Evaluation of the thermal antinociceptive effects and pharmacokinetics of hydromorphone hydrochloride after intramuscular administration to cockatiels (Nymphicus hollanicus)

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OBJECTIVE
To evaluate the thermal antinociceptive effects and pharmacokinetics of hydromorphone hydrochloride after IM administration to cockatiels (Nymphicus hollanicus).

ANIMALS
16 healthy adult cockatiels.

PROCEDURES
During the first of 2 study phases, each cockatiel received each of 4 treatments (hydromorphone at doses of 0.1, 0.3, and 0.6 mg/kg and saline [0.9% NaCl] solution [0.33 mL/kg; control], IM), with a 14-day interval between treatments. For each bird, foot withdrawal to a thermal stimulus was determined following assignment of an agitation-sedation score at predetermined times before and for 6 hours after each treatment. During the second phase, a subset of 12 birds received hydromorphone (0.6 mg/kg, IM), and blood samples were collected at predetermined times for 9 hours after drug administration. Plasma hydromorphone concentration was determined by liquid chromatography–mass spectrometry. Noncompartmental analysis of sparse data was used to calculate pharmacokinetic parameters.

RESULTS
Thermal withdrawal response did not differ among the 4 treatment groups at any time. Agitation-sedation scores following administration of the 0.3- and 0.6-mg/kg doses of hydromorphone differed significantly from those treated with saline solution and suggested the drug had a sedative effect. Plasma hydromorphone concentrations were > 1 ng/mL for 3 to 6 hours after drug administration in all birds.

CONCLUSIONS AND CLINICAL RELEVANCE
Results indicated that IM administration of hydromorphone at the evaluated doses did not increase the thermal withdrawal threshold of cockatiels despite plasma drug concentrations considered therapeutic for other species. Further research is necessary to evaluate the analgesic effects of hydromorphone in cockatiels. (Am J Vet Res 2018;79:820–827)

Birds are frequently examined by veterinarians for conditions such as trauma or surgical procedures for which pain management is necessary to provide compassionate care and maximize the chance for a successful clinical outcome.1 Approximately 20.3 million birds are maintained in households in the United States, and cockatiels (Nymphicus hollanicus) are the most popular species of bird owned in the United States.2 The efficacy of NSAIDs, local anesthetics (ie, lidocaine and bupivacaine), and opioids for pain management in psittacines has been investigated, and considerable interspecies variability in the pharmacokinetics and pharmacodynamics of those drugs has been identified.3

Opioids are a diverse group of drugs that are widely used for pain management. They act by reversibly binding to the δ-opioid, κ-opioid, μ-opioid, and opioid receptor like–1 receptors in the brain and peripheral nervous system.4,5 Binding of opioids to those receptors activates G-proteins, which leads to a reduction in nerve impulse transmission and inhibition of neurotransmitter release.5 Results of multiple studies6–11 indicate that κ-opioid agonist–μ-opioid antagonist opioids such as butorphanol and nalbuphine hydrochloride have significant analgesic effects in psittacines. In fact, those 2 opioids are currently recommended for acute pain management and preemptive analgesia in psittacines.3 Tramadol hydrochloride, a weak μ-opioid agonist and reuptake inhibitor of norepi-
nephrine (noradrenaline) and serotonin, has thermal antinociceptive effects in Hispaniolan Amazon parrots (*Amazona ventralis*). However, it is unclear whether tramadol can induce sufficient µ-opioid activity to produce substantial analgesia in psittacines. In white cockatoos (*Cacatua alba*), administration of fentanyl (a primarily µ-opioid agonist) at a dose of 0.02 mg/kg, IM, did not affect withdrawal thresholds to electrical or thermal stimuli; however, a 10-fold increase in the dose (0.2 mg/kg) and administration of the drug SC produced an antinociceptive response in some birds, and many birds were hyperactive for 15 to 30 minutes after fentanyl injection.

Hydromorphone is a semisynthetic full µ-opioid agonist that has been used in human medicine for alleviation of postoperative and cancer-related pain since the 1920s. In human patients, it is estimated that hydromorphone is 7.5 to 8.5 times and 5 to 7 times as potent as morphine for the alleviation of chronic and acute pain, respectively. Hydromorphone has been extensively studied in mammalian species, and µ-opioid agonists such as hydromorphone are recommended as first-choice options for the treatment of moderate to severe pain in dogs and cats. In American kestrels (*Falco sparverius*), IM administration of hydromorphone at doses of 0.1, 0.3, and 0.6 mg/kg increased the thermal nociception threshold for 3 to 6 hours; however, some birds developed moderate to severe sedation when administered the highest dose. When hydromorphone is administered to American kestrels at a dose of 0.6 mg/kg, IM, the t1/2 is 1.26 hours.

In avian species such as cockatiels, evaluation of nociception is often difficult because those species show minimal physical or verbal signs of pain. The use of a thermal stimulus is a simple, noninvasive, objective method to measure nociceptive withdrawal thresholds and evaluate the extent of cutaneous analgesia following drug administration. That method has been validated for assessment of cutaneous analgesia induced by both µ-opioid and κ-opioid agonists in multiple domestic veterinary species, including several avian species.

The objective of the study reported here was to evaluate the thermal antinociceptive effects, duration of action, and pharmacokinetic profile of hydromorphone hydrochloride following IM administration to cockatiels. We hypothesized that IM administration of hydromorphone to cockatiels would produce significant dose-dependent increases in thermal foot withdrawal thresholds and sedation and that plasma hydromorphone concentrations would be detectable for up to 6 hours after administration of the highest dose (0.6 mg/kg) evaluated.

**Materials and Methods**

**Animals**

The study consisted of 2 phases: a thermal antinociception phase and a pharmacokinetic phase. The pharmacokinetic phase was conducted approximately 2 years after the thermal antinociception phase. For the thermal antinociception phase, 16 adult cockatiels (8 males and 8 females) that ranged in age from 2 to 6 years and body weight from 78.5 to 130.8 g were selected from a research colony on the basis of behavioral cooperation (calmness, response consistency, and perching steadiness) observed during a training trial. For the pharmacokinetic phase, a subgroup of 12 cockatiels (6 males and 6 females) was selected from the 16 cockatiels used in the thermal antinociception phase. All birds were determined to be healthy on the basis of results of a physical examination prior to initiation of each phase.

Birds were individually housed in wire mesh cages, each of which measured 30.5 × 61 × 30.5 cm and contained 2 smooth wooden perches and a hanging toy. They were exposed to 12 hours of light and 12 hours of darkness on a daily basis and provided ad libitum access to water and a pelleted diet formulated for psittacines.

All study procedures were reviewed and approved by the University of California-Davis Institutional Animal Care and Use Committee. Because the study involved a species for which the antinociceptive effects, duration of action, and interindividual variability of other common analgesics have not been well evaluated, the use of a positive control group instead of a negative control group was not considered feasible for either phase.

**Thermal antinociception phase**

**Experimental design**—The thermal antinociception phase had a complete crossover design. Each bird received each of 4 treatments (an IM injection of hydromorphone hydrochloride at doses of 0.1, 0.3, and 0.6 mg/kg and saline [0.9% NaCl] solution at a dose of 0.33 mL/kg) with a 14-day washout period between treatments. A random integer generator was used to determine the order in which the treatments were administered to each bird. Birds were manually restrained, and each treatment was injected into a pectoral muscle.

**Testing procedure**—To measure thermal withdrawal responses, each bird was placed in a test box (52.1 × 10.2 × 34.3 cm) equipped with a thermal stimulus perch. The perch was located 7 cm from the front of the box and 18.4 cm from the bottom of the box. The box also contained a foam ramp that the birds could use to climb onto the perch if necessary. The test box had dark nonreflective sides and a clear front. A small video camera was mounted in front of the box, which allowed behavioral responses to be remotely monitored in real time and uninfluenced by the presence of an observer in the room. All thermal withdrawal responses were measured by 1 observer (ELH) who was unaware of (blinded to) the treatment administered.

The perch contained thermal microchips that delivered a gradually increasing (0.3°C/s) thermal stimulus to the plantar surface of the right foot of
each bird. The temperature range (30° to 60°C) for the thermal stimulus was restricted to avoid thermal damage to the foot. A bird was able to escape the brief noxious thermal stimulus by lifting its right foot (withdrawal response). Once the withdrawal response was observed, the observer activated the test perch’s rapid cooling system, and most birds were able to place the foot back on the perch within 2 to 3 seconds. The thermal withdrawal threshold was defined as the perch temperature concomitant with a foot withdrawal response. For each bird, the thermal withdrawal threshold was determined once at 30 to 60 minutes before (baseline) and at 0.5, 1.5, 3, and 6 hours after administration of each treatment.

**Agitation-sedation score and adverse effects**—While in the test box, each bird was assigned an agitation-sedation score 1 minute after mounting the perch and 1 to 3 minutes before each thermal test (ie, determination of the thermal withdrawal threshold). The agitation-sedation score could range from −4 to 3 (Appendix) and was based on observations of cockatiel-specific behaviors. Our laboratory group used a similar scoring system developed for American kestrels in another study.30

Birds were monitored for adverse effects such as vomiting and diarrhea throughout each test period. When not in the test box, birds were individually housed in towel-covered cages (30.5 X 61 X 30.5 cm) that contained a smooth wooden perch, food, and water. All birds were kept in the same room during the 7-hour data collection period following each treatment, so the observer (ELH) who was measuring thermal withdrawal thresholds could also record any adverse effects.

**Statistical analysis**—The primary outcome of interest was the thermal withdrawal threshold. A mixed linear model was created to assess the effect of treatment (saline solution or hydromorphone at 0.1, 0.3, or 0.6 mg/kg), time (baseline or 0.5, 1.5, 3, or 6 hours after treatment administration), treatment order (1 through 4), and sex on the thermal withdrawal threshold. The model also included fixed effects for all possible 2-way interactions and a random effect for bird to account for repeated measures. Residual plots were used to visually assess linearity, homogeneity of variances, normality, and outliers. Quantile plots of residuals by treatment were also evaluated to assess for normality. Residuals resulting from the fitted model were verified to be normally distributed and had no evidence of heteroscedasticity. Autocorrelation of the residuals over time was assessed with the autocorrelation function method, and no significant autocorrelation of the first or second order was detected. Various correlation structures were used to model data dependence, but none of them significantly enhanced model fit as determined by evaluation of the Akaike Information Criterion. A type III ANOVA was performed on fixed effects, and a Tukey adjustment was used for post hoc comparisons.

Agitation-sedation score data were analyzed with a mixed ordinal logit model. The model included fixed effects for time, sex, thermal withdrawal threshold, and all possible 2-way interactions for those variables as well as a random effect for bird to account for repeated measures. Residuals were graphically evaluated. All analyses were performed by use of commercial statistical software,4 and values of \( P < 0.05 \) were considered significant.

**Pharmacokinetic phase**

**Experimental design**—The 12 birds selected for the pharmacokinetic phase were manually restrained and received hydromorphoneb (0.6 mg/kg, IM) in the left pectoral muscle. Birds were also manually restrained for blood sample collection. The small size of the birds precluded blood sample collection from all birds at the 9 predetermined collection times; therefore, the birds were assigned to 3 groups (A, B, and C), each of which contained 4 birds (2 males and 2 females). Blood samples were collected from the birds in group A at 5 minutes and 1 and 3 hours after hydromorphone administration, from the birds in group B at 15 minutes and 1.5 and 9 hours after hydromorphone administration, and from birds in group C at 30 minutes and 2 and 6 hours after hydromorphone administration. All birds were individually housed in cages with access to food and water in the same room for the duration of sample collection as described for the thermal antinociception phase.

Each blood sample (0.3 mL) was collected by jugular venipuncture into a microtainer tube that contained heparin-lithium as an anticoagulant and immediately placed in an ice-packed container. Within 1 hour after collection, all samples were centrifuged at 3,500 X g for 6 minutes. Plasma was harvested from each sample and stored frozen at −80°C until analysis.

**Measurement of plasma hydromorphone concentration**—Hydromorphone was quantified in plasma samples by use of tandem liquid chromatography–mass spectrometry as described.23 A partial validation was performed with cockatiel plasma as a matrix. The response for hydromorphone was linear with a correlation coefficient of 0.99. The precision and accuracy of the assay were determined by assaying hydromorphone quality control samples (hydromorphone concentrations, 0.30, 40, and 200 ng/mL) in replicates of 6. The accuracy (ie, percentage of the nominal concentration) was 95%, 102%, and 93%, and the precision (percentage of the relative SD) was 11%, 7%, and 14% for hydromorphone concentrations of 0.30, 40, and 200 ng/mL, respectively. The assay was optimized so that the limit of quantitation for hydromorphone was 0.1 ng/mL and the limit of detection was 0.05 ng/mL.

**Pharmacokinetic analysis**—Plasma hydromorphone concentrations over time were evaluated by nonlinear least squares regression performed by use of commercially available software.5 Pharmacokinet-
ic parameters were calculated by noncompartmental analysis of sparse data, in which the plasma drug concentrations from all birds were pooled and analyzed as if they were obtained from the same bird.

Results

Thermal antinociception phase

Thermal withdrawal threshold—No adverse effects were observed following administration of any of the 4 treatments to the 16 cockatiels enrolled in the thermal antinociception phase. For all birds, the baseline thermal withdrawal threshold ranged from 43.6° to 52°C during all 4 experimental (treatment) periods. The mean ± SE thermal withdrawal threshold over time for the 4 treatment groups was summarized (Figure 1). The thermal withdrawal threshold was not significantly affected by treatment (P = 0.085), time (P = 0.259), treatment order (P = 0.378), sex (P = 0.996), or any of the 2-way interactions.

Agitation-sedation scores—The agitation-sedation scores for the saline solution treatment differed significantly from those for 0.3- and 0.6-mg/kg doses of hydromorphone. Compared with the saline solution treatment, the odds of a 1-point increase (ie, bird became more alert) in the agitation-sedation score was significantly decreased for both the 0.3- and 0.6-mg/kg doses of hydromorphone (Table 1), which indicated that hydromorphone at those doses had a sedative effect. The agitation-sedation score was not significantly affected by time (P = 0.77). Birds with low agitation-sedation scores became agitated for several seconds when handled but then resumed sedate behavior.

Pharmacokinetic phase

No adverse effects were observed following hydromorphone administration during the pharmacokinetic phase.

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Table 1—Proportional OR (95% confidence interval) for the comparison of the extent of sedation (as measured by an agitation-sedation score) observed in 16 healthy adult cockatiels (Nymphicus hollandicus) following IM administration of hydromorphone hydrochloride at each of 3 doses (0.1, 0.3, and 0.6 mg/kg) relative to that observed following IM administration of saline (0.9% NaCl) solution (0.33 mL/kg; referent).

<table>
<thead>
<tr>
<th>Hydromorphone dose (mg/kg)</th>
<th>OR (95% confidence interval)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>0.57 (0.30–1.06)</td>
<td>0.073</td>
</tr>
<tr>
<td>0.3</td>
<td>0.40 (0.22–0.75)</td>
<td>0.004</td>
</tr>
<tr>
<td>0.6</td>
<td>0.22 (0.11–0.41)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Each bird received each of the 4 treatments, with a 14-day washout period between treatments. An agitation-sedation score was assigned to each bird 30 to 60 minutes before (baseline) and at predetermined times for 6 hours after each treatment. The agitation-sedation score could range from –4 to 3 such that the extent of sedation increased as the score decreased. The agitation-sedation scores for the 3 hydromorphone treatments were compared with those for the control treatment by means of a mixed ordinal logit model. The outcome was modeled such that the proportional ORs represent the odds that the treatment caused the agitation-sedation score to increase by 1 point (ie, made the bird more alert) relative to the saline solution treatment. Therefore, a proportional OR < 1 indicates the treatment in question had a sedative effect. Values of P < 0.05 were considered significant.

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Figure 1—Estimated mean thermal withdrawal threshold for 16 healthy adult cockatiels (Nymphicus hollandicus) at predetermined times after IM administration of hydromorphone hydrochloride at doses of 0.1 (dotted line), 0.3 (dashed line), and 0.6 (solid line) mg/kg and 0.33 mL of saline (0.9% NaCl) solution/kg (control; dashed and dotted line). Each bird received each of the 4 treatments in a randomized order, and there was a 14-day washout period between treatments. For each bird, the thermal withdrawal threshold was determined once at 30 to 60 minutes before (baseline: designated as 0 minutes) and at 30, 90, 180, and 360 minutes after administration of each treatment. Error bars represent the pooled SE of the difference and are the same for all means.

Figure 2—Mean ± SE plasma hydromorphone concentration over time for 12 healthy adult cockatiels after IM administration of hydromorphone (0.6 mg/kg). The 12 birds were assigned to 3 groups (A, B, and C), each of which contained 4 birds (2 males and 2 females). Blood samples were collected from the birds in group A at 5 minutes and 1 and 3 hours after hydromorphone administration, from the birds in group B at 15 minutes and 1.5 and 9 hours after hydromorphone administration, and from birds in group C at 30 minutes and 2 and 6 hours after hydromorphone administration. Each black circle represents the mean for 1 group (n = 4 birds), and the solid line represents predicted data.
The small size of the birds precluded blood sample collection from all birds at the 9 predetermined collection times. Therefore, the 12 birds were assigned to 3 groups (A, B, and C), each of which contained 4 birds (2 males and 2 females). Blood samples were collected from the birds in group A at 5 minutes and 1 and 3 hours after hydromorphone administration, from the birds in group B at 15 minutes and 1.5 and 9 hours after hydromorphone administration, and from birds in group C at 30 minutes and 2 and 6 hours after hydromorphone administration. Pharmacokinetic parameters were calculated by noncompartmental analysis of sparse data, in which the plasma drug concentrations from all birds were pooled and analyzed as if they were obtained from the same bird.

\[
\text{AUC}_{\text{inf}} = \text{Area under the concentration-time curve extrapolated to infinity.} \quad \text{CIF} = \text{Apparent total plasma drug clearance after extravascular administration.} \quad \text{V/F} = \text{Apparent volume of distribution during the terminal phase after extravascular administration.}
\]

The plasma hydromorphone concentration over time (Figure 2) and pharmacokinetic parameters (Table 2) following IM administration of the drug at a dose of 0.6 mg/kg were summarized. The plasma hydromorphone concentration remained > 6 ng/mL for at least 3 hours and decreased to < 1 ng/mL (ie, the therapeutic concentration for most other species) by 6 hours after IM drug administration.

**Discussion**

Results of the present study indicated that IM administration of hydromorphone to cockatiels at doses of 0.1, 0.3, and 0.6 mg/kg did not significantly increase the thermal withdrawal threshold (ie, did not provide thermal antinociception), compared with the thermal withdrawal threshold following IM administration of saline solution (control). Those results differed from findings for cats,18–20,24 dogs,27 rodents,29 and American kestrels,30 which suggested that hydromorphone did provide thermal antinociception. The hydromorphone doses evaluated in the present study were selected on the basis of doses that induced thermal antinociceptive effects in American kestrels30 (0.1 to 0.6 mg/kg, IM) and were within the recommended dose range (0.05 to 0.6 mg/kg) for dogs and cats.35

Significant sedation was observed in birds following IM administration of hydromorphone at doses of 0.3 and 0.6 mg/kg. American kestrels also became noticeably sedate following IM administration of hydromorphone (0.6 mg/kg).30 However, for the American kestrels of that study,30 the mean sedation score following hydromorphone administration did not differ significantly from that following administration of saline solution (control).

No adverse effects associated with hydromorphone administration were observed in the cockatiels of the present study. In other species, the most frequently observed adverse effects associated with hydromorphone administration include signs of nausea, vomiting, and respiratory depression.20,25,28,30,35 Although no hydromorphone-associated adverse effects were observed for the cockatiels of this study, the drug should be administered with caution in avian species until further studies of its cardiorespiratory and thermal effects in birds have been completed.

For the cockatiels of the present study, IM administration of 0.6 mg of hydromorphone/kg resulted in high plasma concentrations of the drug (Cmax, 135.8 ng/mL within 15 minutes (tmax, 0.25 hours) and then a rapid decrease. The t1/2 of hydromorphone (0.6 mg/kg, IM) for the cockatiels of this study (0.99 hours) was substantially shorter than the t1/2 (1.26 hours) for American kestrels following administration of the drug at the same dose and by the same route.35 For the American kestrels of that study,31 the Cmax (112.1 ng/mL of hydromorphone was lower and the tmax (5 minutes) was shorter than the corresponding values for the cockatiels of the present study. However, when the plasma clearance and volume of distribution were corrected for the bioavailability of hydromorphone for the cockatiels of the present study, both were substantially lower than, but followed similar trends as, the corresponding values for the American kestrels of that other study.31 Additionally, the mean plasma hydromorphone concentration decreased to < 1 ng/mL between 3 and 6 hours after drug administration for the cockatiels of this study but remained > 1 ng/mL for 6 hours after drug administration for American kestrels.31

In the present study, the plasma hydromorphone concentration ranged from 6.31 to 18.90 ng/mL for the 4 birds sampled 3 hours after injection (group A). That concentration range is well above the plasma hydromorphone concentrations considered therapeutic for cats,18–20,24 dogs,25,26 and humans.36,37 A plasma hydromorphone concentration > 1 ng/mL is associated with thermal antinociception in American kestrels,30,31 and plasma hydromorphone concentrations between 2 and 3 ng/mL are expected to have antinociceptive effects in dogs.35 In human subjects with experimentally induced acute pain, plasma hydromorphone concentrations between 0.4 and 6.0 ng/mL were required for effective analgesia.36 In human patients with chronic severe pain, the therapeutic plasma hydromorphone concentration is ≥ 4.0 ng/mL.37 However, a direct relationship between plasma hydromorphone concentration and antinociceptive effects cannot be inferred, especially across species. For example, time (and by extension plasma hydromorphone concentration) had no significant effect on the thermal withdrawal threshold for the cockatiels of this study, which suggested that caution should be used when the extent of analgesia is predicted on the basis of plasma hydromorphone concentration alone. Administration of hydromorphone at doses > 0.6 mg/kg to cockatiels might produce significant antinoci-
ceptive effects. Moreover, hydromorphone at doses of 0.3 and 0.6 mg/kg induced mild sedation in the cockatiels of the present study, and further research is necessary to elucidate the sedative and analgesic effects of the drug in cockatiels.

Phylogenetic differences, as evidenced by varying antinociception among avian species, may affect key pharmacodynamic components of opioids, including cell-signaling pathways and µ-opioid receptor quantity, distribution, and affinity for active metabolites. Fentanyl (0.2 mg/kg, IM) induces significant antinociceptive effects and agitation in some white cockatoos. In another study, administration of morphine (30 mg/kg) to 2 strains of domestic fowl (Gallus gallus domesticus) induced analgesia and hyperalgesia, the extent of which varied by strain. In American kestrels, IM administration of hydromorphone at doses of 0.1, 0.3, and 0.6 mg/kg induced an increase in the thermal withdrawal threshold for 3 to 6 hours. The design of that study was almost identical to that of the present study, which suggested that the pharmacodynamics of hydromorphone vary between American kestrels and cockatiels. Results of other studies indicate that the pharmacodynamics and analgesic efficacy of opioids are related to opioid receptor properties as well as opioid peptide release by leukocyte opioid receptors. The field of opioid neuroimmunopharmacology is still developing, and knowledge gained from that field and future studies will undoubtedly facilitate elucidation of the effects of opioids in various avian species.

Variation in opioid-induced antinociceptive effects among individuals of the same species has been described and appears to be the result of multiple factors such as genotype, sex, age, noxious stimulus type, receptor type, and relative efficacy of the opioid in question. In the present study, sex was not significantly associated with the thermal withdrawal threshold, and intersubject variation accounted for 30% of the total variation observed across all 4 treatment groups of the thermal antinociception phase. For the saline (control) treatment, the SD for the thermal withdrawal threshold 6 hours after treatment administration ranged from 0.20° to 2.39°C, which was similar to, albeit greater in breadth than, that for American kestrels (0.44° to 1.24°C). The breadth of that SD range may have impaired our ability to detect statistical differences. The number of cockatiels (n = 16) evaluated during the thermal antinociception phase of the present study was greater than the number of American kestrels (11) evaluated during a similarly designed study, in which hydromorphone was determined to induce significant thermal antinociceptive effects, as well as the number of cats in other studies, in which the antinociceptive effects of opioids were assessed.

The use of thermal stimuli in conjunction with the natural perching behavior of birds is a noninvasive method for evaluation of opioid-induced modulation of nociceptive thresholds and has been used for measurement of the thermal withdrawal threshold of white cockatoos and American kestrels in addition to the cockatiels of the present study. However, this method may be limited by several species-specific factors such as behavior, sensitivity to thermal stimuli, and capability for learned behavior. A thermal stimulus targets peripheral nociceptive pathways but does not directly assess the complex nociceptive sensory pathways of the deep somatic tissues. The thermal antinociception phase of the present study had a complete crossover design that was balanced between treatment periods, and there was no evidence of carryover or learned behavior.

The small size of the cockatiels of the present study precluded blood sample collection from all birds at all 9 predetermined collection times. Thus, pharmacokinetic parameters were calculated by noncompartmental analysis of sparse data, in which the plasma drug concentrations from all birds were pooled and analyzed as if they were obtained from the same bird. A limitation of that method is that the interindividual variation could not be determined for the pharmacokinetic parameters calculated.

In the present study, IM administration of hydromorphone hydrochloride at doses of 0.1, 0.3, and 0.6 mg/kg did not significantly affect the thermal withdrawal threshold of cockatiels. However, the 0.3- and 0.6-mg/kg doses caused significant sedation, which suggested hydromorphone interacted with some opioid receptors. Additional studies with different hydromorphone formulations (eg, controlled-release liposome-encapsulated hydromorphone) and doses that use different models of nociception are necessary to fully evaluate the analgesic and adverse effects of the drug in cockatiels and other avian species and establish recommendations for its use in clinical settings.

Acknowledgments

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Footnotes

b. Hospira Inc, Lake Forest, Ill.
e. Phoenix WinNonlin, version 6.3, Pharsight Corp, Cary, NC.

References

7th ed. Stockholm, Wis: PharmaVet Inc, 2014;75:527–531. Available at:


## Appendix

Description of the agitation-sedation scoring system used to assess the behavioral responses of adult cockatiels (*Nymphicus hollandicus*) before and after IM administration of each of 4 treatments (hydromorphone hydrochloride at doses of 0.1, 0.3, and 0.6 mg/kg and saline [0.9% NaCl] solution [0.33 mL/kg; control]).

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Cockatiel does not remain on perch and constantly flies off the perch.</td>
</tr>
<tr>
<td>2</td>
<td>Cockatiel intermittently flies off perch but returns to the perch on its own.</td>
</tr>
<tr>
<td>1</td>
<td>Cockatiel remains on perch but constantly and attentively looks around.</td>
</tr>
<tr>
<td>0</td>
<td>Cockatiel remains on perch and does not look around but is reactive to movement that takes place in front of the test box.</td>
</tr>
<tr>
<td>–1</td>
<td>Cockatiel has only a sluggish response to movement that takes place in front of the box or cage and appears off balance or struggles to stay on the perch.</td>
</tr>
<tr>
<td>–2</td>
<td>Cockatiel does not react to movement that takes place in front of the box or cage, reacts only if the back of the test box is opened and a hand is inserted into the box or cage, and repeatedly falls off the perch.</td>
</tr>
<tr>
<td>–3</td>
<td>Cockatiel is responsive only when touched.</td>
</tr>
<tr>
<td>–4</td>
<td>Cockatiel is unresponsive to any visual or tactile stimulus.</td>
</tr>
</tbody>
</table>