Pharmacokinetics of nalbuphine hydrochloride after intravenous and intramuscular administration to Hispaniolan Amazon parrots (*Amazona ventralis*)

Dominique L. Keller, DVM, PhD; David Sanchez-Migallon Guzman, LV, MS; Julia M. Klauer,† BS; Butch KuKanich, DVM, PhD; Steven A. Barker, PhD; Julia Rodríguez-Ramos Fernández, LV; Joanne R. Paul-Murphy, DVM

Objective—To assess the pharmacokinetics of nalbuphine HCl after IV and IM administration to Hispaniolan Amazon parrots (*Amazona ventralis*).

Animals—8 healthy adult Hispaniolan Amazon parrots of unknown sex.

Procedures—Nalbuphine HCl (12.5 mg/kg) was administered IV and IM to all birds in a complete randomized crossover study design; there was a washout period of 21 days between subsequent administrations. Plasma samples were obtained from blood collected at predetermined time points for measurement of nalbuphine concentration by use of liquid chromatography–tandem mass spectrometry. Pharmacokinetic parameters were estimated by use of computer software.

Results—Nalbuphine was rapidly eliminated with a terminal half-life of 0.33 hours and clearance of 69.95 mL/min/kg after IV administration and a half-life of 0.35 hours after IM administration. Volume of distribution was 2.01 L/kg after IV administration. The fraction of the dose absorbed was high (1.03) after IM administration. No adverse effects were detected in the parrots during the study.

Conclusions and Clinical Relevance—In Hispaniolan Amazon parrots, nalbuphine appeared to have good bioavailability after IM administration and was rapidly cleared after IV and IM administration. Safety and analgesic efficacy of various nalbuphine treatment regimens in this species require further investigation to determine the potential for clinical palliation of signs of pain in psittacine species. (*Am J Vet Res* 2011;72:741–745)

Opioids are considered the most effective class of drugs for control of pain in birds.[1] Opioids cause their effects by binding to receptors in the CNS, peripheral nervous system, and many other organ systems.

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From the Departments of Surgical Sciences (Keller, Sanchez-Migallon Guzman, Klauer) and Pathobiological Sciences (Rodríguez-Ramos Fernández), School of Veterinary Medicine, University of Wisconsin, Madison, WI 53706; the Department of Anatomy and Physiology, College of Veterinary Medicine, Kansas State University, Manhattan, KS 66506 (KuKanich); the Department of Comparative Biomedical Sciences, School of Veterinary Medicine, Louisiana State University, Baton Rouge, LA 70803 (Barker); and the Department of Veterinary Medicine and Epidemiology, School of Veterinary Medicine, University of California-Davis, Davis, CA 95616 (Paul-Murphy). Dr. Sanchez-Migallon Guzman's present address is the Department of Veterinary Medicine and Epidemiology, School of Veterinary Medicine, University of California-Davis, Davis, CA 95616.
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Address correspondence to Dr. Sanchez-Migallon Guzman (guzman@ucdavis.edu).
†Deceased.

Abbreviations

AUC_{inf}	Area under the curve from 0 to infinity
Cl	Clearance
Cmax	Maximum plasma concentration
DEA	Drug Enforcement Administration
F	Fraction of the dose absorbed
MRT_{inf}	Mean residence time from 0 to infinity
Vd_{area}	Volume of distribution determined by use of the area method
Vd_{ss}	Volume of distribution at steady state

Opioids have been found to be effective analgesics in birds, and κ-opioid receptor agonists may be the most effective opioids in birds.[2–4] This may be a result of a greater proportion of κ-opioid receptors in the CNS of birds.[5] Butorphanol, a mixed κ-opioid receptor agonist and μ-opioid receptor antagonist, is considered to be the opioid of choice for management of pain in avian species.[3,4,6–9] However, treatment regimens for currently available butorphanol HCl formulations require administration at the accepted dose range (1 to 3 mg/kg) every 2 to 3 hours.[9,10] Additionally, butorphanol is a schedule IV drug that requires extensive maintenance of records and a DEA license for prescription. Of the other opi-

oid receptor agonists-antagonists, such as nalbuphine, pentazocine, and nalorphine, only nalbuphine is not a controlled substance.[11]

Nalbuphine ([-]-17-[cyclobutylmethyl]-4, 5 α-epoxymorphinan-3, 6α, 14-triol) is a κ-opioid receptor agonist and μ-opioid receptor antagonist; therefore, it is expected to have analgesic effects on birds that are similar to those for butorphanol. Although nalbuphine has been used in human patients in the United States for relief of postoperative pain since 1979, it has not been used widely in veterinary medicine. Few studies have been conducted to investigate the sedative or analgesic effects of nalbuphine in domestic animals, and there are even fewer pharmacokinetic reports on this drug. Nalbuphine provides analgesia in rats,[12,13] rabbits,[14] cats,[15] and dogs.[16] However, the pharmacokinetics of nalbuphine vary across species, as indicated by the terminal half-life of the drug, which ranges from 1 to 2.4 hours in rabbits[17] (depending on the age of the rabbits) to 1.8 hours in rats[18] and to 2.5 hours in humans.[19] To our knowledge, there have been no studies conducted to investigate the use of nalbuphine in avian species. The purpose of the study reported here was to determine the pharmacokinetics of nalbuphine HCl after IV and IM administration to Hispaniolan Amazon parrots.

Materials and Methods

Animals—Eight adult (range, 5 to 21 years old; median, 7.3 years old) Hispaniolan Amazon parrots (*Amazona ventralis*) of unknown sex with a mean ± SD body weight of 289.6 ± 17.3 g were used in the study. All parrots were assessed as healthy on the basis of results of physical examination performed before and during the study. Parrots were maintained in flocks (4 parrots/room) in large rooms (11.2 m^2). During the study, parrots were housed in standard stainless steel laboratory cages (0.6 × 0.6 × 0.6 m) with a perch and toys. They were maintained on a 12-hour light cycle (12 hours of light and 12 hours of darkness), fed a commercial pelleted diet[a] formulated for psittacine birds, and provided fresh water ad libitum. The Institutional Animal Care and Use Committee of the University of Wisconsin School of Veterinary Medicine approved the experimental protocol.

Experimental design—A complete randomized crossover experimental design was used to evaluate plasma concentrations of nalbuphine after IV and IM administration of nalbuphine HCl. Parrots were randomly assigned by drawing pieces of paper from a bag to receive a single dose (12.5 mg/mL) of nalbuphine HCl[b] (solution contained 20 mg/mL) IM in a pectoral muscle or IV in the right brachial vein. After a washout period of 21 days, the parrots were administered nalbuphine via the other route of administration. Parrots were manually restrained for nalbuphine administration and collection of blood samples.

Blood samples (0.2 to 0.3 mL/sample) were collected from the jugular veins or brachial veins (except for the right brachial vein used for IV injection) at 5, 15, 30, 60, 90, 180, 360, and 540 minutes after IM admin-

Table 1—Pharmacokinetics of nalbuphine HCl after IV and IM administration at a dosage of 12.5 mg/kg (equivalent to 11.35 mg of nalbuphine/kg) to 8 Hispaniolan Amazon parrots (*Amazona ventralis*).

	IV				IM			
Parameter	**Geometric mean**	**Minimum**	**Median**	**Maximum**	**Geometric mean**	**Minimum**	**Median**	**Maximum**
Noncompartmental								
$AUC_{extrapolated}$ (%)	1.99	0.42	2.80	5.19	1.29	0.10	2.94	8.27
AUC_{inf} (h•g/mL)	2,704.4	1,607.1	2,365.4	5,690.7	2,781.9	1,626.1	2,615.2	6,056.6
$AUMC_{inf}$ (h•h•μg/mL)	1,257.1	572.2	1,144.3	3,357.1	1,611.8	735.5	1,517.4	5,218.4
Extrapolated concentration at time 0 (ng/mL)	4,998.6	2,885.2	4,707.0	9,699.1	NA	NA	NA	NA
Cmax (ng/mL)	NA	NA	NA	NA	3,685.0	2,780.4	3,595.7	5,374.0
Cl (mL/min/kg)	69.95	33.24	79.99	117.71	NA	NA	NA	NA
Cl/F (mL/min/kg)	NA	NA	NA	NA	68.00	31.23	72.87	116.33
Terminal half-life (h)	0.33	0.26	0.34	0.40	0.35	0.17	0.37	0.63
Terminal rate constant (1/h)	2.09	1.73	2.02	2.71	1.96	1.10	1.89	4.15
MRT_{inf} (h)	0.46	0.34	0.48	0.59	0.58	0.40	0.57	0.86
Mean absorption time (h)	NA	NA	NA	NA	NA	–0.08	0.09	0.39
Time to Cmax (h)	NA	NA	NA	NA	0.19	0.08	0.25	0.30
Vd_{ss} (L/kg)	1.95	1.18	2.15	2.79	NA	NA	NA	NA
Vd_{area} (L/kg)	2.01	1.15	2.25	2.70	NA	NA	NA	NA
Vd_{area}/F (L/kg)	NA	NA	NA	NA	2.08	1.35	2.28	2.56
F	NA	NA	NA	NA	1.03	0.42	1.07	2.23
Compartmental								
Absorption rate constant (/h)	NA	NA	NA	NA	12.17	2.76	11.41	41.22
Elimination rate constant (/h)	NA	NA	NA	NA	2.19	1.60	2.03	3.79
Vd_{area}/F (L/kg)	NA	NA	NA	NA	1.95	0.77	2.20	3.10
Correlation of observed and predicted values	NA	NA	NA	NA	0.98	0.92	0.99	1.00

$AUC_{extrapolated}$= Percentage of the area under the curve extrapolated to infinity. $AUMC_{inf}$ = Area under the first moment curve from 0 to infinity. NA = Not applicable.

istration and at 5, 15, 30, 60, 90, 180, and 360 minutes after IV administration. Blood samples were placed in lithium heparin tubes and centrifuged at 1,030 × *g* for 7 minutes within 1 hour after collection. Plasma samples were collected and stored at –70°C until analyzed.

Measurement of nalbuphine concentrations—Plasma nalbuphine concentrations were determined via high-performance liquid chromatography–tandem mass spectrometry by use of electrospray ionization in a modification of a method described elsewhere.[20] The mobile phase consisted of 0.1% formic acid in water and 0.1% formic acid in methanol with a flow rate of 250 µL/min. Separation was achieved by use of a column[c] maintained at ambient temperature (approx 21°C). Sample preparation consisted of adding 300 µL of acetonitrile that contained 250 ng of levorphanol/mL (internal standard) to 100 µL of parrot plasma. The solution was mixed by vortexing, which was followed by centrifugation. The supernatant was removed, placed in a sterile tube, and dried under nitrogen. After the material was dried, 75 µL of 0.1% formic acid in water and 75 µL of 0.1% formic acid in methanol were added to each tube, and the solution was filtered through a 0.45-µm syringe filter into a high-performance liquid chromatography vial. The injection volume was 15 µL. Plasma standard curves were prepared by adding nalbuphine HCl to untreated parrot plasma in concentrations that ranged from 1 to 5,000 ng/mL. The estimated limit of quantification was 1 ng/mL, and the limit of detection was 0.5 ng/mL.

Pharmacokinetic analysis—Pharmacokinetic analyses were performed by use of computer software.[d] The calculated noncompartmental parameters included the AUC_{inf} calculated by use of the linear trapezoidal method, percentage of the AUC extrapolated to infinity, area under the first moment curve from 0 to infinity, plasma Cl, plasma Cl/F, terminal half-life, terminal rate constant, MRT_{inf}, Vd_{area}, Vd_{area}/F, and Vd_{ss}. The Cmax and time to Cmax were determined directly from the plasma concentrations. The extrapolated concentration at time 0 was determined via log-linear regression of the first 2 time points. Mean absorption time was determined by subtracting the MRT_{inf} after IV administration from the MRT_{inf} after IM administration. The value for F was determined by dividing the AUC_{inf} after IM administration by the AUC_{inf} after IV administration.

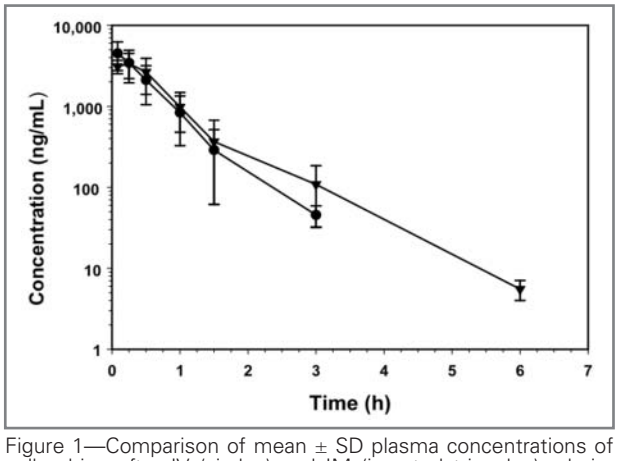

Figure 1—Comparison of mean ± SD plasma concentrations of nalbuphine after IV (circles) and IM (inverted triangles) administration of nalbuphine HCl at a dose of 12.5 mg/kg (equivalent to 11.35 mg of nalbuphine/kg) to 8 Hispaniolan Amazon parrots (*Amazona ventralis*).

A 1-compartment model with first-order input and output with no lag time was chosen for pharmacokinetic modeling after IM administration on the basis of visual examination of the observed versus predicted plots, Aikake information criterion, and residuals. A weighting factor of 1/predicted concentration was used. The calculated parameters included the absorption rate constant, elimination rate constant, and apparent Vd_{area}/F. The correlation of observed and predicted values was determined for the compartmental analysis.

Results

Pharmacokinetic parameters of nalbuphine administered IV and IM to Hispaniolan Amazon parrots were calculated (**Table 1**). Plasma concentrations of nalbuphine decreased rapidly after IV and IM administration (**Figure 1**). Plasma Cl was rapid (69.95 mL/min/kg). The Vd_{area} was 2.01 L/kg. As a result of the rapid Cl and small Vd_{area}, there was a short mean terminal half-life after IV and IM administration (0.33 and 0.35 hours, respectively). Nalbuphine appeared to be well absorbed after IM administration, with a mean F of 1.03. Mean absorption time after IM administration was short (median, 0.09 hours), which suggested rapid absorption. Nalbuphine was detected in the plasma for only 1.5 hours after IM administration in 6 of 8 parrots.

Discussion

To our knowledge, the study described here is the first report on the pharmacokinetics of nalbuphine in an avian species. Nalbuphine HCl administered IV or IM at 12.5 mg/kg rapidly attained high plasma concentrations (Cmax after IM administration, 3,684.96 ng/mL) in Hispaniolan Amazon parrots. Bioavailability was excellent, as indicated by the high value for F. Plasma concentrations of nalbuphine after IV and IM administration decreased rapidly over time. The short half-life of nalbuphine in the Hispaniolan Amazon parrots was related to a small Vd_{area} as well as to a high (rapid) Cl. This is similar to results after IV administration of butorphanol to Hispaniolan Amazon parrots.[21] Only the Vd_{area} of nalbuphine in rabbits[17] (0.32 to 0.5 L/kg) appears to be smaller than that of Hispaniolan Amazon parrots (2.01 L/kg). The Vd_{area} of nalbuphine in rats[18] and dogs[22] is > 10 L/kg, and it is > 3.6 L/kg in humans.[19] Clearance of nalbuphine is slower in humans (21.9 mL/min/kg) than it is in parrots, but it is more rapid than in rats[19] (117 mL/min/kg) and young rabbits[17] (82.2 mL/min/kg). In humans, nalbuphine is metabolized in the liver and excreted primarily in the feces.[23] Therefore, species-specific variations in hepatic metabolism may be the cause of these differences in Cl.

The dose of 12.5 mg/kg used in the present study was selected on the basis of results of a study[24] conducted by our research group to evaluate the antinociceptive effects of nalbuphine HCl in Hispaniolan Amazon parrots. This dose is much higher than that used in humans (0.14 mg/kg for a typical 70-kg adult) and

higher than clinically recommended doses for rodents and rabbits (1 to 8 mg/kg), although it is still approximately the same as the doses used in pharmacokinetic studies[17–19,25] in those species (22 mg/kg for rats and 10 mg/kg for rabbits).

The primary adverse effect of nalbuphine administration in humans is sedation.[26] A low rate of nausea or vomiting is also seen in patients receiving nalbuphine.[27] Patients have also reported transient pain after IV injection of nalbuphine.[28,29] Similarly, cats injected IV with nalbuphine had signs of discomfort at the injection site.[15] In contrast to these findings, nalbuphine injected IV and IM appeared to be well tolerated by the parrots of the present study. No adverse effects were detected, and although we did not include quantification of sedation in the present study, the parrots subjectively did not appear to be sedated after nalbuphine administration.

Although it is not possible to extrapolate analgesic efficacy from pharmacokinetic data, the antinociceptive effects of nalbuphine HCl were evaluated in a separate study[24] in Hispaniolan Amazon parrots. The results from that antinociception study[24] conducted by our research group indicated that nalbuphine has analgesic properties in this species at this dose. Similar to butorphanol, which also has rapid absorption and Cl in Hispaniolan Amazon parrots, red-tailed hawks, and great horned owls, animals receiving nalbuphine will likely require frequent administration.[22,30] In contrast to butorphanol, nalbuphine is not listed as a schedule drug by the DEA and does not require maintenance of extensive records regarding drug administration; therefore, it is easy to incorporate into clinical use. In addition, nalbuphine is less costly, compared with equipotent doses of butorphanol.

However, until additional studies are performed on the use of nalbuphine in various avian species, its use in other psittacine or nonpsittacine species will need to be extrapolated from existing data. As has been discussed elsewhere,[31,32] extrapolation of drug doses among species is fraught with potential problems, so clinicians must be aware of this when deciding on novel drug doses for use in a new species. Several methods, including linear, metabolic, and allometric scaling, have been used to determine new drug doses from existing data.[31,32] Clinicians intending to use the information in a published study for one species as the basis for selection of a drug dose in another species are encouraged to review the potential problems and complications.[31,32]

Additional studies may be warranted in birds to compare effects of long-acting esters of nalbuphine, such as nalbuphine decanoate, or to evaluate effects after oral administration of nalbuphine and expand use of this drug. Long-acting nalbuphine esters can extend considerably the duration of analgesia in rats.[13] Oral administration of nalbuphine is typically problematic because the drug has a high first-pass metabolism. However, the oral use of nalbuphine prodrugs in dogs has been found to result in a 3- to 4-fold increase in bioavailability of the drug.[33] An oral formulation of nalbuphine would potentially result in ease of administration and make it more convenient for owners to administer nalbuphine to their pets at home.

We concluded that analysis of the pharmacokinetics of nalbuphine HCl in Hispaniolan Amazon parrots suggests that nalbuphine may provide an alternative to other commonly used κ-opioid receptor agonists (eg, butorphanol). In addition, nalbuphine has the added convenience that it is not on the DEA list as a schedule drug and has a lower cost than butorphanol.

a. Kaytee Exact Rainbow Parrot, Chilton, Wis.
b. Nalbuphine HCl, Barr Laboratories, Pomona, NY.
c. Agilent Eclipse Plus C_{18} column, Agilent Technologies, Wilmington, Del.
d. WinNonlin, version 5.2, Pharsight Corp, St Louis, Mo.

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