Pharmacokinetic Study of Non–steroidal Anti–inflammatory Drugs in Wildlife Rehabilitation Birds

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Abstract: While the use of non–steroidal anti–inflammatory drugs (NSAIDs) is common in many veterinary practices, there is little information on the efficacy and appropriate dosage levels in avian species. This study examined the pharmacokinetics of one NSAID, meloxicam, given orally to wild birds undergoing rehabilitation. Meloxicam was administered at 1 mg/kg. The primary species studied was Canada goose, but red–tailed hawk was included as a comparison between these species of birds. After administration of meloxicam, blood samples were taken at a series of time intervals to determine the concentration of drug in the serum over time. The study concluded that 1 mg/kg is an appropriate dosage but should be administered twice daily instead of once a day due to the elimination rate in Canada geese. These results suggest that red–tailed hawks absorb and eliminate meloxicam at a different rate, but additional studies are needed to confirm this finding.

INTRODUCTION

The use of NSAIDs is beneficial in reducing pain and inflammation in injured birds in zoos, wildlife rehabilitation centers, and general veterinary practices. Unfortunately, there is very little information currently available on appropriate dosage levels and the effects of these drugs in avian species (Baert and De Backer 2002).

The metabolism of drugs in various avian species varies greatly from mammal models, making it difficult to apply NSAID research on mammals to avian species. Research on the pharmacokinetics of NSAIDs on rehabilitation birds will contribute to the advancement of pain management in birds.

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Meloxicam (Metacam®, Boehringer Ingelheim and Merial, Duluth, GA) is an ideal candidate for use in avian species for a variety of reasons. While many NSAIDs reduce synthesis of prostaglandins through inhibiting both Cyclooxygenase–1 (Cox–1) and Cyclooxygenase–2 (Cox–2), meloxicam primarily inhibits Cox–2, thereby reducing the drugs adverse side–effects which primarily occur because of Cox–1 inhibition. Meloxicam is available in a liquid suspension to be administered orally. The suspension is easier to administer and provide the appropriate dosage than the tablets, which must be broken in pieces for smaller birds. While limited, there are existing studies that report that meloxicam is both effective and safe to use in birds. Unfortunately, the existing research on meloxicam use in birds examined the pharmacokinetics after intravenous administration, but this method is rarely used in rehabilitation centers or at veterinary clinics (Baert and De Backer 2003; Baert and De Backer 2002; Machin et al 2001).

This research not only increases knowledge in an important veterinary field, but it will ultimately help birds on an individual basis. The results of this study confirm that the metabolism of NSAIDs in birds differs from mammals and also differs among the avian species tested. The results will assist veterinarians in selecting the appropriate dosage levels of meloxicam for the species of bird being treated. Currently many veterinarians rely on anecdotal information to determine the appropriate dosage level. This study will allow veterinarians to make more informed decisions based on pharmacokinetic analysis. More informed decisions will allow injured birds to receive the appropriate drug dosages and therefore more humane treatment.

Materials and Methods

This research was a collaboration between Dr. Miller at Tri–State Bird Rescue & Research, Inc. (Tri–State) in Newark, Delaware and Dr. Poppenga's laboratory at New Bolton Center at the University of Pennsylvania School of Veterinary Medicine in Kennett Square, Pennsylvania. Most of the research occurred at the Tri–State facilities, but all pharmacokinetic analysis was performed at Dr. Poppenga's laboratory. Treatment of birds at Tri–State began in late May and continued through August. The pharmacokinetic analysis occurred primarily in July and August.

Selection of Avian Species. The Canada geese and red–tailed hawks used in the study were all healthy rehabilitation birds that received treatment at Tri–State and were released after their participation in the study. Two birds were suspected to have West Nile virus (WNV) and received meloxicam as part of Tri–State's normal protocol for treating WNV suspect cases (both birds subsequently tested negative for WNV). A permit from the US Fish and Wildlife Service was obtained by Tri–State to allow administration of drugs to healthy rehabilitation birds and collection of blood samples from these birds. The primary species used was Canada geese (*Branta canadensis*). Three red–tailed hawks (*Buteo jamaicensis*) and one American crow (*Corvus brachyrhynchos)* were also used in the study. The medical history of all birds was reviewed with special attention to initial injury and previous drugs administered. Only birds with an appropriate body weight were used in the study to ensure blood collection would not be detrimental to the bird.

Drug Administration and Blood Collection. Meloxicam was used during the study. Originally the study was going to examine two dosage levels (1 mg/kg and 10 mg/kg) that spanned the dosages found in the literature and anecdotal evidence. One bird received 10 mg/kg, but after the initial analysis of the plasma levels in this bird it was determined that 1 mg/kg would be a more appropriate dosage level to test. The birds received one oral dose of meloxicam. Blood samples were collected from the medial metatarsal vein or brachial vein before administration (t = 0) and five additional time points after administration. The time points used in the study included 0.5, 1, 1.5, 2, 4, 8, 12, 24, 48, and 96 hours after oral dosing. Samples were only taken from each bird at five time points to minimize the stress of handling. A total of ten geese were used for the study. At each time point five of the geese were sampled, with the exception of the last time point, which only had two samples taken. The location of blood sampling was alternated between sides to ensure there was no damage to the vein. The total sample volume did not exceed 7 percent of the blood volume of the animal. Typically 0.5 ml to 1 ml was taken per sampling point. Blood was collected in serum separator tubes and serum was separated by centrifugation (20 min) and the samples were stored at –20°C (–4°F) until assayed. Extra blood from several birds, pre– and post–drug administration, was also analyzed for kidney and liver function.

Analysis of Serum Concentrations. The prepared samples were analyzed chemically through Liquid Chromatography Mass Spectrometry (LCMS) to determine the concentration of meloxicam. The LCMS is an HP1100 LC/MSD (Agilent Technologies Inc., Santa Clara, CA), with a 30 mm C–18 column. The detector was set at 254 nm. A gradient solvent program was run as follows: 0 to 1 min, 50 percent acetonitrile; 2 to 4 min, 90 percent acetonitrile; 4.5 to 6 min, 50 percent acetonitrile. Flow was 0.6 ml/min with a run time of six minutes. Samples were prepared by pipetting 200 ul of serum into a 1.5 ml eppendorf tube, followed by the addition of 400 ul of acetonitrile. Samples were briefly vortexed, then allowed to sit for 10 minutes. After centrifugation (14,000 x g, 8 min), the supernatant was transferred to an LCMS screw top vial. The protocol used was adapted from Rudik–Miksa et al (2005). The pharmacokinetic parameters, including the absorption half–life, elimination half–life, and peak concentration, were calculated with PKAnalyst version 1.0 for Microsoft® Windows® (Microsoft Corporation, Redmond, WA), a pharmacokinetic software program. The data was analyzed using a One Compartment First–Order Elimination Model. This specific model was used because meloxicam was administered orally, is readily absorbed and distributed, and is eliminated in proportion to the amount that was absorbed.

Results

The mean pharmacokinetic parameters obtained for meloxicam use in Canada geese are as follows: elimination half–life was 6.62 hours, absorption half–life was 0.84 hours, peak concentration was reached at 2.88 hours and the maximum concentration was 2.62 ppm (Figure 1; Table 1). There were no changes in chemistry panel values after the single dose administration of meloxicam for any of the geese tested.

The mean pharmacokinetic parameters obtained for meloxicam administration in red–tailed hawks are: elimination half life was 7.8 hours, absorption half

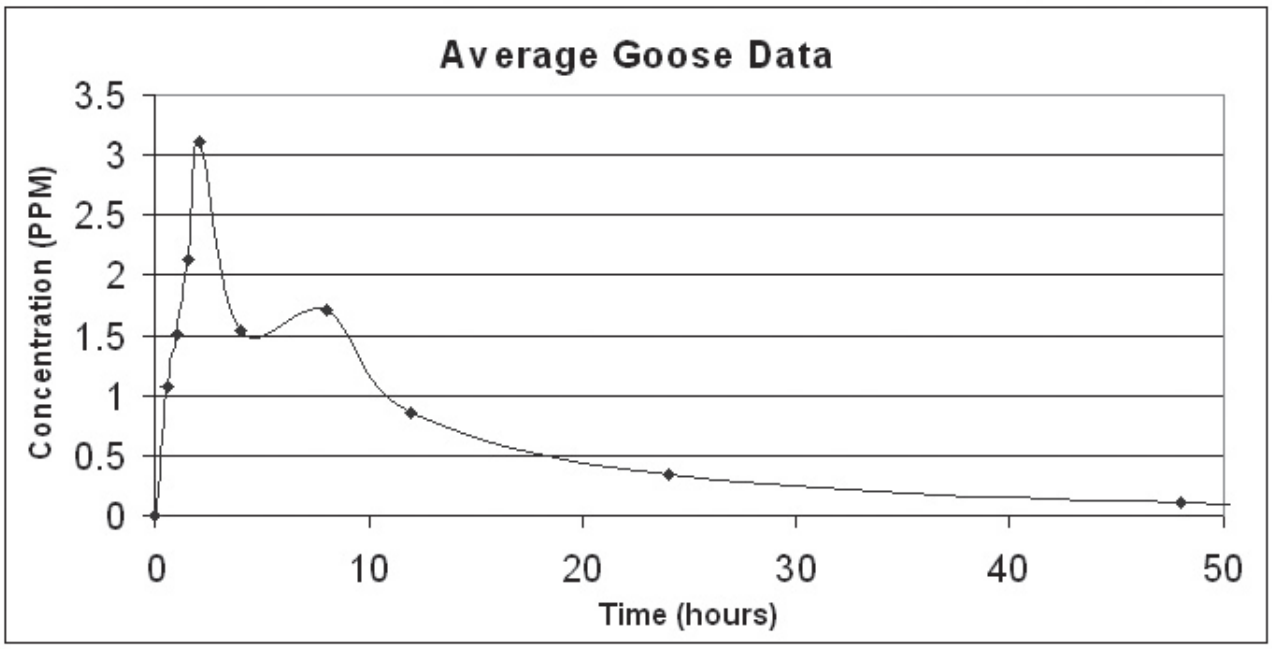

Figure 1. Mean serum concentrations (n = 5) of meloxicam in geese after oral administration of 1.0 mg/kg of meloxicam.

Table 1. Serum concentrations (ppm) of meloxicam in geese after oral administration of 1.0 mg/kg. A total of 10 geese were used with n = 5 for calculating the average serum concentrations, except for time = 96 hours with a n =2.

Hours	Average	G4	G7	G9	G21	G23	G24	G29	G33	G35	G32
0	0	0	0	0	0	0	0	0	0	0	0
0.5	1.07	–	–	–	1.82	0.34	–	1.11	1.56	0.51	–
1	1.5	–	1.26	–	–	1.25	1.4	2.28	1.32	–	–
1.5	2.13	–	–	–	3.71	2.37	–	1.89	0.44	2.21	–
2	3.42	1.89	1.79	4.39	–	–	3.95	–	–	–	3.56
4	1.89	0.13	–	3.05	1.05	–	–	–	–	0.69	2.78
8	2.14	0.01	1.45	2.67	–	–	2	–	–	–	2.45
12	1.06	0.01	–	2.47	0.12	–	–	–	–	0.1	1.55
24	0.35	–	0.43	–	–	0.59	–	0.02	0.02	–	0.67
48	0.13	0.01	0.11	0.38	0	–	–	–	–	0.02	–
96	0.02	–	–	–	–	–	–	0.02	0.02	–	–

life was 2.3 x 10^{-68} hours, peak concentration was reached at 5.2 x 10^{-66} hours and the maximum concentration was 0.16 ppm (Figure 2; Table 2). [***Author's Note:*** The size of these numbers is an artifact of the small sample size and needs further investigation.]

Discussion

The results of administration of meloxicam to the geese demonstrate that while there is a certain amount of variation between absorption and elimination in individual geese, overall the findings show the appropriate dosage to administer. Before this study, Tri–State was administrating 10 mg/kg of meloxicam to an individual goose. This study indicates that this dosage, of 10 mg/kg, is much too high. The individual goose that received 10 mg/kg reached a peak plasma concentration of 68 ppm after a single dose. By comparison, in a study on the use of meloxicam in dogs at the effective dosage, dogs only reached a peak plasma concentration of 0.5 ppm (Boehringer and Merial 2003). The dose in dogs is 0.2mg/kg, followed after 24 hrs by 0.1mg/kg SID (Metacam® package insert, <http://www.METACAM.us>). While a difference is expected in the effective serum level between avian species and mammals, this difference is extreme. At the dosage of 1 mg/kg one goose reached a maximum level of 4.39 ppm (Table 1), which appears to be a more reasonable level but is still ten times the level reached in dogs. It is particularly important that meloxicam not be given at higher levels than needed because of the adverse side effects including gastric irritation and ulcers, prolonged clotting time, and renal and hepatic damage (Livingston 2000; Paul–Murphy and Ludders 2001).

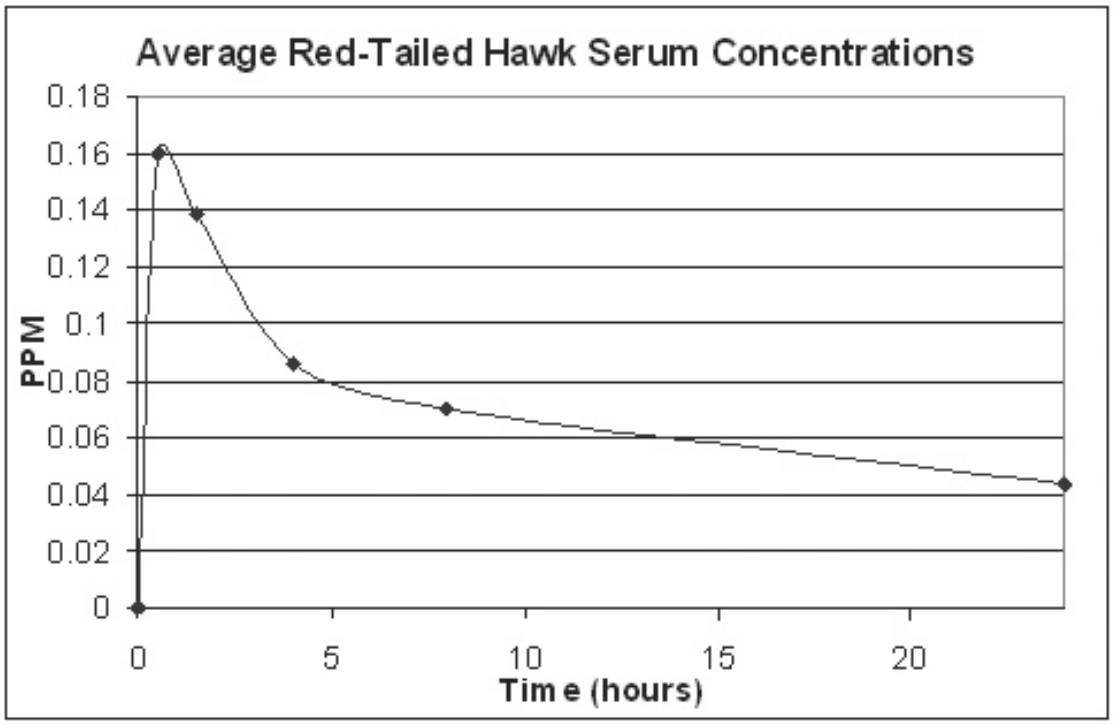

Figure 2. Mean serum concentrations (n = 2) of meloxicam in red–tailed hawks after oral administration of 1.0 mg/kg of meloxicam.

Table 2. Serum concentrations (ppm) of meloxicam in red–tailed hawks after oral administration of 1.0 mg/kg (n=2).

Hours	Average	R778	R1312
0	0	0	0
0.5	0.16	0.15	0.17
1.5	0.14	0.17	0.11
4	0.09	0.1	0.07
8	0.07	0.08	0.07
24	0.04	0.03	0.06

While the serum level reached in geese at 1 mg/kg is still much higher than the study in dogs, the serum levels of NSAIDs may not accurately reflect their physiologic or pharmacologic activity, especially in birds (Machin et al 2001). Some studies suggest that NSAIDs administered at low doses in avian species do not produce the desired analgesic effect (Machin et al 2001).

At Tri–State, the higher concentration of 10 mg/kg was administered once a day. It appears that the lower dose of 1 mg/kg meloxicam should be administered twice a day since the terminal half–life in geese is 6.2 hours (Figure 1). It is interesting to note that in dogs, meloxicam is administered once a day at 0.2 mg/kg, but the half–life of elimination is 24 hours (Boehringer and Merial 2003). It is not surprising that there is a significant difference in the elimination rate between mammals and avian species because within mammals there is a large difference. Previous studies suggest that the half–life of elimination of meloxicam is 13 hours in cattle, 11 hours in rats, 20 to 50 hours in humans, and 4 hours in minipigs (Baert and De Backer 2003).

The results from the red–tailed hawks may suggest that they metabolize meloxicam very different from geese (Figure 2; Table 2). This could be considered normal since within species of mammals there is significant variation in metabolism time. The data from the red–tailed hawks must be interpreted with caution though, because only two birds were used in the study, which is not statistically significant. Also the results indicate the drug was instantaneously absorbed, which may not be credible.

Even though NSAIDs with greater Cox–2 activity have been presumed to have less gastrointestinal side effects, they still do have side effects and still must be used with care (Livingston 2000; Paul–Murphy and Ludders 2001). Therefore it is still important to use caution with the use of meloxicam and monitor for any adverse side effects. This study suggests that the one–time dose of meloxicam administered does not affect liver or kidney function. In order to determine if the geese were having any gastrointestinal irritation from the meloxicam, several of the geese were monitored for changes in weight over the three days they were in the study. All of the birds continued to gain weight at a normal rate indicating that the meloxicam did not affect their appetite and that indi-

rectly suggests they had no gastrointestinal irritation. Additionally, the weight gain suggests that stress from regular handling and restraining for multiple blood draws was minimal and did not adversely disturb their normal eating behavior.

Conclusion

The results of this study suggest that a dosage of 1 mg/kg administered twice a day is appropriate for these families of birds. Unfortunately while we can analyze the pharmacokinetics, the most difficult part is understanding how to interpret if a bird is experiencing pain and if we are in fact providing adequate relief. Some indicators of pain in birds are weight loss, inappetence, and feather picking, but signs can be even more subtle, such as the bird being more subdued, slight increases in restlessness, or changes in posture (Pain Roundtable 1998; Paul–Murphy and Ludders 2001). In order to accurately assess pain the observer needs to not only be familiar with the normal and abnormal behavior for that particular species, but also for the individual bird being studied (Paul–Murphy and Ludders 2001).

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