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High doses of buprenorphine hydrochloride are well tolerated and produce a mild and prolonged thermal antinociceptive effect in orange-winged Amazon parrots (*Amazona amazonica*)

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Objective
To evaluate the duration of action and antinociceptive and sedative effects of buprenorphine hydrochloride following SC administration to orange-winged Amazon parrots (*Amazona amazonica*).

Methods
10 adult, healthy Amazon parrots were included. High-concentration buprenorphine formulation (1.8 mg/mL and 0.1, 1, and 2 mg/kg) and saline solution (0.9% NaCl; 0.55 mL/kg) were administered SC to the parrots in a within-subjects, complete, masked crossover study design. Foot withdrawal thermal threshold was determined prior to administration of treatment and 0.5, 1.5, 3, and 6 hours postinjection. Agitation-sedation scores were determined 1 to 2 minutes prior to each thermal challenge.

Results
Buprenorphine at 2 mg/kg significantly increased the thermal foot withdrawal threshold, whereas lower doses evaluated did not have a significant effect. Although no significant interaction effect of treatment*time was observed, the graphical data suggest that the effect could increase over time and still be present at the 6-hour time point. No significant effect of buprenorphine on agitation-sedation score or nausea-like behavior was observed.

Conclusions
SC administration of buprenorphine at 2 mg/kg has a mild thermal antinociceptive effect in orange-winged Amazon parrots, which graphically appears to have a slow onset and last for the duration of the testing times. In addition, buprenorphine did not cause agitation or sedation, nausea-like behavior, or vomiting. Further studies are needed to fully evaluate the effects of buprenorphine in psittacines.

Clinical Relevance
Buprenorphine hydrochloride could be considered for pain management in the orange-winged Amazon parrot and does not cause significant adverse effects following single SC administration.

Keywords: analgesia, avian, opioid, psittacine, pain management

Birds are the fourth most common companion pet in the US,[1] and Amazon parrots remain 1 of the most popular avian species.[2] Due to their popularity, psittacines are frequently seen in veterinary hospitals as well as in zoological collections and native range wildlife rehabilitation programs.[3–5] When medical care is necessary, providing appropriate pain management is a mandatory facet of patient welfare.[6]

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In small-animal medicine, opioids provide both consistent and effective analgesia.[7] The clinical use of opioids in avian medicine, however, is confounded by inconsistent effects of the drugs and limited studies.[8] Four opioid receptors have been identified: δ-opioid, κ-opioid, μ-opioid, and nociceptin-opioid.[9] Of those receptors, studies[10–15] in grey and Timneh parrots (*Psittacus erithacus* and *Psittacus timneh*), Amazon parrots (*Amazona ventralis* and *Amazona amazonica*), and green-cheeked conures (*Pyrrhura molinae*) have revealed that the κ-opioid agonists μ-opioid antagonists, butorphanol and nalbuphine hydrochloride, provide analgesia. Recent research has shown that

hydromorphone, a full μ-opioid agonist, may be clinically useful as an analgesic in orange-winged Amazon parrots (OWAPs; *A amazonica*), though agitation at higher doses (1 and 2 mg/kg, IM) resulted in the recommendation to utilize the drug at lower doses.[16] Similarly, in an older study[17] with fentanyl in white cockatoos (*Cacatua alba*), another μ-opioid agonist provided analgesia but induced hyperactivity at higher doses (0.2 mg/kg, SC). Additionally, the α-adrenergic, serotonergic, weak μ-opioid agonist tramadol hydrochloride demonstrated significant analgesic properties in Hispaniolan Amazon parrots (*A ventralis*).[18,19] The wide array of response to opioid analgesia in psittacine species alone highlights the importance and need for further investigation to determine the appropriate opioid analgesics for use in parrots.

Buprenorphine hydrochloride acts as both a full μ-opioid agonist and a κ-opioid antagonist.[20] No analgesic efficacy of buprenorphine (0.1 mg/kg) was reported in the grey and Timneh parrots (*P erithacus* and *P timneh*) despite maintaining above-target plasma concentrations for humans for at least 2 hours.[12,21] In cockatiels (*Nymphicus hollandicus*), 0.6, 1.2, and 1.8 mg/kg, IM, of buprenorphine hydrochloride did not increase the thermal antinociceptive threshold. No significant changes in agitation-sedation scores were detected between all doses of buprenorphine and the control treatment.[22] Plasma buprenorphine concentrations in the same study following a 0.6-mg/kg, IM, dose were > 1 ng/mL in all 4 birds evaluated 9 hours post drug administration. Investigation into analgesic efficacy following the delivery of higher doses of buprenorphine in a different psittacine species are warranted given the interspecies variability of opioids in birds and the newly available high-concentration formulation of the drug.

The use of a thermal stimulus to evaluate the efficacy of analgesic drugs at the cutaneous surface is noninvasive and easily conducted. This technique has been used for opioid studies[10–12,14–19,22] in many psittacine species, including the OWAPs. The objective of this study was to determine if buprenorphine would provide thermal antinociceptive effects suggestive of analgesia and evaluate the duration of action, as well as sedation-agitation effects and other adverse effects, in OWAPs. We hypothesized that high-concentration buprenorphine hydrochloride would produce a dose-dependent increase in thermal foot withdrawal threshold and sedation in OWAP.

Methods

Animals

Ten adult OWAPs (5 males and 5 females; 4 to 17 years old; body weight, 327.2 to 543.2 g) were used in this study. All birds were healthy on physical examination prior to experimentation. The 10 birds selected for this study were deemed candidates for the testing procedure as evidenced by their ease of handling, cooperative demeanor, response consistency, and perching steadiness during a full training trial. Parrots were housed in individual wire mesh cages that measured either 66 X 66 X 107 to 114 cm or 81 X 61 X 142 cm. Each cage contained 2 perches and a hanging toy. Birds were exposed to 12 hours of light and 12 hours of darkness daily. All birds were provided ad libitum access to food (Roudybush Daily Maintenance Crumble; Roudybush Inc) and water. A positive control group was employed in this study due to the lack of information (eg, antinociceptive effect, adverse effect, duration of action, interindividual variability) concerning the use of opioid analgesics in this species. This study protocol was approved by the University of California-Davis IACUC (protocol No. 19508).

Experimental design

A within-subjects, masked, complete crossover study was designed. Treatment order was assigned to each bird prior to the study via a randomization procedure (random.org random integer generator by DSMG). The random generation of treatment sequences was repeated until the lowest number of treatment sequence repetition for each day and period of testing was achieved. The 4 treatments included an SC injection of buprenorphine (Simbadol; 1.8 mg/mL) at 0.1, 1, and 2 mg/kg and saline solution (0.9% NaCL at 0.55 mL/kg; same volume to the 1 mg/kg buprenorphine dose). A 7-day washout period was followed between treatments. All treatments were administered SC in the left flank using a 22-gauge needle and 1-mL Luer-lock syringe.

Testing procedure

Thermal withdrawal responses were measured in a constructed testing box (34 cm high, 13 cm wide, and 28 cm deep) equipped with a thermal stimulus perch. The test box had dark, nonreflective sides with a clear front that allowed a masked observer (JMD) to monitor real-time behavioral responses via a small camera placed in front of the box. The perch was placed 11 cm from the front of the box and 13 cm from the bottom of the box.

Thermal microchips in the test perch delivered a gradually increasing (0.4 °C/s) thermal stimulus to the plantar surface of each bird's left foot. The thermal range was limited from 35 to 58.2 °C to avoid tissue damage to the plantar surface of the foot. Birds could escape the brief noxious thermal stimulus by lifting their foot. Upon withdrawal response, the observer activated the perch-rotating system, which caused the left side of the perch, with the thermal apparatus, to rotate 180° to terminate contact between the foot and the heated surface of the perch.

The thermal foot withdrawal threshold was defined as the perch temperature concomitant with a foot withdrawal response. A baseline thermal withdrawal threshold value was generated for each bird within each experimental period using a single measurement obtained 1 to 2 minutes before treatment administration. Measurements of the thermal foot withdrawal threshold were obtained via a single measurement at 0.5, 1.5, 3, and 6 hours after administration of the assigned treatment. All thermal thresholds were determined by a single blinded observer (JMD) who had no knowledge of

treatment allocation and could not visualize each bird's treatment administration.

Agitation-sedation score and adverse effects

All birds were observed in the test box 1 to 2 minutes before each thermal test and assigned an agitation-sedation score. The agitation-sedation scoring system was based on the Ramsay sedation scale and the Richmond agitation-sedation scale and modified for parrot behavior **(Supplementary Table S1)** as reported previously for OWAP.[15] Birds were monitored for adverse effects, such as nausea-like behavior (absent or present as evidenced by opening the beak and moving the tongue back and forth) or regurgitation/vomiting (absent or present). Between testing times, birds were housed individually in carriers (53 X 41 X 38 cm) covered by a towel with access to food and water. Birds remained in the same testing room during the data collection for each experimental period to allow for the monitoring and characterization of adverse effects.

Statistical analysis

Data were analyzed by the use of statistical software (R, version 3.0.1; R Foundation for Statistical Computing; http://www.R-project.org/). The endpoint of interest was the thermal threshold for each OWAP at any time point after each treatment administration. Longitudinal data analysis was performed with linear mixed modeling on the withdrawal temperature as the outcome variable using time, treatments (saline and 0.1 mg/kg, 1 mg/kg, and 2 mg/kg buprenorphine), order of treatments, sex, age, weight, baseline values, and all interactions as fixed effects and birds as a random effect. Residual plots were used to assess linearity, homogeneity of variances, normality, and outliers. Quantile plots were also performed on the residuals by treatment groups for normality assessment. 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 using the autocorrelation function method. A compound symmetry covariance structure was used for the correlation matrix. A type III analysis of variance was performed on the fixed effects, and post hoc comparisons were performed using a Tukey adjustment. Sedation and nausea score data were analyzed using an ordinal logit mixed model with scores as the outcome ordinal categorical variable; time, sex, age, treatment, and interactions as fixed variable; and birds as the random variable. Other binary scores were analyzed using logit mixed models. Residuals were evaluated graphically. Values of $P < .05$ were considered significant.

Results

One bird was removed from study prior to its completion due to the management of an unrelated injury. For the thermal antinociception testing (n = 9), baseline values for thermal withdrawal threshold ranged from 46.1 to 55.7 °C **(Figure 1)**. Individual variability in response accounted for 54% of the total variability of the model, and the SD was 1.0 °C (total SD of the model, 1.9 °C).

There was no significant interaction effect of treatment X time ($P = .15$; Figure 1) on the response accounting for individual baseline withdrawal temperature. However, there was a significant main effect of treatment ($P = .034$), with the 2-mg/kg dose resulting in an overall higher thermal foot withdrawal threshold ($P = .022$) by 1.0 ± 0.4 °C. There was no significant effect of sex, age, weight, or order of treatment (all $P > .05$).

There was a significant effect of the baseline value ($P < .001$) on the foot withdrawal temperature, which was 0.44 ± 0.07 °C for each 1 °C of change in baseline value, suggesting that as the baseline value increased, OWAPs had less tolerance for further increases in perch temperature.

For the agitation-sedation score, there was no significant effect of treatment, time, or their

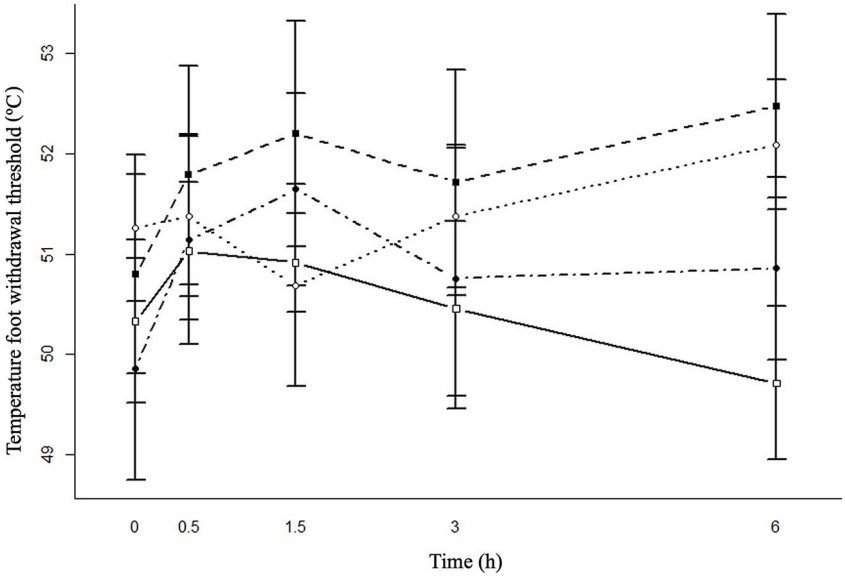

Figure 1—Estimated mean ± SE thermal foot withdrawal threshold for 9 orange-winged Amazon parrots (*Amazona amazonica*) following SC administration of saline (0.9% NaCl) solution (0.55 mL/kg; control treatment, white squares with solid line) and concentrated buprenorphine injection at doses of 0.1 mg/kg (black circles with dashed-and-dotted line), 1 mg/kg (white circle with dotted line), and 2 mg/kg (black squares with dashed lines). Baseline values (time 0) were acquired just prior to receipt of assigned treatment. A 7-day interval was observed between treatments. There was a significant main effect of treatment ($P = .034$) with the 2-mg/kg dose.

interaction. For the nausea score, there was no significant effect of any variable (all $P > .44$). Heavier birds had lower odds of displaying agitation, with an OR of 0.2 (95% CI, 0.07 to 0.6; $P < .001$) with every 100-g increase in weight. Younger birds had higher odds of displaying agitation, with an OR of 14.3 (95% CI, 4 to 49; $P < .001$). There was no regurgitation or vomiting noted.

Discussion

Buprenorphine hydrochloride administered SC to OWAPs at 2 mg/kg significantly increased the thermal foot withdrawal threshold when compared with the results for the control treatment, whereas the evaluated lower doses of 0.1 and 1 mg/kg did not have a significant effect. This contrasts the findings in a similar study[22] in cockatiels, where 0.6, 1.2, and 1.8 mg/kg buprenorphine hydrochloride did not result in thermal antinociception effects. The cockatiel study used a different formulation of 0.3 mg/mL of buprenorphine hydrochloride and a slightly lower high dose. Concentrated buprenorphine is reported to be rapidly absorbed and to reach plasma drug concentrations considered analgesic in the red-tailed hawk, though this bird is a raptor, and pharmacodynamic analysis is not yet reported in this species.[23] While no major difference would be expected from a higher-concentration formulation in terms of pharmacodynamics or SC administration instead of IM, studies of the thermal analgesic effects of concentrated buprenorphine hydrochloride and/or SC administration would need to be performed in the cockatiels to exclude any effect that a different formulation or route of administration may have had.

In the present study, there was a lack of significant time effect observed, even though graphically it is suggested that the effect could increase over time and still be present at the 6-hour time point. The lack of significant effect is likely the result of the relatively small magnitude of thermal antinociceptive effect and the sensitivity of the thermal perch model utilized in this study. Considering these limitations, the exact time to initial effect, as well as the duration of action, could not be captured accurately. In other species, buprenorphine has a relatively slow onset on action and a longer duration of effect than other opioids, which could also be the case in Amazon parrots. This was demonstrated in American kestrels (*Falco sparverius*), where the larger magnitude of the thermal antinociceptive effect was observed at much lower doses.[24] Future evaluation of SC buprenorphine in OWAPs should assess thermal antinociception beyond 6 hours.

A previous study[15] of the thermal antinociceptive effects of IM butorphanol tartrate in OWAPs supported the provision of analgesia when tested 30 minutes after administration but not at 90 minutes postreceipt. In contrast, thermal antinociception of greater magnitude and duration was observed when OWAPs received IM hydromorphone compared to that observed for IM butorphanol.[15,16] These previous results differ from the ones in the present study in terms of the magnitude and presumed onset and duration of the effect. Some of these differences regarding magnitude of effect and duration of action amongst opioids are also observed in mammals. Furthermore, our findings in OWAPs contrast other species of birds where thermal antinociceptive properties of opioids have been demonstrated, such as in the American kestrel, where the magnitude of the effect was greater at much lower doses.[25] One potential explanation for this discrepancy is innate physiological differences that exist when comparing different avian species. In the blue-fronted Amazon parrots (*Amazona aestiva*), a species in the same genus as the OWAP, widespread tissue expression of μ-opioid receptor mRNA has been reported.[26] However, the correlation between mRNA level and protein expression can be as little as 40%, which may factor into the lack of analgesic efficacy of buprenorphine witnessed across parrots.[27]

No sedation or nausea-like behavior was observed following the receipt of buprenorphine injection in the present study. This contrasts an OWAP study[16] performed by our research group where a dose of hydromorphone hydrochloride increased the odds of what was described as nausea-like behaviors. Opioid-induced nausea and vomiting syndrome is frequently observed in veterinary species, attributed to the activation of μ-opioid receptors in the chemoreceptor trigger zone, the delay of gastric emptying, and an increase of vestibular sensitivity.[28] Buprenorphine hydrochloride is classified as a mixed opioid μ-receptor agonist, and it is unknown if the κ-receptor antagonism may reduce nausea-like effects. This contrasts κ-receptor agonism, which, like μ-opioid receptor agonism, is associated with nausea.[28,29] This study also found no significant effect of sex nor age on buprenorphine-associated thermal antinociception, which is similar to the study[16] evaluating thermal antinociceptive effects of hydromorphone in OWAP.

A previous pharmacodynamic study[16] utilizing these parrots reported individual variability in response, accounting for 23.9% of the total variability model. In the present study performing tests on the same population of OWAPs, the individual variability rose to 54% of the total variability. In the present study, OWAPs receiving the saline (control) treatment had a within-bird SD for foot withdrawal temperature of 0.53 to 3.56 °C over the 6-hour period. This range is higher than the 1.34 to 2.24 °C observed in a different study of OWAPs[16] and the 0.23 to 3.09 °C reported in cockatiels[22] but less than that observed in a study in Hispaniolan Amazon parrots,[11] ranging from 0.50 to 7.47 °C. The increased variability observed in this study suggests that the parrots may have been less consistent in their responses, which may be attributed to individual parrots' behavior, effects of the drug, or a combination of the 2.

One limitation of the present study is the small sample size (n = 9) with a wide variation in ages. It is unknown if exploring the antinociceptive effect of buprenorphine in OWAPs in a larger population would yield a significant age effect. The increased odds of younger birds displaying agitation suggests

that selecting older birds as test subjects may reduce the incidence of erratic behavior, although agitation odds as displayed by birds in this study may simply be the result of temporal differences in opioid receptor densities and drug choice. Significant differences in μ-opioid receptor density are reported when comparing adult to juvenile rats.[30] In songbirds, age-related changes in μ- and δ-opioid receptor densities are similarly reported.[31] Opioid receptor density as it pertains to avian analgesia and psittacines and in consideration of temporal development remains unexplored, and its influence in this study is unknown.

In the present study, a highly concentrated buprenorphine hydrochloride administered SC at a dose of 2 mg/kg significantly increased the foot withdrawal threshold to a thermal noxious stimulus in OWAPs. However, the lack of a significant effect on specific time points tested precluded evaluation of the exact time of initial effect and duration of action with accuracy, granted that graphically the data suggest that might have had a slow onset and lasted for the duration of the testing time. In addition, this dose did not cause agitation or nausea-like behavior or vomiting, which makes it safe in that regard. Additional studies with other types of stimulation and doses are needed to fully evaluate the analgesic and adverse effects of buprenorphine in OWAPs and other psittacine species.

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Disclosures

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Supplementary Materials

Supplementary materials are posted online at the journal website: avmajournals.avma.org.