 (2.0–3.4)</td>
<td>15.3 (11.3–19.1)</td>
<td>0.47 (0.30–0.63)</td>
<td>0.50 (0.27–0.73)</td>
<td>0.29 (0.13–0.45)</td>
<td>140 (115–160)</td>
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<tr>
<td>Posttreatment</td>
<td>3.69 (3.45–3.87)</td>
<td>41.1 (41.3–46.3)</td>
<td>15.1 (15.5–21.7)</td>
<td>3.18 (2.27–4.03)</td>
<td>14.4 (12.4–16.4)</td>
<td>0.78 (0.57–0.98)</td>
<td>0.61 (0.34–0.78)</td>
<td>0.08 (0.01–0.17)</td>
<td>130 (104–156)</td>
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<td>Group 2 (n = 5)</td>
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<tr>
<td>Pretreatment</td>
<td>3.62 (3.37–3.67)</td>
<td>46.2 (41.8–49.6)</td>
<td>16.6 (14.8–24.4)</td>
<td>2.30 (1.38–3.22)</td>
<td>16.8 (11.8–19.4)</td>
<td>0.92 (0.35–1.54)</td>
<td>0.61 (0.20–1.02)</td>
<td>0.17 (0.04–0.30)</td>
<td>140 (85–195)</td>
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<td>Posttreatment</td>
<td>3.48 (3.07–3.89)</td>
<td>44.7 (39.5–49.3)</td>
<td>16.0 (13.8–18.2)</td>
<td>3.99 (3.08–4.30)</td>
<td>11.0 (9.5–12.5)</td>
<td>0.35 (0.12–0.58)</td>
<td>0.35 (0.25–0.70)</td>
<td>0.06 (0.01–0.15)</td>
<td>180 (116–216)</td>
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<td>Group 3 (n = 10)</td>
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<tr>
<td>Pretreatment</td>
<td>4.03 (3.87–4.19)</td>
<td>46.7 (41.1–48.3)</td>
<td>14.8 (12.6–17.0)</td>
<td>3.62 (2.67–4.27)</td>
<td>10.3 (8.6–12.0)</td>
<td>0.43 (0.27–0.59)</td>
<td>0.41 (0.26–0.56)</td>
<td>0.05 (0.01–0.09)</td>
<td>120 (118–155)</td>
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<td>Posttreatment</td>
<td>3.42 (2.22–3.62)</td>
<td>42.5 (40.7–44.3)</td>
<td>17.8 (15.3–20.3)</td>
<td>4.92 (2.42–5.62)</td>
<td>11.4 (9.2–13.6)</td>
<td>0.38 (0.27–0.49)</td>
<td>0.04 (0.01–0.09)</td>
<td>100 (104–155)</td>
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<td>Group 4 (n = 5)</td>
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<tr>
<td>Pretreatment</td>
<td>3.64 (3.38–3.80)</td>
<td>43.7 (40.0–46.8)</td>
<td>14.5 (11.8–17.2)</td>
<td>3.37 (2.20–4.54)</td>
<td>10.0 (8.2–11.8)</td>
<td>0.33 (0.14–0.52)</td>
<td>0.54 (0.18–0.30)</td>
<td>0.23 (0.05–0.41)</td>
<td>140 (100)</td>
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<tr>
<td>Posttreatment</td>
<td>3.47 (3.34–3.66)</td>
<td>43.6 (40.0–46.9)</td>
<td>14.0 (10.6–17.4)</td>
<td>3.72 (2.74–4.79)</td>
<td>9.3 (8.6–11.8)</td>
<td>0.38 (0.22–0.54)</td>
<td>0.43 (0.21–0.65)</td>
<td>0.05 (0.01–0.09)</td>
<td>140 (104–176)</td>
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</table>

Data are mean (90% CI).

Birds in group 1 underwent renal biopsy and received meloxicam (2 mg/kg, IM, q 12 h for 14 days). Birds in group 2 underwent renal biopsy and received preservative-free saline solution (0.05 mL, IM, q 12 h for 14 days). Birds in group 3 did not undergo renal biopsy and received meloxicam (2 mg/kg, IM, q 12 h for 14 days). Birds in group 4 did not undergo renal biopsy and received saline solution (0.05 mL, IM, q 12 h for 14 days).
specimens of cohort 1 birds (n = 15) obtained before treatment indicated 5 of the birds had minimal (histologic score, 1) collecting duct ectasia and 5 of the birds had mild (histologic score, 2) collecting duct ectasia. Renal biopsy specimens of all of these birds had a minimal amount (histologic score, 1) of collecting duct luminal mucus. Minimal (histologic score, 1) renal tubular epithelial anisokaryosis was detected in renal biopsy specimens of 3 of the birds.

Gross and histologic necropsy findings—Lesions detected during gross necropsy were limited to connective tissues surrounding jugular veins, the pectoral muscles, and left kidneys and adjacent tissues. Hematomas were detected in connective tissue surrounding jugular veins of birds of all groups. Dark red streaks (hemorrhage) or white-tan streaks (fibrosis) were detected in kidney and renal tubular epithelial changes. The severity of collecting duct ectasia and renal tubular epithelial changes ranged from none to moderate (histologic score, 0 to 3). No significant differences were detected between meloxicam- and saline solution–treated birds regarding severity of collecting duct ectasia (P = 0.89) or renal tubular epithelial histopathologic changes (P = 0.81). Glomerular mesangial thickening or foam cells were detected in kidney specimens of 7 (4 saline solution–treated and 3 meloxicam-treated) of the 30 birds.

Severity of myositis in pectoral muscle specimens of birds ranged from absent to mild (histologic score, 0 to 2); however, severity of pectoral muscle necrosis ranged from mild to severe (histologic score, 2 to 5), and the highest number of grade 5 lesions were detected in muscle specimens obtained from cadavers of birds that were treated with meloxicam. These skeletal muscle lesions were associated with injection sites; the remaining portions of pectoral muscles and other appendicular muscles did not have such lesions. For muscle tissue specimens of 28 of the 30 birds, myofiber necrosis and interstitial fibrosis were detected in at least 2 of the five 200X fields examined. Severities of myofiber degeneration (P = 0.026), interstitial hemorrhage (P = 0.018), and inflammation (P = 0.002) in skeletal muscles were significantly greater for meloxicam-treated versus saline solution–treated birds. Myofiber degeneration was observed in a mean of 3.7 of the five 200X fields examined for each muscle tissue specimen obtained from cadavers of meloxicam-treated birds and in a mean of 2.5 of the five 200X fields examined for each muscle tissue specimen obtained from cadavers of saline solution–treated control birds. Intersitial inflammation was detected in a mean of 3.05 of the five 200X fields examined for each muscle tissue specimen obtained from cadavers of meloxicam-treated birds and a mean of 1.4 of the five 200X fields examined for each muscle tissue specimen obtained from cadavers of control birds.

Histopathologic lesions detected in liver specimens included random lymphohypocytic hepatitis and hepatic lipomas.
idosis. Hepatitis was detected significantly (P = 0.046) more frequently in liver specimens obtained from cadavers of meloxicam-treated birds than it was in liver specimens obtained from cadavers of control birds. Hepatic lipidosis was detected in liver specimens of 17 birds; severity ranged from absent to mild (histologic score, 0 to 2) for 16 birds, and severity was moderate (histologic score, 3) for 1 bird. No significant differences were detected between meloxicam-treated and control birds regarding severity of hepatic lipidosis. No hepatic necrosis was detected in any of the liver specimen sections examined.

All histologic sections of proventriculus specimens evaluated had mild multifocal lymphoplasmacytic inflammation in the mucosa. No mucosal ulceration was detected in any of the sections of proventriculus specimens examined.

Discussion

Meloxicam is frequently used in avian veterinary practice, but data regarding adverse effects of this drug in birds are limited and often extrapolated from findings for mammals. The meloxicam doses that are analgesic for Hispaniolan Amazon parrots are considerably higher than those recommended for clinical use in birds and mammals; therefore, a better understanding of the effects of meloxicam in birds at such doses is vital. To the authors’ knowledge, no studies have been conducted to determine the pharmacokinetics of meloxicam in quail or to determine the analgesic efficacy of meloxicam in birds of the order Galliformes. The dose of meloxicam administered to birds in the present study was selected on the basis of the dose determined to provide analgesia in Hispaniolan Amazon parrots. No adverse effects of meloxicam were detected in the birds in that study; therefore, the dose of meloxicam used in that study was doubled for administration to birds in the present study to increase the likelihood of detecting adverse effects. Although oral bioavailability of meloxicam is high in animals of several species, results of 1 study indicate that maximum plasma concentrations of meloxicam are slowly reached in psittacine birds after oral administration and plasma concentrations of meloxicam expected to be analgesic are not maintained. Therefore, meloxicam was administered IM to birds in the present study.

An important adverse effect of NSAIDs is reduction of renal blood flow via inhibition of prostaglandin E2 synthesis, resulting in ischemia of the kidneys and decreased secretion of uric acid waste products. This would result in hyperuricemia in birds (analogous to azotemia in mammals) and possibly renal failure if the damage was sufficiently severe, as develops in white-backed vultures that ingest diclofenac. In the present study, the mean posttreatment plasma uric acid concentration was significantly higher than the mean pretreatment value for quail that underwent a renal biopsy and received meloxicam, but the mean value (7.8 ng/mL) was still within the pretreatment plasma uric acid concentration reference interval determined for quail in this study. The group of quail that did not undergo renal biopsy and received meloxicam was the only group of quail in the present study for which the mean posttreatment plasma uric acid concentration was lower than the pretreatment value. This finding suggested that biopsy, anesthesia, or both may have contributed to the increase in uric acid concentration in quail of that group. Quail received fluids SC during recovery from anesthesia, but they did not receive fluids IV during laparoscopy because of the brief duration of that procedure; systemic hypotension and resultant renal ischemia may have developed in those birds during anesthesia. In addition, quail that underwent renal biopsy were anesthetized for a slightly longer time than were quail that did not undergo renal biopsy. Results of studies in which meloxicam was administered to dogs indicate that anesthesia and associated hypotension do not induce renal damage (as determined on the basis of serum biochemical analyses and measurement of glomerular filtration rates). Therefore, it was not expected that anesthesia would affect plasma uric acid concentrations of quail in the present study. Increases in plasma uric acid concentrations in quail may be attributable to prerenal (dehydration and gastrointestinal tract hemorrhage) or postrenal causes; however, none of the birds in this study were clinically dehydrated, all of the birds were observed to drink water, and no signs of gastrointestinal tract hemorrhage or urinary tract obstruction were observed in the quail during the study or necropsy. Gross necropsy findings of air sacculitis and adhesions near left kidneys and histopathologic changes on the surface of the parenchyma of left kidneys were attributed to the laparoscopic biopsy procedure because right kidneys in those birds and kidneys in birds that did not undergo renal biopsy did not have such changes.

The finding of minimal to mild collecting duct ectasia in the renal biopsy specimens obtained prior to treatment may have been attributable to mild dehydration; these findings and the renal tubular lesions detected in the renal biopsy specimens were typically mild and were detected with similar frequency in specimens obtained from birds in the control and meloxicam treatment groups. Lesions in kidney specimens obtained from cadavers of birds after treatment may have been attributable to hypotension during anesthesia, which would have reduced renal blood flow and perfusion. More likely, these findings were caused by a preexisting condition in the quail because similar lesions were detected in biopsy specimens obtained from birds before anesthesia. Two of the birds with mild histologic glomerular changes were female and had numerous active ovarian follicles; the presence of mesangial foam cells was suggestive of lipid mobilization for yolk production in those birds.

In mammals, repeated NSAID administration can lead to gastrointestinal tract ulceration and hemorrhage, which may cause anemia. None of the quail in the present study had gross melena. The Hct and RBC counts of the birds did not change substantially during the study, and the absence of histologic findings of ulceration suggested clinically relevant gastrointestinal tract lesions did not develop. Similarly, pigeons treated with carprofen do not develop gastrointestinal tract lesions, which may indicate that birds are less prone to developing gastrointestinal tract ulcers after NSAID treatment than are dogs. The proventriculitis detected in control and meloxicam-treated quail in this study
may have been attributable to clinically normal accessory lymphoid tissue or may have been induced by an undetected antigenic stimulus or pathogen.

One of the most surprising findings of the present study was the prevalence and severity of muscle necrosis in meloxicam-treated birds. Muscle damage causes release of myocellular enzymes, resulting in an increase in circulating AST and CK activities. High plasma AST and CK activities for birds in this study were attributed to release of muscle enzymes. This assumption was supported by gross pathological and histopathologic findings for pectoral muscles, including hemorrhage, myositis, and muscle necrosis. The most severe lesions were observed in pectoral muscle specimens from meloxicam-treated birds; 85% of these birds had moderate to severe muscle necrosis at injection sites. The injectable formulation of meloxicam used in this study contained 13% ethanol, which may have caused tissue irritation. In addition, the high pH of that injectable formulation (pH, 8 to 9) may also have resulted in tissue damage. Plasma CK activity was also high in samples obtained from birds that received saline solution; therefore, repeated muscle trauma from IM injections likely contributed to muscle necrosis, despite the use of physiologic saline solution. Plasma AST activity can also be high in birds with hepatitis. Hepatitis was likely not the cause of high AST activity in birds in the present study because severe hepatic lesions that would result in clinically apparent disease were not detected during histologic evaluation of liver tissue specimens. Pigeons treated IM with carprofen have lesions in pectoral muscles (the site of IM injection; myositis and myodegeneration) and the liver (hepatic necrosis and hepatic lipidosis) and have high circulating AST and alanine aminotransferase activities. Interestingly, mean AST activity was significantly higher in plasma samples obtained from cohort 1 birds before treatment than it was in plasma samples obtained from cohort 2 birds before treatment in the present study; a similar difference between cohorts of birds was detected for mean plasma CK activities. These findings may have been attributable to the fact that venipuncture of birds in the first cohort was performed by inexperienced veterinary students as part of an avian handling and procedures laboratory, and blood samples obtained before treatment of birds in the second cohort and samples obtained from all birds after treatment were obtained by 1 experienced venipuncturist.

Limitations of this study included a small sample size of 30 birds; these birds were allocated to 2 cohorts of 15 birds each (1 cohort that underwent renal biopsy and did not undergo renal biopsy), and 20 birds received meloxicam and 10 received a control treatment (saline solution). Because small numbers of birds were included in each group, significant differences among data may not have been detected that would be detected had larger numbers of birds been included. Calculation of reference intervals for values of variables in blood samples obtained before treatment of birds may have mitigated that limitation because many values for birds after treatment were within those reference intervals. Because of difficulties encountered during laparoscopy of female birds in cohort 1, female birds were not included in cohort 2. This resulted in inclusion of more male than female birds in the study; although this was not expected to have an impact on data, bias may have been introduced in the results. Posttreatment plasma biochemical analysis data for 1 female bird that underwent renal biopsy and received meloxicam were excluded from analysis because of severe lipemia in the blood sample attributable to vitellogenesis; this further reduced the sample size and altered the male-to-female bird ratio. The inability to accurately measure protein and albumin concentrations in plasma samples may have resulted in exclusion of potentially important data.

Reference intervals have previously been published for hematologic and biochemical variables in Japanese quail. These values were used for interpretation of the hematologic variables, but not plasma biochemical analysis variables of birds in this study. Reference intervals were calculated for plasma biochemical analysis values in birds in this study because the previously published reference intervals did not include all analytes studied, particularly CK. Because of the small sample size of birds in this study, these reference intervals may not be applicable for other populations of Japanese quail; however, these reference intervals did aid interpretation of CK activities of birds.

Future studies may be warranted in which adverse effects of the dose of meloxicam used in the present study are determined for birds of other species such as psittacines, because parrots may be evaluated by avian veterinarians more often than birds of any other species of companion birds. Determination of whether the meloxicam dose used in this study has greater analgesic effects than lower doses and determination of the dose at which maximal analgesic effects develop may also be warranted. Longer treatment periods than were used in this study should be evaluated. Results of such a study would be of value for veterinarians treating birds that require long-term NSAID treatment for conditions such as osteoarthritis.

Results of the present study indicated administration of meloxicam (2 mg/kg, q 12 h for 14 days) to Japanese quail did not result in clinically important adverse renal effects. Mild increases in plasma uric acid concentrations were detected in some of the meloxicam-treated quail, but concentrations remained within the reference interval calculated for this group of quail before treatment. Additionally, histopathologic lesions in kidney specimens were mild and similar for saline solution– and meloxicam-treated birds. Caution is recommended when NSAIDs, including meloxicam, are used in birds with preexisting renal disease and dehydration. The most severe histopathologic lesions identified in birds in this study were attributed to the laparoscopy and renal biopsy procedures and IM injection of the commercially available preparation of meloxicam. This finding suggested that IM injection of meloxicam in birds should be limited to short-term use.

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