Adequate pain control is an essential part of therapeutic intervention in acute and chronic disease for all animals, including birds. In humans, pain control is part of a multimodal program for accelerated postsurgical recovery. Consideration of pain management options is also important to the practice of veterinary medicine and is mandated by the Institute of Laboratory Animal Resources for pain management in all vertebrate species.

Nonsteroidal anti-inflammatory drugs are characterized by their anti-inflammatory effects on peripheral tissues and also have centrally acting antinociceptive effects. Nonsteroidal anti-inflammatory drugs block the binding of arachidonic acid to COXs, preventing the conversion of thromboxane A2 to thromboxane B2 and the production of prostaglandins, which are potent mediators of inflammation. Cyclooxygenases are expressed in the CNS of vertebrates, and their relative expression varies depending on the species. A broad tissue distribution of COX is found in chickens. Prostaglandins and COXs participate in avian nociception and act peripherally and centrally similar to prostaglandins and COXs of mammals.

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Galliformes and Anseriformes have been the primary avian orders used to evaluate pharmacokinetics and physiologic and analgesic effects of COX-1 and COX-2 inhibitors. In a study that evaluated foot withdrawal latency to a thermal stimulus in chickens, naproxen administration attenuated inflammation and hyperalgesia. In another study, chickens with naturally occurring chronic lameness improved their walking speed and ability after carprofen administration and self-selected greater amounts of carprofen-laced feed, compared with control chickens. Ducks have

### Objective
To evaluate the analgesic efficacy of meloxicam in parrots with experimentally induced arthritis, with extent of weight bearing and rotational perch walking used as outcome measures.

### Animals
15 adult Hispaniolan parrots (Amazona ventralis).

### Procedures
Arthritis was experimentally induced via intra-articular injection of microcrystalline sodium urate suspension (MSU) into 1 intertarsal joint. Parrots were treated in a crossover design. Five treatments were compared as follows: meloxicam (4 doses) at 0.05, 0.1, 0.5, and 1.0 mg/kg (IM, q 12 h, 3 times) and 0.03 mL of saline (0.9% NaCl) solution (IM, q 12 h, 3 times). The first treatment was given 6 hours following MSU administration. Lameness was assessed by use of a biomechanical perch to record weight-bearing load and a rotational perch to determine dexterity. Feces were collected to assay for occult blood.

### Results
Parrots treated with meloxicam at 1.0 mg/kg had significantly better return to normal (baseline) weight bearing on the arthritic pelvic limb, compared with control parrots or parrots treated with meloxicam at 0.05, 0.1, and 0.5 mg/kg. All fecal samples collected from parrots following induction of arthritis and treatment with meloxicam had negative results for occult blood.

### Conclusions and Clinical Relevance
Meloxicam administered at 1.0 mg/kg, IM, every 12 hours effectively relieved arthritic pain in parrots. (Am J Vet Res 2009;70:1471–1476)

### Abbreviations

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<tr>
<td>COX</td>
<td>Cyclooxygenase</td>
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<td>MSU</td>
<td>Microcrystalline sodium urate suspension</td>
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Galliformes and Anseriformes have been the primary avian orders used to evaluate pharmacokinetics and physiologic and analgesic effects of COX-1 and COX-2 inhibitors. In a study that evaluated foot withdrawal latency to a thermal stimulus in chickens, naproxen administration attenuated inflammation and hyperalgesia. In another study, chickens with naturally occurring chronic lameness improved their walking speed and ability after carprofen administration and self-selected greater amounts of carprofen-laced feed, compared with control chickens. Ducks have
decreased responses to a noxious stimulus (closure of a hemostat around the leg) if they receive ketoprofen more than 30 minutes prior to the noxious stimulus. Pharmacokinetic studies of NSAIDs in birds include ketoprofen,11 sodium salicylate,12,13 flunixin meglumine,11,13 and meloxicam.12,13,16 Pharmacokinetics of meloxicam have been reported for several avian species, including chickens, ducks, pigeons, vultures, ostriches, turkeys, and parakeets.11,13,16 In these studies, plasma concentrations of meloxicam were measured following administration but analgesic efficacy was not evaluated. To our knowledge, there are no published data evaluating analgesic efficacy of meloxicam in birds. The purpose of the study reported here was to evaluate the analgesic efficacy of meloxicam in parrots with experimentally induced arthritis, with extent of weight bearing and rotational perch walking used as outcome measures.

Materials and Methods

Animals—Adult (range, 4 to 20 years old; mean ± SD, 7.33 ± 4.76 years old) Hispaniolan parrots (Amazona ventralis; n = 15) of unknown sex and weighing 281.67 ± 20.41 g were used in this study. Parrots were part of a teaching and research flock at the University of Wisconsin School of Veterinary Medicine, Madison, Wisconsin. Parrots used in the study were in good health on the basis of physical examination findings, with normal range of motion of the joints of the pelvic limbs. Parrots were housed as small flocks with 4 to 5 parrots/animal housing room (11.2 m² [121 sq ft]), and maintained on a 12-hour light to dark cycle at the Charnamy Instructional Facility. Groups of 5 parrots were separated from the large flock 4 to 7 days prior to the experimental testing period and housed individually or in pairs in adjacent standard, stainless steel laboratory cages (52.8 cm width × 52.8 cm length × 55 cm height). A perch and 1 to 2 hanging toys were present inside the cages. Parrots were fed a pelleted psittacine diet and provided water ad libitum. The study was conducted under an Institutional Animal Care and Use Committee protocol approved by the University of Wisconsin School of Veterinary Medicine.

Experimentally induced arthritis—Temporary arthritis was experimentally induced by unilateral injection of 8% MSU into the intra-articular space of the intertarsal joint. The MSU used to induce arthritis in this study was prepared by use of published methods.18 The 4% suspension was autoclaved. Each vial was centrifuged at 390 X g for 15 minutes, the supernatant was decanted and measured, and 50% of the fluid was replaced for resuspension to produce an 8% sodium urate crystal solution suspended in sterile saline (0.9% NaCl) solution.

Parrots were anesthetized with isoflurane (5% isoflurane in 1.5 L of O₂/min via facemask), intubated (2.0-mm noncuffed endotracheal tube), and maintained on isoflurane (2% to 3% isoflurane in 0.8 to 1.0 L of O₂/min) by use of a nonbreathing anesthesia circuit. Each parrot was weighed and positioned in dorsal recumbency on a heated pad. Topical eye ointment was applied for corneal protection. Featherers were plucked from the area of the intertarsal joint of the nonbanded pelvic limb; the limb was aseptically prepared for intra-articular injection. A 22-gauge needle was inserted into the intertarsal joint space toward the plantar aspect of the joint, and 0.1 mL of the 8% MSU was injected. The joint would palpably swell with the correct instillation of MSU. After injection, the joint was massaged and flexed and extended for 15 to 20 seconds to evenly distribute the MSU throughout the joint space. Parrots were removed from isoflurane but maintained on oxygen (0.8 to 1.0 L of O₂/min) until extubation. Subsequently, parrots were returned to their cages for 4 hours.

Study design—All parrots received an injection of MSU into the intertarsal joint of 1 limb prior to analgesic treatment. Five treatments were compared as follows: meloxicam at 0.05, 0.1, 0.5, and 1.0 mg/kg (IM, q 12 h, 3 times) and 0.03 mL of saline solution (IM, q 12 h, 3 times). Intramuscular injections alternated between the left and right pectoral muscles. The first treatment was given 6 hours following MSU administration. The experimental design was a partial crossover study, with 15 parrots, 5 treatments, and 4 periods. Parrots were randomly assigned to 3 groups, each with 5 parrots. During the experimental periods, each of the 5 treatments was randomly assigned to 1 parrot of the 5-parrot groups so that a total of 3 parrots received each treatment in each period. Treatments were administered to parrots in each group in a randomized order. There were 4 periods, with a minimum 2-week washout between periods, and each parrot received a different treatment in each period.

The study protocol required that any parrot with signs of excessive discomfort following the intra-articular injection of MSU, such as loss of appetite or reluctance to move about the cage, to be removed from the study and provided additional medical support. The period of decreased weight bearing in saline solution–treated (negative) control parrots was <38 hours. Because this study involved a species for which the effectiveness of other common analgesics is not yet well established, the use of a positive control group in place of a negative control group, although recommended,19 was not feasible in the evaluation of analgesic effects of meloxicam.

Weight-bearing load perch—An incapacitance meter was modified and used to test Hispaniolan parrots. The standard rodent footpads were converted into a divided perch so that the extent of weight bearing could be measured independently for each foot. A black, 27 X 11.5 X 23-cm plastic box with a transparent front and hinged door was placed around the perch to limit movement by the parrot during assessment. The perch used dual-channel weight averaging, which enabled testing of both pelvic limbs simultaneously. If the parrot shifted from foot to foot, the unit recorded the mean weight in grams during a predetermined test period of 3 consecutive 20-second intervals. Prior to data collection, a 2-week acclimation period was used to condition the parrots to perch inside the test box for 2- to 3-minute intervals. Baseline weight-bearing load data were determined for each parrot 1 week prior to MSU administration.
tion. After induction of arthritis, weight-bearing load data were collected at 4, 6, 8, 12, 18, 26, 30, 32, and 38 hours. Data from each parrot at each time point were calculated to reflect the difference in extent of weight bearing between the MSU-injected and noninjected pelvic limb by use of the following equation: change in weight bearing = (mean weight bearing of noninjected limb – mean weight bearing of injected limb at baseline) – (mean weight bearing of injected limb – mean weight bearing of injected limb at baseline).

Rotational perch—A rotating perch was constructed by use of an 11.5-cm-long perch with a radius of 1.83 cm and was fixed within a black, 23.5 × 13.5 × 51-cm plastic box with transparent front and a sliding door in the back panel, similar to the box used for the weight-bearing load perch. Perch rotation was produced by a direct current gear head and motor combination attached to a variable-speed control box. This device was designed to measure changes in normal pelvic limb dexterity. Rotation of the perch rod encouraged the parrot to actively walk at normal ambulatory speed. Rotational velocity was increased 11.6 ± 1.0 rotations/min every 10 seconds, and time (seconds) on the perch was measured until the parrot fell off. A 2-week acclimation period was used to condition the parrots to the rotating perch for 2- to 3-minute intervals. Baseline rotational perch data were collected for each parrot 1 week prior to MSU administration. Rotational perch data were collected at each evaluation period immediately following weight-bearing load assessment. The change in rotational perch time was determined by use of the following equation: change in rotational perch time = baseline perching time – perching time at each testing period.

Fecal occult blood evaluation—Voided fresh feces were collected from the cage bottom of each parrot or from the testing boxes at the final testing time in each period. If 2 parrots were housed together, parrots were temporarily separated for fecal collection or a group collection was done. Feces were tested fresh or stored frozen at 4°C and thawed for 10 to 30 minutes prior to evaluation with a commercially available fecal occult blood test.

Statistical analysis—Weight-bearing load and rotational perch data were analyzed with a commercially available software program. Two models were fit for each response; each treated dosage differently. The basic structure was a repeated-measures ANOVA, with fixed effects of treatment, period, time, and all associated interactions. Correlations within each parrot across periods were modeled with a compound symmetry structure; correlations within each bird over time within a period were modeled with a spatial power structure. In 1 set of models, dosage was treated as a continuous numeric variable (the actual dose given) and a slope was estimated. In the other set of models, dosage was treated as a 4-level nominal factor. In the latter type of analyses, pairwise comparisons of the treatments, both within each time and over all times, were performed with the Tukey P value correction to account for multiple comparisons. Residuals resulting from the fitted model were verified to be acceptably normally distributed and without evidence of heteroscedasticity. Significance was inferred at values of P < 0.05.

Results

Animals—All 15 parrots completed the study without protocol deviations. Data collection was missed at 1 time point for 5 parrots during 1 testing period. All parrots developed experimentally induced arthritis following MSU administration as expected, and no parrots were excluded for lameness that was too mild or severe. No adverse effects related to the meloxicam treatment were observed.

Weight-bearing load perch—Parrots receiving no analgesia (n = 12 treatments with saline solution) after experimentally induced arthritis had significantly (P < 0.001, all tests) less weight bearing on the affected pelvic limb at 4, 6, and 8 hours after intra-articular injection, compared with weight bearing at baseline. There was a significant (P = 0.035) overall treatment effect (Figure 1). By use of pairwise tests, parrots receiving meloxicam at 1 mg/kg had significantly (P = 0.041) higher weight-bearing load values, bearing more weight on the MSU-induced arthritic pelvic limb, than those of control parrots throughout the testing period. Meloxicam administration at 1 mg/kg also contributed to greater weight bearing on the arthritic pelvic limb than meloxicam administration at lower amounts of 0.05 and 0.1 mg/kg, although these differences were not significant (P = 0.098 and 0.091, respectively). Dos-
Administration of meloxicam at 1 mg/kg, IM, was most effective for reducing lameness, improving rotational perch performance, and alleviating signs of pain associated with MSU-induced arthritis in parrots. These experiments did not show a clear dose-response curve between meloxicam dose and weight-bearing load data. However, the 1.0 mg/kg dosage was clearly more effective at decreasing the change in weight bearing, compared with dosages ≤0.5 mg/kg.

In the present study on parrots, experimentally induced arthritis provided reproducible changes in weight bearing and measured ability to ambulate on the rotational perch within 4 hours of intra-articular injection of MSU. This method of experimentally induced arthritis was reliable for assessment of analgesic efficacy of meloxicam in Hispaniolan parrots because it mimicked clinical conditions in which early inflammatory changes had occurred prior to treatment.

A complete crossover study was planned but was not possible because analysis performed following each treatment period identified significant differences in weight-bearing loads at the initiation of the fourth period, compared with baseline values. Therefore, the study was finalized and the last of the 5 periods was not performed. In the first 3 periods, every parrot returned to balanced weight-bearing stance prior to additional intra-articular injections of MSU, which was interpreted to be a resolution of the previous arthritis. A similar standard was used in a crossover study24 in dogs receiving multiple intra-articular injections of MSU, in which dogs had full return to normal weight bearing within 36 hours. In an in vivo study25 on rats, injection of MSU monohydrate into the air pouch pseudosynovial membrane resulted in an acute exudate. The exudate volume and WBCs peaked at 24 hours and then spontaneously decreased over 3 days, simulating the self-limiting course of acute gout. The histopathologic effects from repeated administration of MSU in an experimental setting have not been reported for any species; therefore, the length of the washout period was determined by return to baseline function or weight bearing. In future studies, a longer washout period may reduce the effects of repeated intra-articular injections of MSU.

There are few tools to definitively assess pain in animals. Frequently, analgesimetry tests involve stressful manipulations of the animal and may not reflect realistic painful states.26-27 For example, evaluation of ground reactive forces by force plate analysis was shown to be a valuable method for objective assessment of lameness in mammals,28,29 but individual variability was great when the technique was applied to chickens.30 Weight-bearing load in arthritic limbs is consistent and reproducible and considered a reliable objective index for severity of arthritic pain in several species.26,27,30-31 The incapacitance meter was developed to assess limb weight-bearing capability of mice and rats with minimal stress.31 This method of assessment was adapted to parrots by use of an ecologically relevant behavior, perching.32,33 The weight-bearing load percent was used to obtain measurements from both pelvic limbs simultaneously and provided a stress-free measurement of weight-bearing load.
Multiple measurement tools provide greater depth of analgesic assessment.14 The rotational perch is a new measurement tool designed specifically for this study and in this species. Parrots with signs of pain associated with experimentally induced arthritis had decreased dexterity and reduced ambulatory time on the rotational perch. Similar techniques are used to evaluate rodents for motor coordination, strength, and dexterity.15 Treadmill performance has been used to evaluate lameness in horses and the effectiveness of NSAIDs.16 A treadmill would not be appropriate for a perching bird as they are not well adapted for ambulating on flat surfaces. Rotational perch data revealed roughly the same pattern as the weight-bearing load data, but the results were not significant at the 5% level, attributed primarily to large amounts of individual variability and the number of comparisons. Our findings suggest that the rotational perch is a useful tool in evaluating lameness in parrots, provided that sample size is adequate.

Control parrots had improvement in the extent of weight bearing over time that may be attributable to simply resting the pelvic limb as well as resolution of the MSU-induced arthritis.31,32 Weight-bearing load was a passive measurement and did not require the use of the MSU-injected pelvic limb. The rotational perch required active use of the arthritic leg, adding repeated stress to the pelvic limbs. Concurrent use of both measurement tools evaluated an arthritic pelvic limb in dynamic motion. It was possible that repeated ambulation during the course of each testing period exacerbated arthritic pain. When 2 testing points are close together, the arthritis may be worse at the second testing, compared with parrots having longer periods of rest. For example, although the changes in the extent of weight bearing were minor, weight bearing improved for all parrots between 18 to 26 hours, but most parrots had slight increases in lameness when tested between 26 to 30 hours and 30 to 32 hours.

Gastrointestinal bleeding secondary to NSAID usage is a known adverse effect in mammals; however, this adverse effect of NSAIDs has not been established for birds. In our study, fecal occult blood test results for all parrots were negative following meloxicam administration and testing cycles.

In our study, parrots with experimentally induced arthritis that received meloxicam at 1.0 mg/kg were able to bear significantly more weight on the affected pelvic limb than parrots receiving meloxicam at dosages ≤ 0.5 mg/kg. Parrots that received meloxicam at 1.0 mg/kg had better performance on a rotating rod. Results of this study indicate that 1 mg/kg can be considered a therapeutic dosage of meloxicam for relief of arthritic pain in Hispanic parrots. Further study is recommended to evaluate the pharmacokinetics of meloxicam at this dosage as well as evaluate the long-term effects of this dosage on renal function in parrots.

References

22. Marx KL. Therapeutic agents. In: Harrison GJ, Lightfoot TL,


