

Pharmacokinetics and egg residues after oral administration of a single dose of meloxicam in domestic chickens (*Gallus domesticus*)

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OBJECTIVE

To determine the pharmacokinetics of meloxicam in domestic hens and duration and quantity of drug residues in their eggs following PO administration of a single dose (1 mg of meloxicam/kg).

ANIMALS

8 healthy adult White Leghorn hens.

PROCEDURES

Hens were administered 1 mg of meloxicam/kg PO once. A blood sample was collected immediately before and at intervals up to 48 hours after drug administration. The hens' eggs were collected for 3 weeks after drug administration. Samples of the hens' plasma, egg whites (albumen), and egg yolks were analyzed by high-performance liquid chromatography.

RESULTS

The half-life, maximum concentration, and time to maximum concentration of meloxicam in plasma samples were 2.8 hours, 7.21 µg/mL, and 2 hours, respectively. Following meloxicam administration, the drug was not detected after 4 days in egg whites and after 8 days in egg yolks.

CONCLUSIONS AND CLINICAL RELEVANCE

Results indicated that meloxicam administered at a dose of 1 mg/kg PO in chickens appears to maintain plasma concentrations equivalent to those reported to be therapeutic for humans for 12 hours. The egg residue data may be used to aid establishment of appropriate drug withdrawal time recommendations. (*Am J Vet Res* 2017;78:965–968)

With the increasing popularity of backyard poultry ownership, veterinarians are faced with the question of how to treat these animals with regard to drug withdrawal times for egg consumption. A recent review¹ describes allowable medications for use in egg-laying poultry, but few authors have recommended doses or withdrawal times for use in egg-laying hens.

Meloxicam is an NSAID that is commonly used in avian medicine. A commercially available liquid form of the drug is readily available and is easily administered to birds. A recent publication¹ reported that the Food Animal Residue Avoidance Databank received more requests for egg withdrawal intervals for hens following meloxicam administration than for any other drug. Although 1 study² examined the pharmacokinetics of meloxicam in chickens following IV administration, no published pharmacokinetic data are available to aid in recommendations regarding dosage of meloxicam for PO administration in chickens or withdrawal times for eggs from hens treated PO with meloxicam.

In a study³ of lame broiler chickens, a single SC injection of meloxicam (5 mg/kg) improved mobility, com-

pared with findings in control birds that received saline (0.9% NaCl) solution SC. Caplen et al⁴ also found that a single SC injection of meloxicam (5 mg/kg) resulted in antinociceptive effects when broiler chickens were exposed to a thermal stimulus. Meloxicam administered PO at doses ranging from 0.5 to 4 mg/kg to backyard poultry resulted in subjective improvements in mobility, and no adverse effects were observed.⁵ Other NSAIDs (diclofenac, carprofen, and ketoprofen) assessed in that study⁵ were associated with deaths at higher doses.

Clinical experience and the aforementioned study findings suggest that meloxicam is a safe and effective choice for analgesia in chickens; however, limited information is available on appropriate dosages for chickens or drug withdrawal times for eggs. The objective of the study reported here was to determine the pharmacokinetics of meloxicam in domestic hens and duration and quantity of drug residues in their eggs following PO administration of a single dose (1 mg of meloxicam/kg).

Materials and Methods

Eight adult White Leghorn hens were obtained from a commercial source and housed in a climate-controlled facility for 2 weeks prior to undergoing any procedures. Hens were determined to be healthy

ABBREVIATIONS

AUC_{0-∞} Area under the plasma concentration–time curve from time 0 to infinity
HPLC High-performance liquid chromatography

on the basis of physical examination findings. The birds were housed individually in large wire cages (61 X 122 X 91.5 cm) that were adjacent to each other so that each hen could see all other hens. Birds were provided water, layer pellets, and scratch feed ad libitum. Fresh greens were provided daily, and mealworms were provided intermittently as enrichment. The birds were maintained on a cycle of 14 hours of light and 8 hours of darkness to encourage egg laying. All study procedures were approved by the University of Tennessee Institutional Animal Care and Use Committee.

At the start of the study, hens were weighed, and a dose of 1 mg of meloxicam^a/kg was calculated. A blood sample (0.3 mL) was collected from each hen on day 0 immediately before administration of the drug (0 hours) via syringe into the oral cavity distal to the glottis. A blood sample (0.3 mL) was then collected at 10, 20, and 30 minutes and 1, 2, 4, 8, 12, 24, and 48 hours after dose administration. Blood samples were collected from a jugular or basilic vein with an insulin syringe and 29-gauge needle. Eggs laid by the dosed hens were collected for 3 weeks starting on the day of meloxicam administration (day 0). Eggs were kept refrigerated until analyzed.

Collected blood samples were each placed into a lithium heparin plasma separator tube and placed on ice. Within 2 hours after collection, each blood sample was centrifuged for plasma separation; the plasma sample was placed into a cryogenic vial and then kept frozen at -80°C until analysis. Plasma samples were analyzed by the University of Tennessee Pharmacology Laboratory within 2 days after collection, and egg samples were analyzed within 2 weeks after collection.

Analysis of plasma and egg white (albumen) samples was conducted with a method developed by Cox et al.⁶ Briefly, analysis of meloxicam in plasma and egg white samples was performed by reversed-phase HPLC. The system consisted of a separations module, a UV absorbance detector, and a computer equipped with analytic software.^b The compounds were separated on a column^c (4.6 X 250 mm; particle size, 5 µm) with a 5-µm guard column.^c The mobile phase was a mixture of 10 mL of glacial acetic acid in 1 L of H₂O (pH 3.0 [adjusted with sodium hydroxide]; 50%) and acetonitrile (50%). Absorbance was measured at 360 nm with a flow rate of 1 mL/min.

Standard curves for egg white analysis were prepared by means of fortifying untreated egg whites with meloxicam to produce a linear concentration range of 5 to 1,500 ng/mL. Calibration samples were prepared exactly as were the egg white samples. The lower limit of quantification during validation was 5 ng/mL. The intra- and interassay variability ranged from

0.5% to 6.6%, and the calculated mean recovery for meloxicam was 90%. Standard curves for plasma analysis were prepared by means of fortifying samples of untreated plasma with meloxicam to produce a linear concentration range of 5 to 10,000 ng/mL. Calibration samples were prepared exactly as were the plasma samples. The lower limit of quantification during validation was 5 ng/mL. The intra- and interassay variability ranged from 1.1% to 10%, and the calculated mean recovery for meloxicam was 95%.

Meloxicam was extracted from egg yolks by means of a solid-phase extraction technique using HPLC. For each egg, 1 mL of yolk was placed in a tube, followed by 75 µL of the internal standard (piroxicam, 5 µg/mL) and 200 µL of 1M HCl and 2 mL of acetonitrile. Samples were vortexed and centrifuged, and then the supernatant was removed and evaporated. The residue was redissolved in methanol and water (1:9 ratio) and added to an extraction cartridge.^d Elution was performed with 2 mL of acetonitrile and methanol (vol/vol, 90:10); the eluate was then evaporated with nitrogen and redissolved in the mobile phase. Standard curves for egg yolk analysis

Table 1—Pharmacokinetic parameters for meloxicam in plasma following PO administration of a single 1-mg/kg dose to 8 domestic hens.

Pharmacokinetic parameter	Mean ± SD
Terminal half-life* (h)	2.79 ± 1.01
Elimination rate constant (λ_z [1/h])	0.28 ± 0.09
T _{max} (h)	2.0 ± 0.92
C _{max} (µg/mL)	7.21 ± 3.29
AUC _{0-∞} (h•µg/mL)	37.92 ± 6.91
MTT _{0-∞} (h)	5.22 ± 2.43

A blood sample (0.3 mL) was collected immediately before (0 hours) and at intervals up to 48 hours after drug administration from each of the hens. Plasma samples were kept at -80°C and analyzed within 2 days after collection. Values for plasma half-life, maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), and AUC_{0-∞} of meloxicam were calculated from noncompartmental analysis. Area under the plasma concentration-time curve was calculated by use of the log-linear trapezoidal rule. Mean transient time from time 0 to infinity (MTT_{0-∞}) was calculated as the total area under the first movement curve divided by AUC_{0-∞}.

*Harmonic mean.

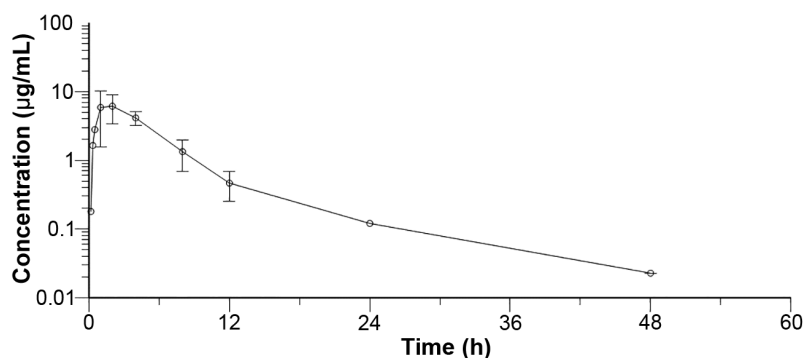


Figure 1—Mean plasma concentration of meloxicam over time following PO administration of a single 1-mg/kg dose to 8 domestic hens. A blood sample (0.3 mL) was collected immediately before (0 hours) and at intervals up to 48 hours after drug administration from each of the hens. Plasma samples were kept at -80°C and analyzed by reversed-phase HPLC within 2 days after collection.

Table 2—Median and range concentration of meloxicam and number of eggs over time in egg yolks and egg whites from eggs laid by 8 domestic chickens that received a single dose of meloxicam (1 mg/kg) PO on day 0.

Day	Egg yolk samples (ng/mL)			Egg white samples (ng/mL)		
	Median	Range	No. of eggs	Median	Range	No. of eggs
0	0	0–6	3	BQ	BQ–BQ	3
1	3.5	0–7	2	5.3	BQ–8	2
2	5	BQ–6	3	BQ	BQ–BQ	3
3	8	BQ–12	3	BQ	0–BQ	3
4	8.3	BQ–14	2	1.3	ND–BQ	2
5	20	16–24	2	ND	ND–ND	2
6	19	0–22	3	ND	ND–ND	3
7	12	NA	1	NS	NS	NA
8	BQ	0–8	5	ND	ND–ND	4
9	0	NA	1	ND	ND	1
10	0	0–0	4	ND	ND–ND	2
11	0	0–0	2	ND	ND	1
12	0	0–0	3	ND	ND–ND	2
13	0	0–0	3	ND	ND–ND	3

Eggs laid by the dosed hens were collected for 3 weeks starting on the day of meloxicam administration (day 0). Eggs were kept refrigerated until analyzed within 2 weeks after collection. Analysis of meloxicam in egg samples was performed by reversed-phase HPLC. Meloxicam was extracted from egg yolks by means of a solid-phase extraction technique for analysis. Eggs were collected for 3 weeks, but the HPLC analysis of egg white and yolk samples was discontinued for each hen once at least 2 consecutive eggs from that hen had no detectable meloxicam. No drug was detected in egg yolks or egg whites after 8 days and 4 days, respectively.

BQ = Below the limit of quantification (designated as 2.5 ng/mL). NA = Not applicable. ND = None detected (designated as 0 ng/mL). NS = No sample analyzed at this time point.

were prepared by means of fortifying untreated egg yolks with meloxicam to produce a linear concentration range of 5 to 1,500 ng/mL. The lower limit of quantification during validation was 5 ng/mL, and the limit of detection was 2.5 ng/mL. Intra- and interassay variability ranged from 1.8% to 7.8%, and the calculated mean recovery for meloxicam was 85%.

Pharmacokinetic parameters for meloxicam were calculated with computer software.^c Values for plasma half-life, maximum plasma concentration, time to maximum plasma concentration, and AUC_{0-∞} of meloxicam were calculated from noncompartmental analysis. Area under the plasma concentration-time curve was calculated by use of the log-linear trapezoidal rule. Mean transient time from time 0 to infinity was calculated as the total area under the first movement curve divided by AUC_{0-∞}.

Results

Hens were observed daily for activity levels and food consumption, and no changes occurred during the 3-week study period. Plasma samples obtained from all 8 hens at 11 time points each were analyzed by HPLC. The mean ± SD terminal half-life, maximum concentration, and time to maximum concentration were 2.79 ± 1.01 hours, 7.21 ± 3.29 µg/mL, and 2.0 ± 0.92 hours, respectively (**Table 1**). A plasma meloxicam concentration-time curve was generated (**Figure 1**). Eggs were collected from hens daily for 3 weeks following meloxicam administration. Only 5 hens laid eggs consistently (every day or every other day) through the collection period. Hens did not lay eggs daily, and 1 hen laid only 1 egg during the col-

lection period. No drug was detected in egg yolks or egg whites after 8 and 4 days, respectively. Eggs were collected for 3 weeks, but the HPLC analysis of egg white and yolk samples was discontinued for each hen once at least 2 consecutive eggs from that hen had no detectable meloxicam. Median meloxicam concentrations in egg yolks and egg whites for all hens for days 0 to 13 were summarized (**Table 2**).

Discussion

In the present study, the pharmacokinetics of meloxicam in domestic chickens following a single PO dose of 1 mg/kg was determined. Pharmacokinetic evaluations of meloxicam administered PO in other avian species have been recently reported.^{7,8} Comparison of these data revealed that the half-life of meloxicam was shortest in the chickens of the present study (2.79 hours), compared with findings in Hispaniolan Amazon parrots (15.8 hours), red-tailed hawks (3.97 hours), and great horned owls (5.07 hours). The time to maximum plasma meloxicam concentration in the study chickens was 2.0 hours, which was shorter than that in parrots (5.0 hours) and owls (7.8 hours), but longer than that in hawks (0.73 hours). In the study chickens, the maximum plasma meloxicam concentration achieved was 7.21 µg/mL, whereas that in parrots was 3.7 µg/mL; both of these species were administered meloxicam PO at a dose of 1 mg/kg. The hawks and owls were administered meloxicam PO at a dose of 0.5 mg/kg and had comparatively lower maximum plasma meloxicam concentrations of 0.182 and 0.368 µg/mL, respectively. Although sample analysis method can affect

some pharmacokinetic parameters, the variability of results among these avian species emphasizes the importance of species-specific study findings as a basis for clinical recommendations.

Although the pharmacokinetics of meloxicam in chickens has been studied,²⁻⁵ a therapeutic plasma concentration has yet to be determined. In Hispaniolan Amazon parrots, it has been suggested that a mean plasma meloxicam concentration of 3.5 µg/mL should adequately provide analgesia⁷; on the basis of that finding, the same dose (1 mg/kg) was selected for use in the chickens of the present study. However, as for any drug, one should anticipate species differences in metabolism; paired pharmacokinetic and pharmacodynamic assessments in a given avian species are needed to determine species-specific recommendations for treatment with meloxicam.^{7,8} The therapeutic plasma meloxicam concentrations reported for humans⁹ should also be considered when dosing recommendations are made. On the basis of a therapeutic plasma concentration in humans of 0.5 to 1.5 µg of meloxicam/mL, PO administration of meloxicam at a dose of 1 mg/kg to domestic chickens should maintain therapeutic plasma meloxicam concentrations for 12 hours.⁹ Because accumulation of meloxicam could occur with repeated administration of doses, additional investigation of the pharmacokinetics of multiple meloxicam doses is needed before recommendation of a multiple-dose regimen. If the therapeutic plasma meloxicam concentration in domestic chickens is determined to be greater than that in humans (ie, more similar to that suggested for Hispaniolan Amazon parrots), more frequent administration or higher doses of meloxicam may be required. However, considering the potential adverse effects associated with NSAID administration, a lower-dose regimen is recommended until paired pharmacokinetic and pharmacodynamic studies can be performed.

To our knowledge, the present study was the first to examine drug residues in eggs following PO administration of meloxicam to domestic chickens. The drug was present for a longer period in egg yolks than in egg whites, which is consistent with the formation of eggs.¹⁰ The white (albumen) is laid onto the yolk later in egg formation; therefore, once meloxicam is no longer present systemically in an egg-laying hen, drug concentration in the egg white quickly decreases. Drug residues could persist in eggs for longer periods owing to the duration of yolk (follicle) formation, but residues of drugs are reported to typically persist for < 2 weeks.¹⁰ Although the number of eggs collected and analyzed each day during the present study was small, the data suggested that a 2-week withdrawal time should be adequate to avoid meloxi-

cam residue in eggs following a single PO 1-mg/kg dose to domestic hens. Additional research will be needed to determine withdrawal times for multiple-dose regimens.

With the increasing popularity of backyard poultry, additional investigations of meloxicam, as well as other commonly used medications, will be needed to provide accurate withdrawal times for eggs intended for consumption. The present study has provided an initial assessment of the use of meloxicam in domestic laying hens, but additional research is needed to determine the pharmacokinetics and egg residues associated with multiple-dose administration as well as to establish species-specific therapeutic plasma meloxicam concentrations through paired pharmacokinetic and pharmacodynamic studies in domestic hens and other birds.

Footnotes

- a. Metacam, Boehringer Ingelheim Vetmedica, St Joseph, Mo.
- b. Empower 3 Chromatography Data Software, Waters, Milford, Mass.
- c. XBridge, Waters, Milford, Mass.
- d. Oasis HLB (3 mL) extraction cartridge, Milford, Mass.
- e. Phoenix, version 6.4, Pharsight Corp, Mountain View, Calif.

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