Pharmacokinetics of buprenorphine hydrochloride following intramuscular and intravenous administration to American kestrels (*Falco sparverius*)

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Objective—To determine the pharmacokinetics of buprenorphine hydrochloride after IM and IV administration to American kestrels (*Falco sparverius*).

Animals—13 healthy 3-year-old captive-bred American kestrels.

Procedures—Buprenorphine hydrochloride (0.6 mg/kg) was administered IM to all birds. Blood samples were collected at 9 times, ranging from 5 minutes to 9 hours after drug administration. Plasma buprenorphine concentrations were measured by use of tandem liquid chromatography–mass spectrometry. Pharmacokinetic parameters were determined by use of least squares linear regression and noncompartmental analysis of naïve pooled data. After a washout period of 2 weeks, the same dose of buprenorphine was administered IV to all birds and blood samples were collected at the same times after drug administration.

Results—Maximum plasma buprenorphine concentration was achieved within 5 minutes after IM administration. For IM administration, bioavailability was 94.8% and elimination half-life was 92.1 minutes. For IV administration, steady-state volume of distribution was 4,023.8 mL/kg, plasma clearance was 49.2 mL/min/kg, and elimination half-life was 105.5 minutes.

Conclusions and Clinical Relevance—Buprenorphine was rapidly absorbed, and bioavailability was good after IM administration to American kestrels. Plasma buprenorphine concentrations were > 1 ng/mL for 9 hours after both IM and IV administration. These results, in combination with those of a pharmacodynamic study, suggested that the analgesic effects of buprenorphine could last at least 6 to 9 hours in this species. Further investigations of the duration of analgesic effects, multiple-dose protocols, and potential adverse effects of buprenorphine are warranted in American kestrels and other raptors. (*Am J Vet Res* 2014;75:711–715)

Opioids are widely used as analgesics in veterinary medicine and are considered the most effective drugs for moderate to severe pain.[1,2] Literature on the use of analgesic drugs in avian species is sparse, and extrapolation from other species may not result in safe and effective dosing. The κ-opioid receptor agonists butorphanol and nalbuphine have been recommended for management of signs of acute pain and preemptive analgesia in psittacine birds.[2] However, there is growing evidence for differences in the analgesic efficacy of μ- and κ-opioid receptor agonists in raptors. Specifically, administration of the κ-opioid agonist butorphanol (1, 3, and 6 mg/kg, IM) to American kestrels (*Falco sparverius*) did not induce thermal antinociception despite plasma concentrations consistent with those that induce analgesia in other species,[3] whereas administration of the μ-opioid agonist hydromorphone (0.1, 0.3, and 0.6 mg/kg, IM) significantly increased thermal withdrawal threshold.[4]

Buprenorphine is a semisynthetic opioid drug.[5] Pharmacology of buprenorphine is complex, but there is a consensus that clinically relevant analgesia in mammals is attributable to action as a full agonist at the μ-opioid receptor.[6,7] Domestic pigeons (*Columba livia*) were used to discriminate between injections of

Abbreviations

AUC_{inf}	Area under the curve extrapolated to infinity
$t_{1/2}$	Elimination half-life

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μ- and κ-opioid receptor agonists[8,9]; injections of buprenorphine elicited the response assigned to μ-opioid agonists, which suggests that μ-opioid receptor agonism is the predominant effect of buprenorphine in that species.

Buprenorphine is attractive for use as an analgesic in veterinary medicine because of its long duration of action and favorable safety profile.[1,7] However, evaluation of the analgesic efficacy of buprenorphine in avian species has yielded variable results. Administration of buprenorphine (0.25, 0.5, and 0.75 mg/kg, IM) increased the response threshold to an electrical stimulus in domestic pigeons.[10] Administration of buprenorphine (0.1 mg/kg, IM) did not affect electrical stimulus threshold in African grey parrots (*Psittacus erithacus*), despite the fact that this dose achieved a plasma concentration consistent with the concentration that results in analgesia in humans for 2 hours.[11,12] Intra-articular administration of buprenorphine (0.05 to 1 mg/kg) increased resting behavior in domestic chicks (*Gallus gallus domesticus*), with no detectable difference between birds with and without experimentally induced arthritis.[13] Red-tailed hawks (*Buteo jamaicensis*) with acute traumatic injuries that received buprenorphine (0.25 mg, SC, q 12 h) had a significant difference in putative pain-related behavior, compared with the behavior for uninjured hawks[14]; however, they were not compared with injured hawks that did not receive buprenorphine. In a pharmacodynamic study[15] conducted by our research group, administration of a single dose of buprenorphine hydrochloride (0.1, 0.3, or 0.6 mg/kg, IM) to American kestrels increased thermal withdrawal threshold for up to 6 hours.

The pharmacokinetics of buprenorphine has been evaluated for various routes of administration in a number of mammalian species,[16–25] in red-eared slider terrapins (*Trachemys scripta elegans*),[26] and in African grey parrots.[12] To the authors' knowledge, buprenorphine pharmacokinetics has not been determined for any raptor species. American kestrels are small, easily maintained members of the family Falconidae and can serve as a representative for falconiformes and other raptors commonly encountered in zoological, falconry, and wildlife rehabilitation settings.[27] The purpose of the study reported here was to evaluate pharmacokinetics for a 9-hour period after IM and IV administration of buprenorphine hydrochloride to American kestrels.

Materials and Methods

Animals—Thirteen captive-bred 3-year-old American kestrels (7 females and 6 males) were used in the study. All kestrels originated from the US Geological Survey Patuxent Wildlife Research Center and were housed at the University of California-Davis for 20 months prior to this study. The same colony of kestrels was used previously to evaluate the pharmacodynamics of buprenorphine.[15] Kestrels were housed in 3 small groups in rooms (2.5 × 2.5 × 3.2 m) equipped with several perches. Kestrels were fed killed, previously frozen adult mice and had ad libitum access to water. They were maintained on a cycle of 12 hours of light to 12 hours of darkness, and temperature was controlled at 20°C. The kestrels were healthy as determined on the basis of physical examination at the beginning of the study. Food consumption and body weight were monitored during the 2-week study period. The experimental protocol was approved by the Institutional Animal Care and Use Committee at the University of California-Davis.

Experimental design—Two experiments were performed, with a 2-week washout period between the experiments. Buprenorphine was administered IM and IV, and blood samples were collected over a 9-hour period. During each 9-hour experiment, kestrels were housed in transport carriers (23 × 30.5 × 43 cm) equipped with a perch covered in artificial turf and monitored for signs of adverse effects, including apnea, vomiting, and diarrhea. Behavioral effects (sedation or excitation) were also monitored.

Twelve kestrels (6 males and 6 females) were assigned to 3 groups (A, B, and C) balanced for sex. Each group consisted of 4 birds (2 males and 2 females). One additional female kestrel was included in group B for IV administration only.

Buprenorphine was initially administered IM to the kestrels. Each kestrel was manually restrained, and 0.6 mg of buprenorphine hydrochloride[a]/kg was administered IM in the right pectoral muscle. Blood samples were collected from each kestrel before buprenorphine administration (time 0). Blood samples were also collected from group A kestrels at 5 minutes, 1 hour, and 3 hours after drug administration; from group B kestrels at 15 minutes, 1.5 hours, and 9 hours after drug administration; and from group C kestrels at 30 minutes, 2 hours, and 6 hours after drug administration. At each time point, kestrels were manually restrained and 0.3 mL of blood was collected from a jugular vein into lithium-heparin tubes.

After a 2-week washout period, buprenorphine was administered IV to the kestrels. Each kestrel was manually restrained, and 0.6 mg of buprenorphine hydrochloride/kg was administered IV in the left jugular vein. Blood samples were collected as described for IM administration. Samples were collected exclusively from the right jugular vein for at least the first 30 minutes after drug administration.

For both experiments, blood samples were stored on ice for ≤ 4 hours and then centrifuged at 3,800 × *g* for 6 minutes. Plasma was harvested and stored at –80°C until analysis.

Measurement of plasma buprenorphine concentrations—Buprenorphine was quantified in kestrel plasma by means of tandem liquid chromatography–mass spectrometry by use of a method reported elsewhere.[28] A partial validation was performed that used kestrel plasma as a matrix. The response for buprenorphine was linear (R^2 = 0.99). The precision and accuracy of the assay were determined by assaying replicates (n = 6) of buprenorphine quality control samples. Accuracy was 103% for buprenorphine concentrations of 0.30 and 40 ng/mL. Precision (relative SD) was 8.0% and 6.0% for buprenorphine concentrations of 0.30 and 40 ng/mL, respectively. The assay was optimized to provide a limit of quantitation of 0.1 ng/mL. Limit of detection was 0.05 ng/mL. Analysis was performed by personnel at the K. L. Maddy Equine Analytical Chem-

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istry Laboratory at the California Animal Health and Food Safety Laboratory, University of California-Davis.

Pharmacokinetic analysis—The IM experiment included 9 time points, with samples from 4 birds at each time point. For the IV experiment, 3 birds (1 in group A and 2 in group B) received partial injections and were excluded from analysis. One additional female kestrel was added as a replacement; therefore, the analysis for the IV experiment was based on samples from 3 birds at 6 time points and from 4 birds at the remaining 3 time points. Naïve pooling of data points[29] was used to combine data from different birds at each time point. Nonlinear least squares regression was performed on the plasma buprenorphine concentration at each time point by the use of commercially available software.[b] Noncompartmental analysis for sparse data was used for determination of pharmacokinetic parameters. Bioavailability after IM administration was calculated as follows: AUC_{inf} after IM administration/AUC_{inf} after IV administration.

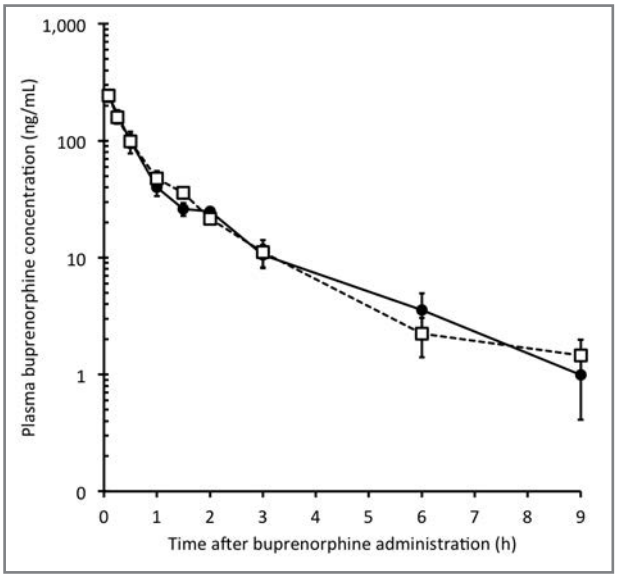

Figure 1—Mean ± SD plasma buprenorphine concentration after IM (white squares) and IV (black circles) administration of 0.6 mg of buprenorphine hydrochloride/kg to American kestrels (*Falco sparverius*). Blood samples were collected before (time 0) and 5, 15, and 30 minutes and 1, 1.5, 2, 3, 6, and 9 hours after drug administration from 12 birds (IM administration) or 10 birds (IV administration). Results represent naïve pooled data, with samples collected from 3 or 4 birds at each time point.

Table 1—Pharmacokinetic parameters obtained from noncompartmental analysis of plasma concentrations after IM and IV administration of 0.6 mg of buprenorphine hydrochloride/kg to American kestrels (*Falco sparverius*).*

Parameter	IM	IV
Cmax (ng/mL)	242.9	—
C(0) (ng/mL)	—	299.3
Tmax (min)	≤ 5	≤ 5
$t_{1/2}$ (min)	92.1	105.5
Cl (mL/min/kg)	—	49.2
Vss (mL/kg)	—	4,023.8
AUC_{inf} (min•ng/mL)	11,560.5	12,189.3
Bioavailability (%)	94.9	—

*Buprenorphine was administered to 12 (IM administration) or 10 (IV administration) kestrels; results represent naïve pooled data for samples collected from 3 or 4 birds at each of 9 time points over a 9-hour period.

C(0) = Plasma concentration extrapolated to time of administration. Cl = Clearance. Cmax = Maximum plasma concentration. Tmax = Time of the maximum plasma concentration. Vss = Volume of distribution at steady state. — = Not applicable.

Results

Plasma buprenorphine concentrations after IM and IV administration were plotted (**Figure 1**). Selected pharmacokinetic parameters were derived from these data (**Table 1**). For IM administration, the maximum plasma concentration was detected in the sample obtained at the first time point after drug administration; therefore, the time of the maximum plasma concentration was ≤ 5 minutes. Bioavailability after IM administration was high (94.8%). There were similar elimination kinetics after IM and IV administration; $t_{1/2}$ was 92.1 and 105.5 minutes after IM and IV administration, respectively.

Mild to moderate sedation was recorded within 15 to 30 minutes after both IM and IV administration of 0.6 mg of buprenorphine/kg, although the birds remained reactive to physical handling at all time points. There were no clinically apparent adverse effects, and all kestrels were alert and able to fly when returned to their rooms 9 hours after drug administration.

Food consumption remained stable during the study period. No kestrel lost > 3% of body weight during the 2-week study period.

Discussion

In the study reported here, we evaluated the pharmacokinetics of buprenorphine hydrochloride after administration to American kestrels. To our knowledge, this is the first report of buprenorphine pharmacokinetics in a raptor. Intramuscular administration of buprenorphine was characterized by rapid absorption and high bioavailability, with elimination kinetics similar to those after IV administration. The large volume of distribution at steady state (4,023.8 mL/kg) is typical of buprenorphine pharmacokinetics in other species[12,18,22–25,30–32] and indicated extensive distribution of this lipophilic drug from the plasma. Nine hours after both IM and IV administration, mean plasma concentrations remained > 1 ng/mL, which is a concentration associated with analgesia in humans.[33]

Considerable species variability in the absorption and elimination kinetics of buprenorphine exists. Bioavailability was approximately 95% for kestrels in the present study, but bioavailability after IM administration to African grey parrots is only 68%.[12] To the authors' knowledge, that is the only other avian species for which buprenorphine pharmacokinetics has been reported. In mammals, reported bioavailability after IM administration ranges from 45.7% in cats[32] to 100% in goats.[24] Substantial interindividual variability in bioavailability has also been reported in humans[16] and horses.[25] The naïve-pooled analysis, which was necessary because of the small volume of blood that could safely be obtained from each kestrel, prevented evaluation of interindividual variability in the present study.

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Elimination of buprenorphine was slower in kestrels than in African grey parrots, which had a $t_{1/2}$ of 62.4 minutes for IV administration.[12] Elimination in both kestrels and African grey parrots is faster than that in mammals, for which $t_{1/2}$ values after IV administration range from 73.8 minutes for goats[24] to 420 minutes for cats.[32] Species differences in buprenorphine bioavailability and elimination do not appear to depend on taxa or correlate with body size, which highlights the potential risk of overdosing or underdosing medications when extrapolating from distantly related species.

Mild to moderate sedation was recorded as a subjective observation after both IM and IV administration of 0.6 mg of buprenorphine/kg in the present study. A pharmacodynamic study[15] conducted by our research group also revealed increases in objectively measured sedation scores in kestrels after IM administration of 0.6 mg of buprenorphine/kg. Sedation is a common effect of opioid analgesics[1] and may be desirable for some clinical applications. Because the kestrels remained reactive to physical handling at all time points, this dose of buprenorphine (when administered alone) would likely not provide sufficient sedation for intrusive procedures.

Buprenorphine is considered relatively safe among opioid drugs,[7] although there is considerable species variability in the type and severity of adverse effects. Reported effects at clinically relevant doses include mild respiratory depression in humans[34] and rodents[35]; agitation or increased physical activity in rodents,[36] horses,[37] and ruminants[18,24]; and decreased gastrointestinal tract motility in rodents,[36] horses,[37] and goats.[24] No adverse effects of buprenorphine were reported with a dose of 0.1 mg/kg in African grey parrots,[11] 0.25 mg/kg in red-tailed hawks,[14] or up to 40 mg/kg in pigeons,[38] although those studies were not designed to detect mild respiratory or gastrointestinal tract changes. In the present study, there were no clinically apparent adverse effects in American kestrels receiving doses of 0.6 mg/kg via IM and IV administration. However, it is important to mention that there has been only limited clinical evaluation of buprenorphine in raptors with traumatic injuries.[14] Caution should be exercised in applying results for single-dose experiments to clinical use for management of ongoing pain, particularly in compromised patients.

Buprenorphine hydrochloride is rapidly absorbed and has high bioavailability after IM administration to American kestrels. A single dose of 0.1, 0.3, or 0.6 mg of buprenorphine/kg administered IM induced significant thermal antinociception in kestrels for at least 6 hours.[15] In the present study, the mean plasma buprenorphine concentration for 9 hours after both IV and IM administration was above the concentration associated with analgesia in humans. Therefore, it is possible that the duration of antinociceptive effects of buprenorphine in kestrels is > 6 hours. Further pharmacodynamic and clinical evaluations are warranted in kestrels and other raptors to establish accurate dosing recommendations.

a. Buprenex, 0.3 mg/mL, Reckitt Benckiser Healthcare Ltd, Hull, Yorkshire, England.
b. Phoenix WinNonlin, version 6.0, Pharsight Corp, Cary, NC.

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