Pharmacokinetics and Safety of Intramuscular Meloxicam in Zebra Finches (*Taeniopygia guttata*)

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Meloxicam is the most frequently used NSAID in birds; however, its elimination $t_{1/2}$ is highly variable among species. Because zebra finches that require analgesia could benefit from receiving meloxicam, we performed a pharmacokinetic study involving a single intramuscular dose of 1 or 2 mg/kg. Data analysis showed that C_{max} , $t_{1/2}$, and elimination rate constants were not significantly different between the 2 doses. In contrast, C_{max} for 1- and 2-mg/kg doses of meloxicam approached a significant difference, and those for $AUC_{0-\infty}$ were significantly different. Importantly, a plasma concentration of 3500 ng/mL, considered a target level for meloxicam in other avian species, was maintained for approximately 9.5 h in finches that received 2 mg/kg, which was 4 h longer than in birds given 1 mg/kg. Both doses reached low plasma concentrations by 12 h after administration. Subsequently, 8 total doses of 1 or 2 mg/kg were administered to birds at 12-h intervals; these regimens caused no significant changes in select biochemical analytes or the Hct of meloxicam-treated birds. In addition, histopathologic changes for injection sites, kidney, liver, proventriculus, and ventriculus were minimal and similar between control and experimental groups after the multiple doses. These results suggest a 12-h or more frequent dosing interval is likely needed in zebra finches and that meloxicam at 1 or 2 mg/kg IM twice daily for 4 d is safe. The higher dose might provide longer analgesia compared with the lower dose, but a pharmacodynamics evaluation of meloxicam in zebra finches is needed to confirm analgesic efficacy.

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Zebra finches (*Taeniopygia guttata*) are songbirds that often undergo surgical procedures as part of research into learning and memory; these surgeries include those for intracranial injections and cranial implants. At our institution, birds receive subcutaneous lidocaine (a local anesthetic) and intramuscular buprenorphine (an opioid analgesic) preoperatively, with buprenorphine continued every 12 h postoperatively for 2 to 3 d. More recently, the possibility of substituting meloxicam (a COX2-selective NSAID) for buprenorphine, or adding meloxicam to the existing analgesia regimen for a more multimodal approach, has been suggested. The enhanced pain control derived from using lidocaine, buprenorphine, and meloxicam could be of particular benefit in finch surgeries that are particularly invasive or complicated. However, although meloxicam is the most popular NSAID used in birds,⁷ the optimal dose and frequency for zebra finches are unknown. Publications that describe the pharmacokinetics of meloxicam in diverse, nonpasserine avian species (doses ranging from 0.5 to 3.0 mg/kg IM, IV, SC, or PO)^{1,2,6,8-10,12-15,18} report a wide range of elimination half-lives ($t_{1/2}$). For example, vultures dosed once with 2 mg/kg meloxicam IM had an elimination $t_{1/2}$ of 0.42 h,¹⁵ whereas African grey parrots had a $t_{1/2}$ of 35.3 h after a dose of 1 mg/kg IM.¹² Such results have caused numerous authors to emphasize the need for species-specific pharmacokinetic analyses before administering meloxicam to any bird. Additional concerns when giving an NSAID include the potential for renal damage, as reflected in uric acid levels and kidney histology,^{16,17} and for gastrointestinal effects; with intramuscular administration,

another potential sequela is necrosis at the injection site. As is often the case in laboratory animal medicine, giving meloxicam to zebra finches constitutes an extralabel use.

We performed a study using healthy, adult zebra finches that entailed the administration of 1 or 2 mg/kg meloxicam intramuscularly to help elucidate an optimal dosing regimen, as well as to reveal any evidence of toxicity. Pharmacokinetic parameters were assessed after a single dose, whereas biochemical analytes, Hct, and histology were evaluated after multiple doses. Our findings are the first to characterize the use of meloxicam in a passerine species.

Materials and Methods

Animals. Male ($n = 46$) and female ($n = 46$) wildtype zebra finches older than 90 d were involved in the study; all the birds were in good health clinically and had adequate body condition scores. Finches were maintained in an AAALAC-accredited facility under a 12:12-h light:dark cycle, with temperatures from 73 to 77 °F (22.8 to 25.0 °C) and ambient humidity set at 30% to 70%. The main diet was a fortified millet–canary grass seed–oat mix (Supreme Fortified Daily Diet: Finch, Kaytee Products, Chilton, WI), to which a high-protein supplement (High Potency Mash, Harrison’s Bird Foods, HBD International, Brentwood, TN), moistened and mixed with minced hard-boiled eggs, was added 2 or 3 d weekly; fresh drinking water was always available. Flight cages were used to house same-sex conspecifics (maximum of 20 birds per cage), and smaller breeding cages contained 4 compatible adults or parents with their offspring. Routine health surveillance monitoring was performed for ectoparasites and enteric pathogens. All animal work had the approval of Massachusetts Institute of Technology’s IACUC.

Experimental design. In the initial study, finches were dosed intramuscularly with 1 or 2 mg/kg meloxicam (Loxicom injectable, 5 mg/mL, Norbrook Laboratories, Newry, Northern

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Ireland); a 1/2-mL tuberculin syringe with a 28-gauge, 0.5-in. needle was used for injection into one side of the pectoral musculature. At 1 of 5 time points after dosing (0.5, 1, 6, 12, and 24 h), birds were sedated with isoflurane for a terminal intracardiac blood draw; each group comprised 8 birds (4 male, 4 female; total of 10 groups). Each bird provided a single sample (owing to their small size and the need for a terminal blood collection); therefore, time points were based on composite sampling rather than serial samples from the same subject. Blood was placed into lithium heparin microfuge tubes and centrifuged at $8000 \times g$ for 5 min within 1 h of collection. Supernatant plasma was collected and frozen at -80°C until analysis by HPLC.

To assess any adverse effects from giving meloxicam over several days, 4 birds (2 male, 2 female) per group were dosed intramuscularly with saline (control), 1 mg/kg meloxicam, or 2 mg/kg meloxicam twice daily for 8 total doses (starting the evening of day 1 and ending the morning of day 5). The injections were alternated between the right and left sides of the pectoral musculature. Within 2 h of the last dose, each bird was sedated with isoflurane, followed by cardiac blood collection and sample handling as described earlier. Plasma was submitted to a commercial laboratory for the measurement of select biochemical values; spun Hct were determined also. Complete necropsies were undertaken, followed by routine processing for histopathology and evaluation by a veterinary pathologist blinded to treatment group. Throughout the study, injection volumes were standardized to approximately 30 μL per dose (birds were weighed individually to calculate the exact volumes of meloxicam required), and appropriate concentrations were prepared by diluting the drug with sterile saline prior to administration.

HPLC analysis. Measurements of meloxicam in plasma samples were conducted at the University of Tennessee by using a reversed-phase HPLC method.⁴ The system consisted of a model 2695 separations module, a model 2487 UV absorbance detector, and a computer equipped with Empower software (Waters, Milford, MA). The compounds were separated by using an Xbridge C₁₈ column (4.6×250 mm, 5 μm) with a 5- μm Xbridge guard column. The mobile phase was a mixture of (A) 10 mL of glacial acetic acid in 1 L of H₂O (pH 3.0, adjusted with sodium hydroxide) and (B) acetonitrile (50:50). Absorbance was measured at 360 nm at a flow rate of 1 mL/min.

Meloxicam was extracted from the finch samples by using liquid-liquid extraction. After previously frozen plasma samples were thawed and vortex-mixed, 100 μL of plasma was transferred to a screw-top tube, and 15 μL of piroxicam (internal standard, 5 $\mu\text{g/mL}$), 100 μL of 1 M HCl, and 2 mL of chloroform were added. The tubes were vortexed for 60 s and then centrifuged for 20 min at $1070 \times g$. The organic phase was transferred to a clean glass tube and evaporated to dryness by using nitrogen. Samples were reconstituted in 250 μL of mobile phase, and 100 μL was injected into the chromatography system. Standard curves for plasma analysis were prepared by fortifying untreated plasma with meloxicam to produce a linear concentration range of 5 to 15,000 ng/mL. Calibration samples were prepared exactly as the plasma samples. The lower limit of quantification during validation was 5 ng/mL. Intra- and interassay variability ranged from 0.4% to 10%, and the average recovery for meloxicam was 93%.

Data analysis. For the pharmacokinetic data, results from each bird were pooled into groups according to dose and time point (total of 10 groups). Because each bird was used as a single observation, intraindividual variation could not be assessed. The mean plasma concentration of meloxicam was plotted for the 5 time points to generate plasma concentration-time curves,

Figure 1. Plasma concentration-time curve showing mean plasma concentration (error bars, SEM) after a single intramuscular dose of 1 (red line) or 2 mg/kg (blue line) meloxicam relative to time. The horizontal dashed line depicts the target plasma concentration of 3500 ng/mL.

which were compared between dose groups. The distribution of data at the 0.5- through 12-h time points conformed to a normal distribution and warranted the use of parametric testing. The data were best suited to a noncompartmental analysis that assumed no pharmacokinetic model and total-body exposure to the drug. The parameters calculated by noncompartmental analysis included maximal concentration (C_{max}), time to maximal concentration (T_{max}), terminal elimination half-life ($t_{1/2}$), area under the curve from time 0 extrapolated to infinity ($\text{AUC}_{0-\infty}$), and elimination rate constant. The data were analyzed by using linear mixed-effects ANOVA to compare the effect of dose and sex (fixed effects) on meloxicam plasma concentration (dependent variable). This analysis assumed log-linear distribution for the pharmacokinetic parameter, and a P value of 0.05 or less was defined as significant. A plasma concentration of 3500 ng/mL meloxicam, which was determined to be efficacious in Hispaniolan parrots with experimentally induced arthritis³ and used by other authors,^{2,10,12,14} was considered a target level in the current study. Pharmacokinetic analysis was completed by using Phoenix WinNonlin version 8.1 (Certara, Princeton, NJ).

During the safety portion of the study, plasma analyte and Hct data were assessed by using one-way ANOVA followed by Tukey posthoc testing for multiple comparisons. Histologic scores for pectoral muscle (injection sites), kidneys, liver, proventriculus, and ventriculus were assigned based on a 5-point grading scale: 0, no observable pathology; 1, minimal; 2, mild; 3, moderate; and 4, severe. For muscle tissue specimens, scores for myofiber necrosis and degeneration, myofiber regeneration, hemorrhage, inflammation, and fibrosis were determined. Histopathologic changes in kidney tissue were judged in regard to tubular necrosis, collecting duct ectasia, renal tubular epithelium anisocytosis and anisokaryosis, renal tubular casts, and interstitial nephritis. Liver specimens were analyzed for hepatocellular necrosis and degeneration, hepatic lipidosis, and hepatitis, whereas sections from proventriculus and ventriculus were examined for inflammation, hemorrhage, and ulceration. Kruskal-Wallis one-way ANOVA with Dunn posttests was used to compare histopathology scores between control and treatment groups. Statistical analysis was conducted by using Prism software (version 7.03, GraphPad Software, La Jolla, CA). A P value of 0.05 or less was defined as significant.

Results

Figure 1 depicts the mean plasma concentration of meloxicam at 1 and 2 mg/kg plotted against the 5 time points; the dashed

Table 1. Pharmacokinetic parameters (mean $\pm$ SEM) of zebra finches given a single intramuscular dose of 1 or 2 mg/kg meloxicam

Parameter	1 mg/kg meloxicam	2 mg/kg meloxicam	P
C _{max} (ng/mL)	8569.88 $\pm$ 166.70	12238.74 $\pm$ 1905.04	0.08
T _{max} (h)	0.5 $\pm$ 0.0	0.5 $\pm$ 0.0	0.42
t _{1/2} (h)	3.24 $\pm$ 0.62	5.68 $\pm$ 2.14	0.22
AUC _{0-∞} (h $\times$ ng/mL)	46723.34 $\pm$ 1994.95	90855.55 $\pm$ 19677.57	0.05
Elimination rate constant (h ⁻¹)	0.22 $\pm$ 0.04	0.13 $\pm$ 0.05	0.21

Doses were compared by using linear mixed-effects ANOVA.

Table 2. Plasma analyte and Hct data (mean $\pm$ 1 SD) after zebra finches were dosed 8 times with saline or 1 or 2 mg/kg meloxicam

	Saline	1 mg/kg meloxicam	2 mg/kg meloxicam	P
Uric acid (%)	13.5 $\pm$ 3.3	13.2 $\pm$ 2.7	9.4 $\pm$ 1.7	0.11
Albumin (g/dL)	0.7 $\pm$ 0.2	0.7 $\pm$ 0.2	0.8 $\pm$ 0.2	0.78
AST (IU/L)	853.3 $\pm$ 295.5	819.8 $\pm$ 286.1	1316.5 $\pm$ 1012.8	0.49
BUN (mg/dL)	3.8 $\pm$ 1.7	3.5 $\pm$ 0.6	8.5 $\pm$ 11.1	0.50
Ca ²⁺ (mg/dL)	6.4 $\pm$ 0.8	6.4 $\pm$ 0.6	6.4 $\pm$ 0.7	1.00
Creatine kinase (IU/L)	1682.5 $\pm$ 614.3	2106.0 $\pm$ 1247.2	2564.3 $\pm$ 1247.2	0.47
Glucose (mg/dL)	351.8 $\pm$ 64.5	326.3 $\pm$ 14.0	339.3 $\pm$ 28.7	0.70
Total protein (g/dL)	2.0 $\pm$ 0.3	2.1 $\pm$ 0.4	2.2 $\pm$ 0.5	0.85
Hct (%)	47.8 $\pm$ 2.8	43.3 $\pm$ 3.6	43.3 $\pm$ 7.7	0.85

Data for 1 and 2 mg/kg meloxicam were compared with control (saline) values using one-way ANOVA followed by Tukey posthoc testing for multiple comparisons.

horizontal line shows the plasma concentration (3500 ng/mL) considered to provide analgesia in previous reports regarding various bird species.^{2,10,12,14} A noncompartmental model was used to estimate the pharmacokinetic parameters presented in Table 1. Neither T_{max}, t_{1/2}, nor elimination rate constants differed significantly between the 2 doses. However, dose had a significant ($P = 0.05$) effect on AUC_{0-∞}, and the effect of dose on C_{max} approached statistical significance ($P = 0.08$). For both doses, C_{max} was achieved within approximately 30 min. At 12 h after dosing, the meloxicam plasma concentration did not differ between finches given 1 mg/kg compared with 2 mg/kg ($F = 0.3475$, $P = 0.5665$, $n = 12$). The target concentration of 3500 ng/mL was maintained for as long as 9.5 h with the 2-mg/kg dose, which was 4 h longer than for the 1 mg/kg dose (5.5 h). There was no significant effect of sex on the plasma meloxicam concentration ($F = 0.1409$, $P = 0.7085$, $n = 72$).

When 8 doses of saline or meloxicam (1 or 2 mg/kg) spaced 12 h apart were administered, all birds behaved normally and continued eating. Analysis of biochemical analyte data and Hct revealed no significant effect of treatment (Table 2). Gross necropsies were unremarkable except for infrequent focal hematomas or regional areas of pallor with dark-red streaks at the injection sites. In addition, there were no significant differences between the 3 groups in either individual or cumulative histopathology scores from the pectoral musculature, kidney, liver, proventriculus or ventriculus. Representative photomicrographs of pectoral musculature (injection sites) and renal tissue (Figures 2 and 3) demonstrate that saline controls had histopathologic changes similar to the birds that were treated with meloxicam.

Discussion

Data from zebra finches receiving a single intramuscular dose of meloxicam at 1 or 2 mg/kg revealed several pharmacokinetic parameters (T_{max}, t_{1/2}, and elimination rate constant) that did not significantly differ from each other; this outcome was expected given that the same drug was administered by the same route

in both groups. Maximal drug levels in plasma were achieved quickly, within 30 min of dosing. The elimination half-lives of 3.24 h for 1 mg/kg meloxicam and 5.68 h for 2 mg/kg in zebra finches are short relative to those after a single intramuscular dose in Hispaniolan Amazon parrots (15.1 h, 1 mg/kg IM),¹⁰ African grey parrots (35.3 h, 1 mg/kg IM),¹² and African penguins (31.87 h, 0.5 mg/kg IM).¹⁴ Conversely, t_{1/2} values in finches were longer than those determined for a single intramuscular dose of meloxicam in American flamingos (1.83 h, 1 mg/kg IM),² vultures (0.42 h, 2 mg/kg IM),¹⁵ and lesser flamingos (1.93 h, 0.5 mg/kg IM).¹⁸ Unique properties of protein binding and biotransformation likely influence interspecies differences in meloxicam t_{1/2}.

In the current study, we considered only the intramuscular route of administration because intravenous dosing is impractical in birds weighing less than 20 g, absorption into the bloodstream is rapid after intramuscular injection, and, unless a gavage tube is used, a finch typically resists oral dosing by shaking its head. In addition, other studies in avian species found that giving meloxicam orally can be associated with slow absorption and poor or variable bioavailability.^{2,6,9,10,12}

In contrast to the lack of dose effect on T_{max}, t_{1/2}, and elimination rate constants, AUC_{0-∞} values differed significantly between the 1- and 2-mg/kg doses. With 2 mg/kg meloxicam achieving a C_{max} of 12,239 ng/mL and a t_{1/2} of 5.68 h, the target plasma concentration of 3500 ng/mL was maintained for approximately 9.5 h; this duration was considerably longer than the 5.5 h for birds given 1 mg/kg. Sex had no effect on pharmacokinetic outcome.

All NSAID have the potential to adversely affect kidney function and the digestive system, in particular. In the present study, we determined the safety of treating finches with intramuscular meloxicam twice daily for 4 d by measuring selected blood parameters and evaluating histopathologic changes at the conclusion of dosing. Biochemical analytes, Hct, and histology did not differ between meloxicam- and saline-treated controls. Likewise, a study in budgerigars found no evidence of renal damage after treatment with 0.1 mg/kg IM meloxicam once

Figure 2. Representative histopathology in pectoral musculature of zebra finches after multiple doses of saline or meloxicam. (A) In a saline-inoculated zebra finch, pectoral myofibers have minimal to mild regional areas of regeneration intermixed with few degenerated and necrotic myofibers and hemorrhage. Regenerating myofibers are characterized by the presence of numerous activated satellite cells, few multinucleated satellite cells, and myoblasts with cytoplasmic basophilia (star). (B) In a zebra finch that received 2 mg/kg meloxicam, areas of myofiber regeneration (star), degeneration, and necrosis are infiltrated or surrounded by small numbers of macrophages. Necrotic myocytes are often shrunken and fragmented, with pyknotic nuclei and pale eosinophilic sarcoplasm that lacks cross-striations (arrow). Hematoxylin and eosin stain; scale bar, 20 μ m.

Figure 3. Representative histopathology in kidneys of zebra finches following multiple doses of saline or meloxicam. (A) A saline-dosed bird has renal interstitium that is infiltrated focally by perivascular aggregates of lymphocytes (arrow). (B) A bird treated with 2 mg/kg meloxicam has renal interstitium focally (arrowhead) to multifocally infiltrated by small numbers of lymphocytes. Hematoxylin and eosin stain; scale bar, 100 μ m.

daily for 3 or 7 d,¹⁶ and nonsignificant renal changes occurred in African grey parrots after 14 d of 0.5 mg/kg IM meloxicam twice daily.¹¹ Similarly, Japanese quail given 2 mg/kg IM meloxicam twice daily for 14 d lacked clinically relevant renal effects.¹⁷ Although occasional quail showed mild increases in uric acid, all of these values remained within calculated reference ranges; nevertheless, pectoral muscle necrosis was more severe in quail that received meloxicam compared with those that received saline.¹⁷

Because our results indicate that both doses of meloxicam reached low plasma concentrations in zebra finches by 12 h after dosing, twice-daily or more frequent dosing likely is warranted in this species. A second consideration is whether 1 or 2 mg/kg is clinically appropriate in zebra finches, given that both of these doses appeared to be nontoxic under the study conditions. According to a report in Hispaniolan parrots that demonstrated

a therapeutic plasma concentration of 3500 ng/mL,³ 2 mg/kg might provide analgesia for a longer period in zebra finches than the 1 mg/kg dose. In fact, however, what actually constitutes an efficacious plasma concentration of meloxicam in zebra finches is unknown, and a pharmacodynamics study would be of great value, especially given that the plasma concentration of a drug does not necessarily reflect its tissue levels. Unfortunately, the analgesic efficacy of meloxicam has been measured in only 2 bird studies to date. In arthritic Hispaniolan parrots, 1 mg/kg IM twice daily was more efficacious than lower doses,³ whereas 2 mg/kg IM twice daily, the highest dose investigated, was required for adequate analgesia in pigeons with postoperative orthopedic pain.⁵

In a recent report evaluating African grey parrots, an important finding was that plasma concentrations of meloxicam increased over time when the birds were dosed intramuscularly

for 7 d or orally for 12 d.¹³ If drug accumulation occurs in other bird species, this factor would need to be included in the design of meloxicam dosing regimens. Currently, researchers at our institution who perform intracranial injections in zebra finches have been asked to administer 1 or 2 mg/kg meloxicam instead of buprenorphine and then to subjectively assess postoperative levels of analgesia. Further studies are required to determine whether zebra finches require the higher or lower meloxicam dose depending on the scope and degree of tissue injury.

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