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Original Study

Comparison of Intramuscular and Intranasal Midazolam in Great Horned Owls (*Bubo virginianus*)

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Abstract: There are few studies evaluating safe and effective sedatives for wild birds. Most sedatives are injectable drugs that are commonly administered intramuscularly (IM) or subcutaneously (SC); however, needle injuries occasionally occur from the bird struggling during the injection. Previous research in parrots and other bird species explored the effects of intranasal (IN) midazolam compared with IM administration; however, this delivery method has not been well studied in wild birds, such as raptors. To our knowledge, there is only 1 study that has been published evaluating midazolam IN in a raptor. In the present study, we compared midazolam sedation via IM and IN administration in great horned owls (*Bubo virginianus*; GHOW). Six GHOWs were randomly assigned to receive midazolam at 2 mg/kg IN or IM using a crossover study design. For each treatment type, sedation score, heart rate, respiratory rate, and muscle tone were recorded. Linear mixed models were used to interpret and compare the data. Results for both IN and IM treatments showed no significant difference in onset of sedation, overall muscle tone in the wings, legs, and jaw, heart rate, or respiratory rate over time. These data indicate that IN midazolam sedation at the same dose used IM is a viable option for sedation of GHOWs. Further research is needed for other species of raptors.

Key words: avian, great horned owl, *Bubo virginianus*, midazolam, intranasal, raptor

INTRODUCTION

Sedation is routinely and successfully used in raptors for various procedures, including physical examination, radiographic imaging, and venipuncture, to reduce stress and increase animal welfare. While sedation methods have been explored in many domesticated animals, including birds, sedation protocols for wild birds are still lacking. Studying the effects of different sedation delivery methods in wild birds of prey is extremely useful in rehabilitation and conservation settings.

Midazolam is a benzodiazepine sedative and anxiolytic similar in action to diazepam. Midazolam is an injectable sedative and is usually administered intramuscular (IM) or intravenous (IV) in small animals, based on the package insert. Several published studies have evaluated the differences in dosing and/or effects of midazolam administered intranasally (IN) to birds.[1–15] Intranasal administration of xylazine, diazepam, and midazolam in budgerigars (*Melopsittacus undulatus*) was found to be safe and effective,[2] and midazolam and ketamine IN exhibited faster onset of sedation but slower recovery times compared with IM administration in the same species.[3] Intranasal midazolam and butorphanol led to a rapid onset of sedation in cockatiels (*Nymphicus hollandicus*), causing deeper sedation than midazolam alone.[4] Intranasal midazolam, butorphanol, and alfaxalone provided adequate sedation in Quaker parrots (*Myiopsitta monachus*) for radiographic positioning.[5] Additionally, IN midazolam provided adequate sedation for gastrointestinal contrast studies in cockatiels.[14] Intranasal midazolam was inadequate for immobilizing pigeons (*Columba livia domesticus*) for ventrodorsal radiographs; however, the birds could be placed into dorsal recumbency once IN dexmedetomidine was administered.[6] Even though faster recovery with less agitation and

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vocalization occurred, midazolam and ketamine IN provided less consistent sedation than when administered IM in chickens (*Gallus gallus domesticus*).[13]

Intranasal midazolam has also been evaluated in some wild bird species. Adequate sedation was obtained in wild-caught blue-fronted Amazon parrots (*Amazona aestiva*) and orange-winged Amazon parrots (*Amazona amazonica*).[7] The odds of mortality were 5.3 times higher in Surf scoters (*Melanitta perspicillata*) administered 0.9% saline IN than those given midazolam IN during intracoelomic transmitter placement.[16] To our knowledge, the only raptor species in which midazolam IN has been investigated are Eurasian buzzards (*Buteo buteo*).[1] Midazolam 2 mg/kg IN effectively sedated Eurasian buzzards in 6.7 ± 1.6 minutes (mean ± SD); heart rate and respiratory rate were mildly decreased for the duration of sedation; and flumazenil 0.05 mg/kg IN reversed midazolam completely in 14.1 ± 1.8 minutes.[1]

This study aimed to determine whether midazolam IN was as effective as midazolam IM for providing sedation in great horned owls (*Bubo virginianus*; GHOW). We hypothesized that the same dose of midazolam IN would be as effective as IM administration for performing a physical examination without adverse effects.

MATERIALS AND METHODS

Six adult GHOW were used for this study. The birds were deemed unreleasable due to their injuries and were permanent residents of the California Raptor Center (School of Veterinary Medicine, University of California-Davis, Davis, CA, USA). The birds were determined to be healthy based on a physical examination, complete blood count, and biochemistry panel. This study was approved by the Institutional Animal Care and Use Committee (IACUC #23435). All birds were fasted for 12 hours before sedation to prevent possible regurgitation. Before each trial, birds were hooded using a stockinette and weighed on a scale to ensure accurate dosing. In the first trial, each GHOW was randomly assigned a number from 1 to 6 using a random number generator to determine the order that birds would be sedated (www.random.org). On the first morning of the study, the route of administration (IN or IM) was determined by pulling a piece of paper with either IM or IN written on it from a basket; that was then the administration route used for that day for that bird. Only the handler and the person delivering the drug were not blinded to the route of administration for each bird; the person collecting all data was blinded. A 7-day washout period was provided between trials. The second treatment for each bird used the route of administration not used during the first trial.

Table 1. Sedation scoring system used for great horned owls (n = 6; *Bubo virginianus*) administered 2 mg/kg of midazolam either intramuscular or intranasal.

Score 0:	No sedation
Score 1:	Minimal sedation; wide-based stance, resists manual restraint, head and/or wing droop
Score 2:	Mild sedation; sternal recumbency, resists manual restraint, head and/or wing droop
Score 3:	Moderate sedation; can be placed in dorsal recumbency but with some resistance, head and/or wing droop
Score 4:	Heavy sedation; can be placed in dorsal recumbency without resistance, head and/or wing droop

The sedation scoring system used in this study was previously published.[16]

Before the delivery of midazolam, each bird was hooded again, and a complete physical examination was performed. The muscle tone of the wings and legs was assessed by a single person, extending each limb to its fullest extent just before sedation, which served as the baseline. Muscle tone was scored subjectively from 0.5 to 3 in 0.5 increments, based on the bird's resistance or lack thereof to extension. Heart and respiratory rates were recorded as baseline data before sedation. Midazolam HCl, 2 mg/kg (Midazolam HCl 5 mg/mL, Hospira, Lake Forest, IL, USA) was administered IM or IN while the bird was still under manual restraint. For IN sedation, half the dose of midazolam (approximately 0.20–0.25 mL per nostril) was administered into each nostril. Sneezing, struggling, or incomplete delivery of the drug was recorded. For IM sedation, a dose of 2mg/kg was administered IM into the pectoral muscles using a 25-G needle on a 1-mL syringe. Fifteen minutes after the sedatives were administered, a physical examination was repeated, and heart rate, respiratory rate, sedation scores, and wing and leg muscle tone via extension were then recorded every 5 minutes throughout the sedation period. The time to sedation was determined by the owl's stance and level of awareness. Sedation scoring was determined using a published scoring system by Escalante et al (Table 1).[17] Muscle tone was also scored using previously published criteria (Table 2).[18] Birds were monitored throughout the sedation period closely for any adverse effects, and any abnormal behaviors were recorded.

Flumazenil (Flumazenil, 1 mg/10 mL, Fresenius Medical Care, Waltham, MA, USA), the reversal agent for midazolam, was administered at 0.05 mg/kg IM or IN, depending on the administration route of that day,

Table 2. Muscle tone scoring used for great horned owls (n = 6; *Bubo virginianus*) administered midazolam 2 mg/kg intramuscular and intranasal.

Score 0: None/no muscle tone
Score 1: Mild detectable but reduced muscle tone
Score 2: Moderate detectable contraction of the muscle
Score 3: Strong marked contraction and/or defense movements in response to extension

Muscle scoring was determined using a previously published scoring scale.[17]

30 minutes after midazolam injection. Recovery was monitored for the following 30 minutes. The bird was considered recovered when it was alert and responsive (tracking personnel with their eyes), had no evidence of head or wing droop, and could stand without ataxia.

Linear mixed models were used to assess the effects of treatment, time, and their interaction on heart and respiratory rates, with individual owls serving as the random effect. Assumptions of linearity, homoscedasticity, and the absence of outliers were assessed using residual plots and quantile plots of residuals. Post-hoc tests were performed using analysis of variance on the fixed effects with a Tukey adjustment. Sedation, muscle scores (wing and leg), and treatment were assessed using mixed ordinal logit models with individual owls as the random effect. The proportional odds assumption was checked using a likelihood ratio test. The R version 4.3.2, 2024 (R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analysis. A $P < 0.05$ was used to determine statistical significance.

RESULTS

Intranasal administration of midazolam did not produce sneezing or head-shaking behaviors, thus the entire IN dose was administered without loss in any bird. Midazolam administered either IM or IN did not have a significant effect on heart rate ($P = 0.26$; Fig 1) or respiratory rate ($P = 0.48$; Fig 2) between the 2 treatments over the sedation period. Regardless of treatment, when comparing changes over time, heart rate did not significantly change in any GHOW ($P = 0.14$), whereas respiratory rate increased ($P = 0.004$). Specifically, respiratory rate significantly increased at 40 and 45 minutes from baseline in both the IM and IN treatments during the second treatment period ($P < 0.001$ and $P = 0.04$, respectively). There was no significant difference in sedation score ($P = 0.21$; Fig 3) nor muscle (leg [Fig 4] and wing [Fig 5]) scores (all $P > 0.05$) between the 2 treatments. However, 3 birds withdrew their wings during extension; in all cases, the GHOWs had old injuries in the wings that were withdrawn. Three birds took slightly longer than 30 minutes to recover from sedation but less than 45 minutes to stand without ataxia. In the second treatment period, 1 bird was still considered to have a sedation score of 3 at 40 minutes postreversal; however, once stimulated with touch, it stood without ataxia and remained standing with its eyes

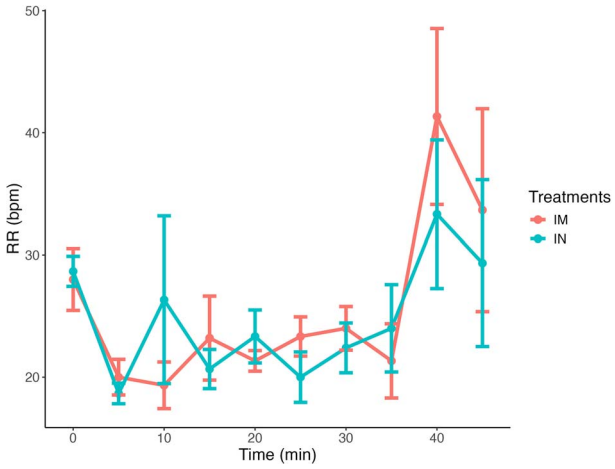

Figure 1. Lineplot of respiratory rate (RR) in breaths per minute (bpm) in great horned owls (*Bubo virginianus*) (n = 6) over time in minutes after administration of 2 mg/kg midazolam intranasal (IN) and intramuscular (IM). Respiration increased significantly at 40 and 45 minutes in both groups. Mean ± standard error of the mean (SEM).

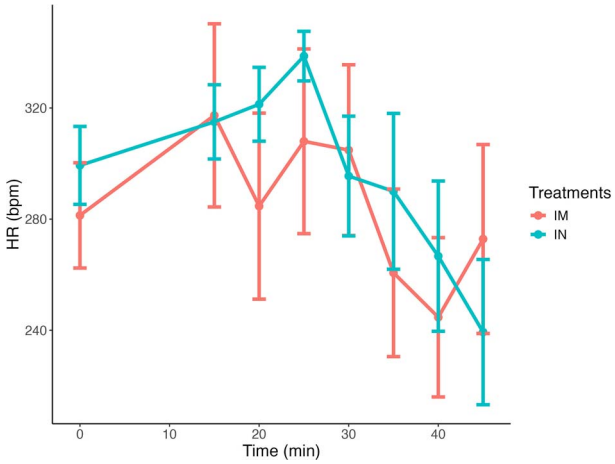

Figure 2. Lineplot of heart rate (HR) in beats per minute (bpm) in great horned owls (*Bubo virginianus*) (n = 6) over time in minutes after administration of midazolam 2 mg/kg intranasal (IN) and intramuscular (IM). No significant changes were identified between treatment groups. Mean ± standard error of the mean (SEM).

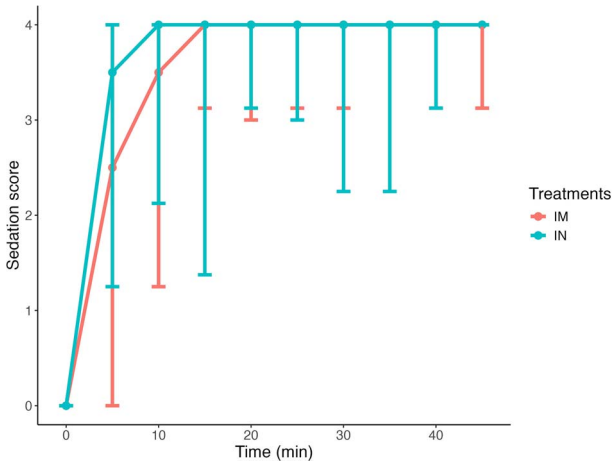

Figure 3. Lineplot of sedation scores for great horned owls (*Bubo virginianus*) (n = 6) over time in minutes after administration of midazolam 2 mg/kg intranasal (IN) and intramuscular (IM). No significant changes were identified between treatment groups. Median ± interquartile range.

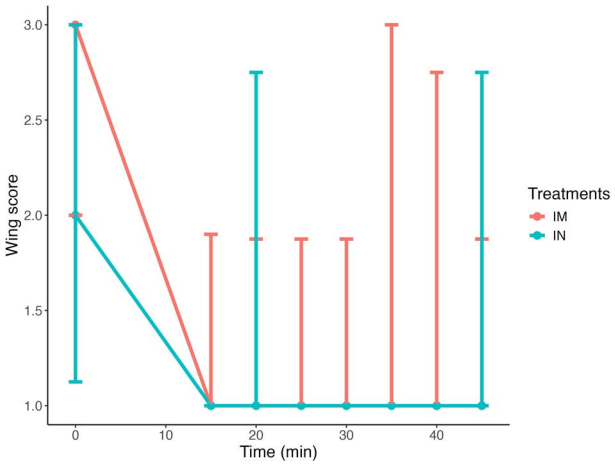

Figure 5. Lineplot of wing muscle tone scores (wing score) for great horned owls (*Bubo virginianus*) (n = 6) over time in minutes after administration of midazolam 2 mg/kg intranasal (IN) and intramuscular (IM). No significant changes were identified between treatment groups. Median ± interquartile range.

open. All birds were able to be returned to their outdoor enclosures within 2 hours.

DISCUSSION

No significant differences in heart rate, respiratory rate, and sedation or wing/leg muscle scores between the 2 treatment groups suggests that IN midazolam sedation, at the same doses administered IM, is a viable sedation option for GHOWs. Intranasal administration negates the risk of needle injuries and accidental injury to the handler, as well as reduces pain that can be associated with IM injections.

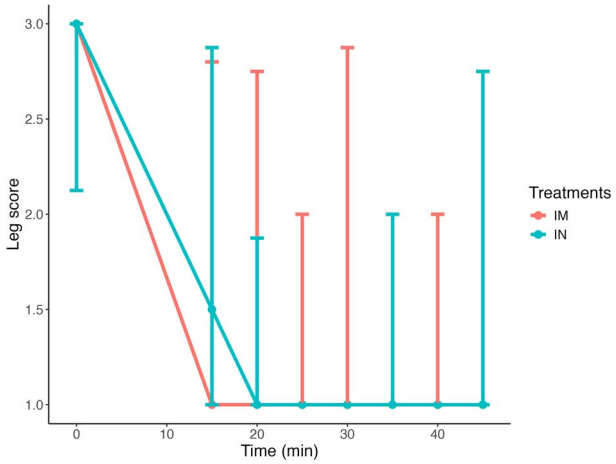

Figure 4. Lineplot of leg muscle tone scores (leg score) for great horned owls (*Bubo virginianus*) (n = 6) over time in minutes after administration of midazolam 2 mg/kg intranasal (IN) and intramuscular (IM). No significant changes were identified between treatment groups. Median ± interquartile range.

Problems such as sneezing and incomplete drug delivery that accompanied IN sedation in Eurasian buzzards[1] were not observed in this study. All deliveries during the experiment appeared complete and without signs of discomfort. Great horned owls have large nares compared with some species with narrower nares or feathers surrounding their nares that may obstruct total delivery of the drug.

Midazolam at 2 mg/kg IN alone minimized the effects of low-level stimuli associated with procedures such as a physical examination. Radiographic positioning was not evaluated in this study, so it is unclear whether midazolam alone at this dosage would allow for ventrodorsal and laterolateral radiographic positioning. Dorsal recumbency for ventrodorsal radiographs could not be attained with midazolam 5 mg/kg IN alone in pigeons; however, when dexmedetomidine 80 µg/kg IN was added to midazolam, the sedation became deep enough for changes in positioning.[6] When administered at an even higher dosage (7.3 mg/kg IN), midazolam provided sufficient sedation to position Indian ring necked parakeets (*Psittacula krameri manillensis*) for ≥ 5 minutes in dorsal recumbency; a lower dose (3.65 mg/kg IN) combined with xylazine or ketamine increased that duration and positioning.[9] Budgerigars administered an even higher dose of midazolam IN (13.2 ± 1.3 mg/kg) had shorter onset and recovery times compared with xylazine and diazepam IN.[2] Future studies evaluating higher midazolam dosages, as well as combinations of sedatives with

midazolam IN, should be evaluated in GHOWs to determine dosages necessary for deeper sedation.

Midazolam does not provide analgesia with its sedative effects. In a painful setting, opioid medications, such as hydromorphone, or -2 agonists, such as dexmedetomidine, can be used with midazolam in GHOWs.[19] The GHOWs in this study are primarily in captivity due to injuries that prevent them from flying. When the old injuries were examined, such as extending the wing fully, some birds reacted and by moving or pulling away, suggesting that this might have been painful. Birds without wing injuries did not react to wing extension.

We chose to monitor and record data for 30 minutes postsedation because most birds took longer than 30 minutes to fully awaken and stand without ataxia. The half-life of the reversal drug, flumazenil, is shorter than that of midazolam,[20] and, in some cases, sedation reemerges following reversal that may require a second dose of flumazenil. However, none of the birds in this study were considered resedated. When stimulated by touch or movement, all owls became alert, and the birds were able to return to their outdoor enclosures within 2 hours of reversal. Future pharmacokinetic and pharmacodynamic studies of midazolam and flumazenil in this species are necessary, and birds should be closely monitored for signs of sedation reemergence in the postreversal period.

Several limitations in this study should be addressed. The small number of study subjects available was a limitation, and it is possible that with additional birds, other trends in the data may have become evident. Different species of raptors react differently to drugs and drug doses; what works in 1 species often does not work the same way in another.[21–23] Pharmacokinetics and pharmacodynamics should be performed for each drug in each targeted species to determine the proper dose and efficacy. In addition, there was a slight increase in respiratory rate toward the end of the second trial period for both routes of administration. This was likely due to a change in the rooms in which the experiments were conducted; during the second trial period, a different room, which was slightly warmer than the previous one, had to be used. The increase in respiratory rate did not occur during the first trial period, which took place in a cooler room. Unfortunately, the room temperatures were not recorded in this study, but both rooms used are inspected by the campus IACUC and are maintained at room temperatures between 20°C and 22°C (68°F and 72°F). It is wise to maintain the same environment and environmental temperatures for all trials in future studies.

In conclusion, midazolam at 2 mg/kg IN or IM showed no significant differences in the onset of sedation, overall muscle tone in the wings, legs, and jaw, or heart and respiratory rates over time. This indicates that IN midazolam sedation at the same dose as IM is a viable option for sedation of GHOW. Further research is necessary to evaluate midazolam dosages for other raptor species.

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