Pharmacokinetics of hydromorphone hydrochloride after intravenous and intramuscular administration of a single dose to American kestrels (*Falco sparverius*)

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

**Animals**—12 healthy adult American kestrels.

**Procedures**—A single dose of hydromorphone (0.6 mg/kg) was administered IM (pectoral muscles) and IV (right jugular vein); the time between IM and IV administration experiments was 1 month. Blood samples were collected at 5 minutes, 1 hour, and 3 hours (n = 4 birds); 0.25, 1.5, and 9 hours (4); and 0.5, 2, and 6 hours (4) after drug administration. Plasma hydromorphone concentrations were determined by means of liquid chromatography with mass spectrometry, and pharmacokinetic parameters were calculated with a noncompartmental model. Mean plasma hydromorphone concentration for each time was determined with naive averaged pharmacokinetic analysis.

**Results**—Plasma hydromorphone concentrations were detectable in 2 and 3 birds at 6 hours after IM and IV administration, respectively, but not at 9 hours after administration. The fraction of the hydromorphone dose absorbed after IM administration was 0.75. The maximum observed plasma concentration was 112.1 ng/mL (5 minutes after administration). The terminal half-life was 1.25 and 1.26 hours after IV and IM administration, respectively.

**Conclusion and Clinical Relevance**—Results indicated hydromorphone hydrochloride had high bioavailability and rapid elimination after IM administration, with a short terminal half-life, rapid plasma clearance, and large volume of distribution in American kestrels. Further studies regarding the effects of other doses, other administration routes, constant-rate infusions, and slow release formulations on the pharmacokinetics of hydromorphone hydrochloride and its metabolites in American kestrels may be indicated. (*Am J Vet Res* 2014;75:527–531)

opioids are a diverse group of drugs that bind to specific receptors in the brain, spinal cord, and peripheral tissues, modifying the transmission and perception of noxious stimuli in all vertebrate species tested. Opioid drugs are used for their analgesic properties, acting on the µ-, κ-, and δ-opioid receptors as well as the orphanin opioid-like receptor in the CNS and peripheral nervous system. The action of opioid drugs on these receptors activates G-proteins, leading to a reduction in transmission of nerve impulses and inhibition of neurotransmitter release. Few studies regarding the distribution, quantity, and function of each opioid receptor type in birds have been reported.

Hydromorphone is a µ-opioid receptor agonist with a potency approximately 5 to 7 times that of morphine in humans and analogesic efficacy and duration of action similar to oxymorphone in dogs and cats. Hydromorphone is administered by parenteral, transmucosal, and epidural routes to humans for the management of acute and chronic pain. That drug is metabolized in the liver, primarily by glucuronidation in most species, and the metabolite is excreted by the kidneys. Cost and availability have made hydromorphone an accepted alternative to oxymorphone for treatment of dogs and cats in North America. In addition, hydromorphone is an accepted alterna-

**ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Cmax</th>
<th>Maximum observed plasma concentration</th>
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<td>MRT</td>
<td>Mean residence time</td>
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effective to morphine because it does not cause histamine release after IV administration.\textsuperscript{11,13} Recent studies have provided additional information indicating the potential analgesic effects of opioid drugs in raptors. Hydromorphone hydrochloride has a dose-responsive (0.1, 0.3, and 0.6 mg/kg) thermal antinociceptive effect after IM administration to kestrels, suggesting that the drug has analgesic properties in this species.\textsuperscript{14} In contrast, butorphanol tartrate, a \( \kappa \)-opioid receptor agonist and \( \mu \)-opioid receptor antagonist, does not have a significant thermal antinociceptive effect after IM administration to kestrels at doses of 1, 3, and 6 mg/kg.\textsuperscript{15} Tramadol hydrochloride significantly increases the foot withdrawal threshold temperature for kestrels after administration of a dose of 5 mg/kg, PO; however, higher doses (15 and 30 mg/kg) result in lower antinociceptive effects.\textsuperscript{16}

Other studies have been conducted to determine the pharmacokinetics of opioid drugs in raptors. The pharmacokinetics of butorphanol has been determined for American kestrels (\textit{Falco sparverius}),\textsuperscript{13} red-tailed hawks (\textit{Buteo jamaicensis}),\textsuperscript{17} and great horned owls (\textit{Bubo virginianus}),\textsuperscript{17} and the pharmacokinetics of fentanyl has been determined for red-tailed hawks.\textsuperscript{18} The pharmacokinetics of tramadol hydrochloride has been determined for bald eagles (\textit{Haliaeetus leucocephalus})\textsuperscript{19} and red-tailed hawks.\textsuperscript{20} To our knowledge, the pharmacokinetics of hydromorphone hydrochloride has not been determined for any species of bird. The objective of the study reported here was to determine the pharmacokinetics of hydromorphone hydrochloride after IM administration to American kestrels.

Materials and Methods

Animals—Twelve 2-year-old American kestrels (6 females and 6 males) were used in the study. The mean \( \pm \) SD weight of the birds was 115 \( \pm \) 6.2 g (median, 115 g; range, 105.6 to 126.4 g). All kestrels originated from the US Geological Survey Patuxent Wildlife Research Center in Maryland, were shipped to the University of California-Davis 18 months prior to the start of the study, and were determined to be healthy on the basis of physical examinations performed prior to and during the study. Kestrels were maintained in small social groups in three 8 \( \times \) 10.3-foot rooms, with perches spaced throughout each room. They were maintained on a 12-hour light-dark cycle and fed thawed, previously frozen, medium-sized mice and provided water ad libitum. The experimental protocol was approved by the Institutional Animal Care and Use Committee of the University of California-Davis.

Experimental design—The kestrels were assigned by means of a randomization procedure to 3 groups of 4 birds each; each group had predetermined blood sample collection times. At the start of the experimental period (0 minutes), each kestral was manually restrained and received hydromorphone hydrochloride\textsuperscript{a} (0.6 mg/kg, IM) in the left pectoral muscle. Birds were manually restrained for collection of blood samples (0.3 mL) from the jugular veins or medial metatarsal veins at the following predetermined times after drug administration: 5 minutes, 1 hour, and 3 hours (\( n = 4 \) kestrels); 0.25, 1.5, and 9 hours (4); and 0.5, 2, and 6 hours (4). The birds were kept in carriers throughout the blood sample collection period without access to food or water. Blood samples were collected into tubes containing heparin lithium and placed in ice-packed containers. Within 1 hour after collection, blood samples were centrifuged at 3,500 \( \times \) g for 6 minutes. Plasma was collected and stored at \(-80^\circ\text{C}\) until analysis.

Another experiment was performed 1 month later. During the second experiment, birds were assigned to the same blood sample collection groups. Kestrels were manually restrained and received 0.6 mg of hydromorphone hydrochloride IV in the right jugular vein. Blood sample collection and processing was performed with the same procedures used during the first experiment.

Measurement of plasma hydromorphone concentrations—Hydromorphone plasma concentrations were determined by means of liquid chromatography\textsuperscript{b} with mass spectrometry.\textsuperscript{c} The qualifying ion for hydromorphone\textsuperscript{d} had an m/z of 286.077, and the quantifying ion had an m/z of 185.091 (m/z, 286.077 \( \rightarrow \) 185.091). The qualifying ion for the internal standard (hydromorphone-D\textsubscript{6})\textsuperscript{e} had an m/z of 292.193, and the quantifying ion had an m/z of 185.132 (m/z, 292.193 \( \rightarrow \) 185.132). The mobile phase consisted of acetonitrile and a 0.1% formic acid solution (500 mL, containing hydromorphone-D\textsubscript{6} [5 ng/mL] in 2% ammonium hydroxide in water) was added to 0.05 mL of plasma. Solid phase extraction cartridges\textsuperscript{f} were conditioned with methanol (1 mL) followed by 2% ammonium hydroxide in water (1 mL); then, the plasma sample or standard was loaded (total volume, 0.6 mL), the solid phase extraction cartridges\textsuperscript{f} were rinsed with 2% ammonium hydroxide in 5% methanol (1 mL), and hydromorphone was eluted with methanol (1 mL). The eluate was evaporated until dry in a water bath (40\(^\circ\text{C}\)) under a stream of air for 25 minutes and reconstituted with 200 \( \mu \)L of 2% acetonitrile in 0.1% formic acid. The injection volume was 30 \( \mu \)L. Owing to the low volume of pooled kestrel plasma samples, the standard curves were made with pooled canine plasma samples. The plasma standard curve was linear from 1 to 1,000 ng/mL and accepted if the predicted concentrations were within 15% above or below the actual concentration and the correlation coefficient was at least 0.99. The accuracy of the assay was determined with 3 replicates for each of the following hydromorphone concentrations: 2.5, 50, and 500 ng/mL in pooled kestral plasma; results were compared with the standard curve determined with canine plasma samples. On the basis of the standard curve determined with canine plasma samples, the accuracy was 98% and the coefficient of variation was 7% for detection of hydromorphone in kestral plasma samples.

Pharmacokinetic analysis—Plasma sample hydromorphone concentrations were analyzed with a naïve
Pharmacokinetic parameter | Estimate
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IV administration |  |
AUC∞ | 1.90
AUC∞(ng/mL) | 141.80
AUC∞(ng/mL) | 139.02
Plasma concentration extrapolated to 0 minutes (ng/mL) | 166.10
Plasma clearance (mL/min/kg) | 62.32
Terminal half-life (h) | 1.25
Terminal rate constant (h⁻¹) | 0.554
MRT (h) | 1.14
Volume of distribution |  |
Steady-state method (L/kg) | 4.26
Area method (L/kg) | 6.75
IM administration |  |
AUC∞ | 2.30
AUC∞(ng/mL) | 106.90
AUC∞(ng/mL) | 104.43
Plasma clearance corrected for bioavailability (mL/min/kg) | 82.66
Cmax (ng/mL) | 112.10
Terminal half-life (h) | 1.26
Terminal rate constant (h⁻¹) | 0.548
MRT (h) | 1.16
Time of Cmax (h) | 0.03
Fraction of dose absorbed (%) | 75

AUC∞ = Area under the curve extrapolated to infinity.
AUC∞ = Area under the curve up to the last measurable concentration.

Blood samples/time, except times of 0.5, 2, and 6 hours after IM administration, for which the sample size was 3 because insufficient blood sample volumes were collected for determination of plasma hydromorphone concentrations. Uniform weighting of the hydromorphone plasma concentrations was used.

**Results**

Plasma concentration-time curves and pharmacokinetic parameters of hydromorphone hydrochloride after IM and IV administration to American kestrels were summarized (Figure 1; Table 1). Hydromorphone was detected in plasma samples obtained from 2 and 3 birds at 6 hours after IM and IV administration, respectively; hydromorphone was not detected in any plasma sample obtained 9 hours after administration. For IM administration, the fraction of drug absorbed was 0.75. The Cmax was 112.1 ng/mL at 0.0833 hours (5 minutes), suggesting rapid absorption after IM administration. The terminal half-life was 1.25 and 1.26 hours after IV and IM administration, respectively.

**Discussion**

To our knowledge, the study reported here is the first in which the pharmacokinetics of hydromorphone hydrochloride was determined for a species of bird. Hydromorphone hydrochloride administered at a dose of 0.6 mg/kg, IV or IM, rapidly attained Cmax (Cmax after IM administration, 112.1 ng/mL at 5 minutes) in American kestrels. Hydromorphone was well absorbed after IM administration as indicated by the high bioavailability. Plasma concentrations of hydromorphone decreased rapidly after IV and IM administration. The short half-life of hydromorphone following IM administration (1.26 hours), the rapid plasma clearance after IV administration (62.32 mL/min/kg; hepatic blood flow, approx 59 mL/min/kg⁸), and the large volume of distribution after IV administration as determined with the area method (6.75 L/kg) for the American kestrels were similar to values of those parameters for opioids in other species.²² Interestingly, the half-life after IM administration (1.25 hours) was slightly longer than the MRT (1.16 hours). This could have been attributable to elimination of most of the drug during the distribution phase, which would result in an MRT shorter than the terminal half-life. This finding could also have been attributable to differences in the methods of calculation; the MRT was determined by dividing the area under the first moment time curve by the area under the concentration-time curve, but the terminal half-life was determined on the basis of log linear regression of the last 3 data values.

The dose of hydromorphone (0.6 mg/kg) used in the present study was the highest effective dose determined in another study conducted by personnel in...
our laboratory to evaluate the antinociceptive effects of hydromorphone hydrochloride in American kestrels. The low doses of hydromorphone evaluated in that other study14 (0.3 and 0.1 mg/kg) also had thermal antinociceptive effects. Dose-dependent pharmacokinetics of hydromorphone has been reported for dogs23; that drug could have similar pharmacokinetics in American kestrels. Thus, extrapolation of the findings of the present study for lower or higher doses during clinical use (eg, determination of low-dose continuous-rate infusions) should be performed cautiously. On the basis of results of the present study, a hydromorphone continuous-rate infusion of 0.015 mg/kg/h would result in a steady-state plasma concentration of 4 ng/mL, 0.03 mg/kg/h would result in a steady-state plasma concentration of 8 ng/mL, and 0.037 mg/kg/h would result in a steady-state plasma of 10 ng/mL. If the plasma clearance remains constant. These values were calculated with the following equation: rate = clearance × concentration at steady state. The minimum effective concentration of hydromorphone in kestrels is not known, but the pharmacokinetics and antinociceptive effects of various infusion rates of hydromorphone could be evaluated in future studies to determine minimum infusion rates and plasma concentrations associated with antinociception.

Administration of 0.6 mg of hydromorphone/kg yielded plasma concentrations > 1 ng/mL for 6 hours in 2 and 3 kestrels after IM and IV administration, respectively, with data for that time in the present study. Thermal antinociceptive effects were detected 3 to 6 hours after administration of that dose of hydromorphone in kestrels in another study.14 Plasma concentrations of hydromorphone of 2 to 3 ng/mL are anticipated to have antinociceptive effects in dogs25; in humans, analgesic effects of hydromorphone are variably related to plasma concentrations of 0.5 to 4.5 ng/mL.24 However, a direct relationship between plasma drug concentrations and antinociceptive effects cannot be inferred, and caution should be used when predicting analgesia on the basis of plasma concentration alone. Antinociceptive effects of opioids are likely determined by concentrations at receptors, which lag behind plasma concentrations.25 Also, the affinity of a drug for receptors, the quantity and distribution of receptors, and the interactions with other receptors might also determine the antinociceptive effect. Furthermore, the presence of active metabolites of hydromorphone was not determined in the present study and might vary among species. Liquid chromatography–tandem mass spectrometry analysis results for urine and plasma samples obtained from rats20 and urine samples obtained from humans27 treated with hydromorphone indicate dihydromorphine, dihydroisomorphine, and the 3-glucuronide of hydromorphone and its 6-hydroxy metabolites can be identified in these species, with the 3-glucuronide present in the highest concentrations. Domestic cats have a significantly lower capacity to glucuronidate exogenous drugs and a different metabolite profile, compared with most other mammalian species.20 Hydromorphone metabolite concentrations may be different in American kestrels versus other species.

The pharmacokinetic method used in the present study was naïve averaged pooling of drug concentrations determined for multiple birds; this was necessary because the small size of the birds precluded collection of blood samples from each kestrel at all times. A limitation of this method was that it did not allow measurement of variability in the calculated pharmacokinetic parameters because pooled concentrations were analyzed as though they were determined for a single bird.20 However, high interindividual variation in the pharmacokinetics and duration of the effects of hydromorphone has been determined for other species.13,22,23

Adverse effects of administration of hydromorphone at a dose of 0.6 mg/kg include moderate to severe sedation in some American kestrels.29 In dogs, reported adverse effects of hydromorphone include signs of nausea, vomiting, defecation, panting, vocalization, sedation, CNS depression, bradycardia, and decreased gastrointestinal tract motility after chronic use.10 Adverse effects of hydromorphone in cats include signs of nausea, ataxia, hyperesthesia, hyperthermia, and behavioral changes without concomitant tranquilization.10 Hydromorphone should be administered with caution to American kestrels and other species of birds until further studies have been conducted to evaluate cardiorespiratory and thermoregulatory effects and more clinical information is available for such animals.

Results of the present study indicated hydromorphone hydrochloride had high bioavailability and rapid elimination after IM administration, with a short terminal half-life, rapid plasma clearance, and large volume of distribution in American kestrels. Further studies would be needed to determine effects of other doses, other administration routes, constant rate infusions, and slow release formulations on the pharmacokinetics of hydromorphone hydrochloride and its metabolites in American kestrels and other avian species. Results of such studies may allow determination of further recommendations regarding administration of hydromorphone to such animals.

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