Pharmacokinetics of fentanyl after intravenous administration in isoflurane-anesthetized red-tailed hawks (Buteo jamaicensis) and Hispaniolan Amazon parrots (Amazona ventralis)

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OBJECTIVE
To compare the disposition of fentanyl citrate after a single IV injection in isoflurane-anesthetized red-tailed hawks (Buteo jamaicensis) and Hispaniolan Amazon parrots (Amazona ventralis).

ANIMALS
6 adult red-tailed hawks and 6 adult Hispaniolan Amazon parrots.

PROCEDURES
Anesthesia was induced and maintained with isoflurane; intermittent positive-pressure ventilation was provided. The minimum alveolar concentration of isoflurane was determined for each bird by use of the bracketing method and a supramaximal electrical stimulus. Fentanyl (20 µg/kg) was administered IV. Arterial (red-tailed hawks) or jugular venous (Hispaniolan Amazon parrots) blood samples were obtained immediately before and 1, 2, 4, 8, 15, 30, 60, 120, 180, 240, and 480 minutes (red-tailed hawks) and 1, 5, 10, 15, 30, 60, 120, and 180 minutes (Hispaniolan Amazon parrots) after fentanyl administration.

RESULTS
A 3-compartment and a 2-compartment model best described fentanyl pharmacokinetics in red-tailed hawks and Hispaniolan Amazon parrots, respectively. Median apparent volume of the central compartment and volume of distribution at steady state were 222 mL/kg and 987 mL/kg, respectively, for the red-tailed hawks and 5,108 mL/kg and 13,079 mL/kg, respectively, for the Hispaniolan Amazon parrots. Median clearance and elimination half-life were 8.9 mL/min/kg and 90.22 minutes, respectively, for the red-tailed hawks and 198.8 mL/min/kg and 51.18 minutes, respectively, for the Hispaniolan Amazon parrots.

CONCLUSIONS AND CLINICAL RELEVANCE
Pharmacokinetic results for fentanyl in isoflurane-anesthetized red-tailed hawks and Hispaniolan Amazon parrots indicated large differences and should strongly discourage extrapolation of doses between these 2 species. (Am J Vet Res 2018;79:606–613)

It is common for avian practitioners to have patients that require anesthesia and pain management to enable proper and humane treatment of their conditions. For example, raptors (eg, hawks and other birds of prey) are frequently affected by traumatic injuries. Similarly, parrots (including those kept as pets) may also receive traumatic injuries. Avian practitioners are often forced to extrapolate doses and dosing intervals from mammalian pharmacokinetic data and from the limited information available for specific avian species. Because there can be substantial variations in the disposition of pharmacological agents among species, drug doses extrapolated from one species may be ineffective or harmful when administered to another species.1,2

Fentanyl, a synthetic µ-opioid receptor agonist with a relatively short time to peak analgesic effect and a short duration of action when administered as a single IV bolus, has gained widespread popularity as an adjunct anesthetic agent. Fentanyl is metabolized in the liver in mammals, and the inactive metabolites are excreted in the urine.3 The metabolic pathway has not been described in birds, but norfentanyl (a metabolite of fentanyl) has been detected in chicken after application of a fentanyl patch.3 Fentanyl is one of the most commonly used intraoperative opii-
oid analgesics in human and small animal medicine. Intravenous administration of fentanyl reportedly decreases the requirements for inhalation anesthetics in humans, dogs, and pigs. Evidence suggests that fentanyl has the ability to decrease isoflurane requirements in red-tailed hawks (Buteo jamaicensis) and Hispaniolan Amazon parrots (Amazona ventralis) by up to 55% in a dose-dependent manner.

Rational use of drugs is achieved by linking pharmacokinetic behavior with information on pharmacodynamic activity. Although the pharmacokinetics of fentanyl administered IV has been reported for various veterinary species, including dogs, horses, goats, and sheep, there are only 2 reports in which the pharmacokinetics of fentanyl in avian species has been described. Both of those studies involved SC administration and noncompartmental analysis. The elimination half-life was 29 minutes for chickens and 1.2 to 1.4 hours for cockatoos. The objective of the study reported here was to characterize the pharmacokinetics of fentanyl after IV administration to isoflurane-anesthetized red-tailed hawks and Hispaniolan Amazon parrots.

Materials and Methods

Animals

Six healthy adult red-tailed hawks (sex unknown; mean ± SD body weight, 1.21 ± 0.15 kg) and 6 healthy adult Hispaniolan Amazon parrots (3 males and 3 females; mean body weight, 280 ± 16 g) were used in the study. Birds were as assessed as healthy on the basis of results of a physical examination, CBC, serum biochemical analysis, and fecal evaluation for endoparasites (red-tailed hawks only) conducted within 14 days before the start of the study. The hawks were permanent residents of the California Raptor Center at the University of California-Davis and had been deemed as unreleasable to the wild owing to orthopedic injuries, visual deficits, or beak malformations. The parrots were part of a research colony at the University of California-Davis. Both the hawks and parrots had been used in previous studies, but none of the birds had been used within 90 days prior to this study. The study was approved by the University of California-Davis Institutional Animal Care and Use Committee.

Procedures

Birds were anesthetized and instrumented on the day of the experiment. Briefly, anesthesia was induced with isoflurane in oxygen delivered via a face mask and maintained with isoflurane in oxygen delivered via a nonrebreathing system. Body temperature was continuously measured by use of a thermistor, which was calibrated against a certified thermometer before the start of each experiment and then positioned in the esophagus caudal to the thoracic inlet. External heat was supplied with a circulating warm water pad or forced-air blanket (or both) to maintain body temperature between 38° and 40°C for the hawks and 37.4° and 40.2°C for the parrots.

After anesthesia was induced, 24-gauge, 19-mm catheters were inserted in a median ulnar vein and a superficial ulnar artery of the red-tailed hawks; a 26-gauge, 19-mm catheter was inserted in a median ulnar vein and a 22-gauge, 25-mm catheter was inserted in a jugular vein of the Hispaniolan Amazon parrots. Arterial catheterization was initially attempted percutaneously; if this failed, a surgical cutdown with aseptic techniques was performed. Catheters were secured in place with sutures.

Lactated Ringer solution was administered into the venous catheter of the hawks and parrots at a rate of 5 or 3 mL/kg/h, respectively. The arterial catheter was connected to a blood pressure transducer, which was calibrated daily against a mercury manometer and zeroed at the level of the sternum. Arterial blood pressure measurements (systolic, diastolic, and mean arterial blood pressure) and pulse rate were recorded on a physiograph. For the Hispaniolan Amazon parrots, heart rate was measured from an ECG, and blood pressure was measured by use of Doppler ultrasonography of an ulnar artery with the cuff placed at the base of the wing (cuff width, 40% of the circumference of the wing).

As part of another study, the MAC of isoflurane was determined for each bird by use of the bracketing method and supramaximal electrical stimulation. The end-tidal isoflurane concentration was then set at 0.75 times the MAC. Each bird was allowed an equilibration period of ≥ 20 minutes. Then, a bolus of fentanyl (20 µg/kg diluted with saline [0.9% NaCl] solution to achieve a standard volume of 1 mL) was administered IV; the bolus was administered over a 1-minute period to minimize the risk of adverse effects. Samples of arterial blood (red-tailed hawks) or jugular venous blood (Hispaniolan Amazon parrots) were obtained immediately before and 1, 2, 4, 8, 15, 30, 60, 120, 180, and 240 minutes (hawks) or 1, 5, 10, 15, 30, 60, 120, and 180 minutes (parrots) after the end of fentanyl administration. Samples were used for subsequent analysis of plasma concentrations of fentanyl.

After the last sample was collected, the arterial catheter in the red-tailed hawks was flushed with heparinized saline solution and the catheterized wing was bandaged to stabilize the catheter. The venous catheters were removed from the hawks, and all catheters were removed from the Hispaniolan Amazon parrots; direct compression was applied until no hemorrhage was evident. Isoflurane was then discontinued, and birds continued to receive oxygen via the nonrebreathing system until extubation. Birds then were placed in a dark holding area for recovery. An additional arterial blood sample was collected from the red-tailed hawks 480 minutes after the end of fentanyl administration by manually restraining each hawk and placing a hood over its head. For birds in which the catheter was not patent or had been removed by the hawk, a venous blood sample was col-
lected. After the final sample was collected from the hawks, the arterial catheter was removed and digital pressure applied to the area until hemostasis was achieved. Each hawk received butorphanol tartrate\(^{5}\) (1 mg/kg, IM) for analgesia following removal of the arterial catheter.

All samples were collected with a syringe and immediately transferred to tubes containing sodium heparin. Samples were stored on ice for \(\leq 30\) minutes before processing (centrifugation at 2,000 \(\times\) g for 10 minutes). Plasma was harvested, stored at \(-20^\circ\)C (maximum of 4 weeks), and then thawed for measurement of fentanyl concentrations.

**Drug analysis**

Analytical reference standards of fentanyl and fentanyl-d\(_4\) were obtained from a commercial source\(^{6}\) (solutions at concentrations of 1.0 and 0.1 mg/mL, respectively). Fentanyl working solutions were prepared by dilution of the 1-mg/mL stock solution with methanol to achieve concentrations of 10, 0.1, and 0.01 ng/mL. Fentanyl was quantified in plasma of red-tailed hawks and Hispaniolan Amazon parrots with LC-MS-MS. Plasma test, calibration, and quality control samples (blank plasma from each of the respective species fortified with analyte at 2 concentrations within the standard curve) were processed for analysis by diluting 0.2-mL aliquots with 2 mL of 0.1M phosphate buffer (pH 7.0) containing an internal standard (fentanyl-d\(_4\), 4.0 ng/mL), which was followed by centrifugation (3,000 \(\times\) g for 3 minutes).

Plasma samples were loaded onto solid-phase extraction columns\(^8\) at a flow rate of 1 to 2 mL/min by use of low-pressure nitrogen gas. Columns were rinsed with 3 mL of water, 2 mL of 1M acetic acid, and 3 mL of methanol. Each column cartridge was dried with nitrogen gas (138 kPa) for 2 minutes. Two milliliters of a methanol:ammonium hydroxide solution (97:3) was applied to the column to elute fentanyl and fentanyl-d\(_4\) into clean tubes. The fraction was collected, and the eluent was dried in a nitrogen gas evaporator. Extracts were reconstituted in 150 \(\mu\)L of the initial mobile phase (10% acetonitrile in water with 0.2% formic acid), and 30 \(\mu\)L was injected onto the LC-MS-MS system. Species-specific calibration curves were generated from species-specific matrix-matched calibrators from 0.05 to 100 ng/mL with a quadratic-weighted (1/X) regression by use of the ratio of analyte peak area to internal standard.

Quantitative analyses were performed on a triple-quadrupole mass spectrometer\(^8\) equipped with a liquid chromatography system.\(^1\) Separation of fentanyl and fentanyl-d\(_4\) was performed on a C18 column\(^\) (internal diameter, 10 cm \(\times\) 2.1 mm; particle size, 3 \(\mu\)m) with a linear gradient of acetonitrile in water and a constant concentration (0.2%) of formic acid at a flow rate of 0.4 mL/min. The initial acetonitrile concentration was held at 10% for 0.4 minutes, increased to 90% over 6.6 minutes, held at 90% for 0.3 minutes, and reequilibrated at initial conditions for 4.7 minutes. The guard column was the same composition and size as that described previously.

Detection and quantification involved the use of selective reaction monitoring of LC-MS-MS transitions for the initial product ions for fentanyl (m/z, 357.2) and fentanyl-d\(_4\) (m/z, 342.1). Fentanyl recovery was 62%. Fentanyl response curves yielded a correlation coefficient \(\geq 0.99\). The technique was optimized to provide a minimum limit of quantitation for fentanyl of 0.05 ng/mL. Accuracy (percentage of nominal concentration) for fentanyl was 104% and 98% at 1.0 and 10 ng/mL, respectively, and precision (percentage of the relative SD) was 3% and 2% at 1.0 and 10 ng/mL, respectively.

**Pharmacokinetic analysis**

Two- and 3-compartment models, with movement into and elimination from the central compartment, were fitted to plasma fentanyl concentration–time data for each bird by use of nonlinear least squares regression analysis and a computer software program.\(^{8}\) Coefficient of variation of parameter estimates, Akaike information criterion values,\(^{23}\) and visual inspection of the residual plots were used to determine the goodness of fit of models. The appropriate weighting scheme was determined by visual inspection of observed versus predicted concentrations and residual plots.

Pharmacokinetic parameters were estimated by use of a standard compartmental equation for each subject, as follows:\(^{24}\):

\[
C_t = (A X e^{-\alpha t}) + (B X e^{-\beta t}) + (C X e^{-\gamma t})
\]

where \(C_t\) is the concentration at time = \(t\); \(A\), \(B\) and \(C\) are the intercepts; \(\alpha\), \(\beta\), and \(\gamma\) are the slope of rapid distribution, slow distribution, and elimination phases of the concentration-time relationship, respectively; and \(e\) is the Euler number (ie, 2.7183). Data were reported as the median and range.

Resulting volume and rate-constant values were used to determine the amount of fentanyl delivered in separate experiments to the same birds as target-controlled infusions for pharmacodynamic evaluations. Target-controlled infusion software\(^1\) run on a personal computer was used to drive a syringe pump.\(^{26}\) During the infusion, the amount delivered as displayed by the pump was frequently verified against the computer calculation of the amount delivered and the actual amount remaining in the syringe. At each targeted concentration, the MAC of isoflurane was determined in duplicate, and blood samples were collected at the second and third positive (or negative) response points. Actual mean infusion rate was calculated as the total amount of drug administered after the computer program reported that the target had been reached divided by the duration of the infusion. Rate for the infusion was calculated as the target concentration times clearance.
Results

Arterial blood samples were collected from only 4 red-tailed hawks at 480 minutes; jugular venous samples were collected at 480 minutes from the other 2 red-tailed hawks owing to loss of the arterial catheter from those hawks. Samples were collected from the parrots at all time points.

A 3-compartment model best described the decrease in plasma fentanyl concentration after IV injection in isoflurane-anesthetized red-tailed hawks (Figure 1). A 2-compartment model best described the decrease in plasma fentanyl concentrations after IV injection in isoflurane-anesthetized Hispaniolan Amazon parrots. Pharmacokinetic parameters for fentanyl in isoflurane-anesthetized birds were summarized (Table 1).

Actual mean infusion rates, duration of the infusions, rates of infusion, and mean percentage of the target achieved were calculated (Table 2). Administration of the controlled infusions determined on the basis of the pharmacokinetic parameters calculated from the pharmacokinetic evaluation for the Hispaniolan Amazon parrots consistently resulted in plasma fentanyl concentrations lower than the target concentrations.

Discussion

Differences in fentanyl pharmacokinetics between these species indicated the ongoing need for species-specific assessments and underscored challenges and concerns when extrapolating drug doses among species. The fact that a 2-compartment model fit the data for the Hispaniolan Amazon parrots and a 3-compartment model fit the data for the red-tailed hawks was likely attributable to the sampling times for the parrots for which the circulation was more rapid; thus, even though the sampling times were similar, samples were collected after more distribution of the drug in the smaller species. When data for these 2 species, which are quite distant taxonomically, are compared, it might be expected that there would be detectable differences in the pharmacokinetic data for a given species.

Table 1—Median and range values for pharmacokinetic parameters of fentanyl after IV administration of fentanyl (20 µg/kg administered over a 1-minute period) to 6 isoflurane-anesthetized red-tailed hawks (Buteo jamaicensis) and 6 isoflurane-anesthetized Hispaniolan Amazon parrots (Amazona ventralis).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Red-tailed hawks</th>
<th>Hispaniolan Amazon parrots</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td>A (ng/mL)</td>
<td>49.2</td>
<td>38.0–82.8</td>
</tr>
<tr>
<td>B (ng/mL)</td>
<td>16.5</td>
<td>8.5–24.7</td>
</tr>
<tr>
<td>C (ng/mL)</td>
<td>8.4</td>
<td>3.7–17.7</td>
</tr>
<tr>
<td>α (/min)</td>
<td>0.409</td>
<td>0.296–1.213</td>
</tr>
<tr>
<td>β (/min)</td>
<td>0.039</td>
<td>0.020–0.100</td>
</tr>
<tr>
<td>γ (/min)</td>
<td>0.008</td>
<td>0.005–0.0105</td>
</tr>
<tr>
<td>t_{1/2α} (min)</td>
<td>1.70</td>
<td>0.57–2.34</td>
</tr>
<tr>
<td>t_{1/2β} (min)</td>
<td>18.89</td>
<td>6.96–35.29</td>
</tr>
<tr>
<td>t_{1/2γ} (min)</td>
<td>90.22</td>
<td>73.22–151.77</td>
</tr>
<tr>
<td>V₁ (mL/kg)</td>
<td>222</td>
<td>172–332</td>
</tr>
<tr>
<td>V₂ (mL/kg)</td>
<td>335</td>
<td>225–529</td>
</tr>
<tr>
<td>V₃ (mL/kg)</td>
<td>424</td>
<td>312–847</td>
</tr>
<tr>
<td>V_{ss} (mL/kg)</td>
<td>987</td>
<td>899–1,688</td>
</tr>
<tr>
<td>CL (mL/kg/min)</td>
<td>8.9</td>
<td>7.3–11.4</td>
</tr>
</tbody>
</table>

Pharmacokinetic parameters were estimated by use of a standard compartmental equation for each subject, as follows: \( C_t = (A \times e^{-\alpha t}) + (B \times e^{-\beta t}) + (C \times e^{-\gamma t}) \), where \( C_t \) is the concentration at time (t); A, B and C are the intercepts; α, β, and γ are the slope of rapid distribution, slow distribution, and elimination phases of the concentration-time relationship, respectively; and e = the Euler number (ie, 2.7183).

CL = Clearance. NA = Not applicable. t_{1/2α} = First-distribution half-life. t_{1/2β} = Second-distribution half-life for red-tailed hawks and elimination half-life for Hispaniolan Amazon parrots. t_{1/2γ} = Elimination half-life for red-tailed hawks. V₁ = Apparent volume of the first peripheral compartment. V₂ = Apparent volume of the second peripheral compartment.

Figure 1—Mean ± SD plasma fentanyl concentrations after IV administration of fentanyl (20 µg/kg administered over a 1-minute period) to 6 isoflurane-anesthetized red-tailed hawks (Buteo jamaicensis; black circles) and 6 isoflurane-anesthetized Hispaniolan Amazon parrots (Amazona ventralis; white circles).
Table 2—Mean ± SD values for variables determined for infusion of fentanyl to 6 isoflurane-anesthetized red-tailed hawks and 6 isoflurane-anesthetized Hispaniolan Amazon parrots.

<table>
<thead>
<tr>
<th>Variable</th>
<th>8</th>
<th>16</th>
<th>32</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Red-tailed hawks</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage of target concentration</td>
<td>106</td>
<td>93</td>
<td>91</td>
</tr>
<tr>
<td>Calculated infusion rate (µg/kg/min)</td>
<td>0.09 ± 0.02</td>
<td>0.17 ± 0.03</td>
<td>0.35 ± 0.06</td>
</tr>
<tr>
<td>Actual infusion rate (µg/kg/min)</td>
<td>0.12 ± 0.04</td>
<td>0.19 ± 0.06</td>
<td>0.39 ± 0.16</td>
</tr>
<tr>
<td>Duration of infusion (min)</td>
<td>171 ± 52</td>
<td>197 ± 86</td>
<td>156 ± 52</td>
</tr>
<tr>
<td><strong>Hispaniolan Amazon parrots</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage of target concentration</td>
<td>63</td>
<td>76</td>
<td>78</td>
</tr>
<tr>
<td>Calculated infusion rate (µg/kg/min)</td>
<td>1.49 ± 0.49</td>
<td>2.97 ± 0.97</td>
<td>5.95 ± 1.94</td>
</tr>
<tr>
<td>Actual infusion rate (µg/kg/min)</td>
<td>1.89 ± 0.52</td>
<td>3.63 ± 1.18</td>
<td>6.83 ± 2.03</td>
</tr>
<tr>
<td>Duration of infusion (min)</td>
<td>132 ± 39</td>
<td>88 ± 22</td>
<td>107 ± 22</td>
</tr>
</tbody>
</table>

Infusion rates were calculated from volumes delivered by a syringe pump and the duration of the infusions and on the basis of pharmacokinetic values for individual birds (clearance X target plasma concentration).

drug. Differences in pharmacokinetics of butorphanol tartrate after IM administration to Hispaniolan Amazon parrots and American kestrels (Falco sparverius), another raptor species, were attributed to a variety of factors (eg, differences in drug metabolism and protein binding or dissimilarities in the quantity, distribution, or functionality of opioid receptors) between the species. However, surprising differences in pharmacokinetic data for a given drug have been identified even among more closely related avian taxa, so it is necessary to know the pharmacokinetics of any specific drug in the target species to design an effective dosing regimen.

Plasma concentrations of fentanyl were still evident in all birds at the final sample collection time point (180 minutes for the Hispaniolan Amazon parrots and 480 minutes for the red-tailed hawks). It is interesting that at the first sample collection point, the measured concentration for the Hispaniolan Amazon parrots was less than a tenth of that measured for the red-tailed hawks and that all subsequent concentrations were less than a tenth of those for the red-tailed hawks, which indicated that clearance of the drug was much more rapid in the parrots.

To the authors’ knowledge, the apparent \(V_c\) and \(V_{ds}\) in Hispaniolan Amazon parrots of the present study are higher than those reported for any other species. These volumes were theoretical constructs because they exceeded values for the size of the birds, which would be slightly < 1 L/kg (assuming that the specific gravity of tissue exceeds that of water). The value reported for \(V_c\) was extremely high and may have been affected by the rapid circulation times and the low albumin concentrations in this species. By use of allometric estimates of cardiac output and the assumption that blood volume is 50 mL/kg, the blood volume would circulate approximately 1.6 times as fast in Hispaniolan Amazon parrots as in red-tailed hawks. In cats, for which cardiac output after dexmedetomidine administration is half the baseline value, the \(V_c\) is approximately half that obtained when cardiac output is maintained by use of a peripheral \(\alpha_2\)-adrenoreceptor antagonist. Fentanyl is thought to bind mainly to albumin in mammals, and the albumin concentrations in Hispaniolan Amazon parrots and red-tailed hawks are typically 1.3 to 1.9 g/dL, so the lower binding of albumin might have led to a higher estimate of \(V_c\) as a result of the availability of more free drug. Values for \(V_{ds}\) that exceed an animal’s size are usually found with drugs that are highly lipid soluble, but the values for the study reported here were extremely high and may have been related to the body composition of the birds. In contrast, \(V_c\) and \(V_{ds}\) for the red-tailed hawks were smaller than values reported for awake dogs, goats, and sheep; larger than values reported for awake horses and cats. The relatively small \(V_c\) for the red-tailed hawks may have been attributable, in part, to the fact that arterial blood samples were used in this study, compared with the use of venous blood samples in studies that involved other species. However, studies of horses and cats involved the use of venous blood samples, and values similar to those for the arterial blood samples of the birds in the present study were reported. Venous blood samples collected during initial phases of drug distribution may have lower concentrations than arterial blood samples collected at the same time point because of drug uptake by tissues. Additionally, collection of blood samples was started at earlier time points in the present study, compared with time points in studies involving other species for which higher \(V_c\) values were reported. This was also likely to have impacted estimated values because a delay in the onset of blood sample collection will result in lower initial concentrations and, in turn, lower concentrations extrapolated to time 0. The low \(V_{ds}\) values for the red-tailed hawks could presumably have been affected by their relatively lean body composition, compared with that of the Hispaniolan Amazon parrots, which would have resulted in lower tissue distribution for a highly lipid-soluble molecule such as fentanyl.
Clearance of fentanyl was more rapid in the Hispaniolan Amazon parrots of the present study than in any other species, and the value reported appeared to be excessive because it represented approximately 70% of the cardiac output of these birds. However, the measured fentanyl concentrations suggested that the infusion rates were still inadequate to achieve target values, so it is possible that even the high estimate of clearance did not predict the true clearance in this species. Clearance of fentanyl was slower in the red-tailed hawks than that of dogs, cats, goats, and sheep and slightly more rapid than that of horses. An attempt to use allometric scaling to determine clearance of a number of drugs in birds had only minimal success, and the formulas did not work well in birds that weighed < 1 kg. Both fentanyl clearance and terminal elimination half-life were shorter in the Hispaniolan Amazon parrots than in the red-tailed hawks, which suggested that more frequent administration may be necessary for the parrots. The terminal elimination half-life was not prolonged in the hawks because the lower volumes of distribution offset the slower clearance.

The mean infusion rate delivered by the pump for maintenance of each concentration was compared with the calculated constant infusion rate. The target-controlled infusion system calculated the administration rate by use of the following equation:

$$T \times V_c \times (k_{10} + [k_{12} \times e^{-k_{21} \times t}] + [k_{13} \times e^{-k_{31} \times t}])$$

where $T$ is the target concentration, $k_{10}$ is the elimination microrate constant, $k_{12}$ is the microrate constant for the intercompartamental drug movement between compartments 1 and 2, $k_{21}$ is the microrate constant for the intercompartamental drug movement between compartments 2 and 1, $t$ is the infusion time, $k_{13}$ is the microrate constant for the intercompartamental drug movement between compartments 1 and 3, and $k_{14}$ is the microrate constant for the intercompartamental drug movement between compartments 3 and 1 after administration of a bolus calculated from $T \times V_c$. The target-controlled infusion system updated its rate of administration every 10 seconds. From the aforementioned equation, when $t$ was large (ie, after steady state was achieved), the value for $(k_{12} \times e^{-k_{21} \times t}) + (k_{13} \times e^{-k_{31} \times t})$ approached 0; thus, the equation simplified to $T \times V_c \times k_{10} = T \times X$ clearance, which is how the rate for the calculated constant infusion was determined. Before steady state was achieved, the target-controlled infusion system administered the drug at a rate faster than the constant infusion rate because it was loading a bird with the drug. As time progressed, the rate decreased because the amount of drug to be replaced was a function of both distribution and clearance. As the drug saturated peripheral sites, the loss to be replaced was a function of both distribution and cause it was loading a bird with the drug. As time progressed, the target-controlled infusion system administered the drug at a rate faster than the constant infusion rate because it was loading a bird with the drug. As time progressed, the rate decreased because the amount of drug to be replaced was a function of both distribution and clearance. As the drug saturated peripheral sites, the loss to be replaced was a function of both distribution and clearance.
el, and the mean concentration of the 2 venous samples (0.19 ng/mL) was very close to the mean concentration of the 4 arterial blood samples (0.21 ng/mL). For the Hispaniolan Amazon parrots, the last sample was obtained at 180 minutes and had a plasma concentration of 0.12 ng/mL, but it was still possible that this short sampling time may have influenced the final models. However, extrapolating values to infinity only contributed approximately 9% of the area under the curve, which suggested that most of the data had been captured, although it was possible that if the rate of elimination decreased further, the proportion of the curve after 180 minutes might have represented a greater proportion than was predicted by use of this model.

The pharmacokinetic variables reported for the present study could provide information necessary for determination of suitable fentanyl loading and infusion doses in isoflurane-anesthetized red-tailed hawks. Results for the Hispaniolan Amazon parrots suggested that the derived pharmacokinetic parameters greatly underestimated the actual infusion rate needed to achieve a specific target concentration. There is a need for further clinical studies to determine the role of fentanyl as an anesthetic adjunct for red-tailed hawks and Hispaniolan Amazon parrots. By combining these pharmacokinetic data with the isoflurane-sparing effects of fentanyl, we can establish whether the anesthetic-sparing effects would be beneficial during surgery of clinical patients and whether these effects would carry over to provide better recoveries from anesthesia and improvements in analgesia during the postoperative period.

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Footnotes
a. ES1000 recorder, Gould Inc, Cleveland, Ohio.
c. GE/DateX-Ohmeda S/5compact, GE Healthcare Technologies, Madison, Wis.
d. Hospira Inc, Lake Forest, Ill.
e. Torbugesic, Fort Dodge Animal Health, Fort Dodge, Iowa.
f. Cerrilliant, Round Rock, Tex.
g. 5-mL 35-mg Cerex Polychrom Clin II, Cera Inc, Baldwin Park, Calif.
h. TSQ Quantum Ultra, Thermo Scientific, San Jose, Calif.
i. Model 1100, Agilent Technologies, Palo Alto, Calif.
k. WinNonlin professional, Pharsight Corp, Mountain View, Calif.
l. Rugloop I, Demed, Temse, Belgium.

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