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Original Study

Effective Dose 50 of Intranasal Lorazepam for Clinical Sedation in Zebra Finches (*Taeniopygia guttata*)

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Abstract: Sedation is a common procedure in avian practice and benzodiazepines are often used as sole agents or in combination with other drugs to sedate avian patients. Midazolam and diazepam have been evaluated in zebra finches (*Taeniopygia guttata*); however, lorazepam has not. Our aim was to determine the sedation effective dose 50 (ED_{50}) of intranasal (NAS) lorazepam in zebra finches. Using the Dixon up-and-down method, the first randomly selected finch received 0.25 mg/kg NAS lorazepam. Sedation was scored after 20 minutes: 1) recumbent = 0 versus not recumbent = 1; 2) captured at first attempt = 0 versus not captured at first attempt = 1; 3) absence of righting reflex within 2 seconds = 0 versus righting reflex within 2 seconds = 1. Total sedation score was calculated by adding the 3 parameters; birds were classified as *sedated* if scored ≤1 and as *not sedated* if scored ≥2. Based on the first bird's classification, the next random bird received an increase (if preceding bird was not sedated) or deduction (if preceding bird was sedated) by a factor of 2. Crossover events (contradictive responses between 2 sequential animals) were noted. A total of 15 animals (5 males, 10 females), weighing 12.16–18.80 g, were used. A total of 6 crossover events were identified. The highest and the lowest dose administered were 1 and 0.0625 mg/kg, respectively. Lorazepam NAS ED_{50} was 0.3 mg/kg by the Dixon up-and-down method. No morbidity or mortality was noted, and all birds recovered uneventfully. Future studies evaluating this sedation protocol are needed to further determine the practical clinical value of lorazepam as a sedative drug in passerine species.

Key words: benzodiazepines, intranasal, sedation, Dixon up-and-down method, Passeriformes, avian, zebra finch, *Taeniopygia guttata*

INTRODUCTION

Sedation is a common procedure in avian medicine to facilitate examinations, diagnostic tests, and minimally invasive procedures. It can also be used as an alternative to anesthesia for specific case presentations and procedures. Anesthesia-associated mortality in birds has been retrospectively assessed at a veterinary teaching hospital and within a zoological collection. Anesthetic-associated mortality at these 2 facilities was reported to range from 3.4% to 3.88%.[1,2] Within a zoological collection setting, mortality risk increased with the length of the procedure and the poor health status of the patient, without any overrepresentation of one species, out of 37 patients.[2] Within a teaching hospital, there was no significant parameter that increased the risk of anesthesia-related death, including type of bird (eg, pet, wild), American Society of Anesthesiologists status, age, weight, or length of procedure.[1] Although no study has compared anesthesia-related mortality with sedation-related mortality in birds due to the known risks of anesthesia, it is important to investigate safe and effective sedation options in avian species.

Benzodiazepines are widely used in avian sedation protocols, inducing sedation without analgesic effects. These drugs are γ-aminobutyric acid type A receptor agonists, leading to sedative, hypnotic, anxiolytic, anticonvulsant, and skeletal muscle relaxant effects. Benzodiazepine effects can be reversed with flumazenil, a γ-aminobutyric acid type A receptor antagonist. There are 3 different types of benzodiazepines classified in human medicine according to the length of action,

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including short (eg, midazolam), intermediate (eg, lorazepam), and long acting (eg, diazepam).[3] Length of action and effect are influenced by multiple factors. Although all benzodiazepines rapidly cross the blood-brain barrier, the diffusion rate into the brain is drug dependent and significantly influenced by its lipophilicity; the faster the diffusion rate, the faster the onset of effect.[4] Benzodiazepines are highly bound to plasma proteins, and their metabolism and elimination are influenced by the lipid solubility of the drug.[4] Therefore, the length of action or duration of sedation of these different classes of benzodiazepines is not directly transferable across species. Several studies evaluated the duration of sedation of different benzodiazepines in bird species. Intranasal (NAS) midazolam is considered to have a shorter duration of sedation when compared with NAS diazepam in zebra finches (*Taeniopygia guttata*), budgerigars (*Melopsittacus undulatus*), and canaries (*Serinus canarius*),[5–7] whereas NAS midazolam had a longer duration of sedation when compared with NAS diazepam in juvenile ostriches (*Struthio camelus*).[8] Intramuscular (IM) midazolam and IM lorazepam did not show a significant difference in their duration of sedation in budgerigars.[9] Therefore, the duration of action of benzodiazepines in bird species must not be assumed to match that in humans. Midazolam is commonly used in birds due to its ease of administration and effectiveness, and because it can be administered intravenously (IV), IM, or NAS.[5,10] Although diazepam has also been frequently used, concerns associated with possible pain and reliable absorption following IM administration have been raised due to its being dissolved in propylene glycol. A similar effect is seen in human medicine.[11,12] Although midazolam and diazepam have been used in birds, few studies have evaluated their safety and sedative efficacy in the zebra finch.[5,13]

Lorazepam, like midazolam, can be administered NAS,[14] making it a possible option for sedation in birds. Commercial formulations of lorazepam are fully soluble in sterile water for injection, thereby avoiding the concerns associated with propylene glycol. Theoretically, lorazepam may provide an equivalent or longer duration of sedation in birds than midazolam; therefore, research into its safety and efficacy can be beneficial in providing clinicians a wider range of options. The aim of this study was to determine the effective dose 50 (ie, effective dose that will induce sedation in 50% of the population; ED_{50}) of NAS lorazepam to induce clinical sedation of zebra finches. The hypothesis of this study was that NAS lorazepam produces dose-dependent sedation in zebra finches, allowing the determination of an ED_{50}.

MATERIALS AND METHODS

Animals

A population of 31 adult zebra finches, 15 males and 16 females, were available for the study. Animals originated from a breeding colony at Oklahoma State University (Stillwater, OK, USA). At the time of the study, the subjects were kept in powder-coated steel mesh cages (76.2 × 45.7 × 45.7 cm) with ad libitum water and seed mixture (Stillwater Milling Co. A&M Poultry Feed, Stillwater, OK, USA). Food and water were replaced daily, and containers were cleaned and sterilized weekly. The bird room was kept at typical laboratory temperatures of 20–25°C (68–77°F) and ~40% humidity, with a day : night cycle of 12:12 hours. Subjects were separated by sex and lived in groups of 4–6 animals. The study was approved by the Oklahoma State University Institutional Animal Care and Use Committee (IACUC 20-06).

Pilot study

Two randomly selected birds were used for the pilot study. The first bird received a dose of 0.1 mg/kg lorazepam (2 mg/mL; Hospira Inc, Lake Forest, IL, USA) NAS and the second bird received a 0.2 mg/kg dose by the same route. Oral lorazepam at 0.1 mg/kg has been previously suggested and was therefore selected as the low dose.[15] Given the generally wide safety margin of benzodiazepines, the authors selected a dose twice as high for the higher dose for the pilot study. Once the drugs were administered, the birds were placed into individual wired-top, plastic-bottom enclosures (32 × 20 × 18 cm). The sedation status of the animals was evaluated after 20 minutes, as described in the "Experimental Design" section. These animals were not used in the main study.

Experimental design

The study was a randomized Dixon up-and-down design. All randomizations within the study were done by an online resource (www.randomizer.org). Randomization was performed on individual cages first, then each bird in the selected cage was randomized, and the selected bird was gathered for the experiment. This eliminated using the easiest-to-catch animal and gave equal chance to selecting an all-male versus all-female cage. Each morning, prior to the start of the experiment, lorazepam was diluted 1:10 by mixing 10 μL of lorazepam and 90 μL of sterile water (sterile water for

Table 1. Intranasal lorazepam sedation score in zebra finches (*Taeniopygia guttata*). Sedation scores for each category, posture (recumbent versus nonrecumbent), ability to capture (capture at first attempt versus not captured at first attempt), and righting reflex (no reflex within 2 seconds in dorsal recumbency versus reflex present within 2 seconds) range from a score of 0 to 1. Total score is depicted on the rightmost column and ranges from 0 to 3. Total sedation scores of 0 and 1 represented a sedate animal. Total scores of 2 and 3 represented a nonsedate animal.

Posture (recumbent versus not recumbent)	Capture (first attempt versus not captured)	Righting reflex (present within 2 seconds or not present)	Total score
0–1	0–1	0–1	0–3
0 = recumbent	0 = captured first attempt	0 = not present	0–1 = sedate
1 = not recumbent	1 = not captured	1 = present within 2 seconds	2–3 = not sedate

injection, USP, Hospira) by a calibrated laboratory-grade single-channel micropipette (Fisherbrand Elite Adjustable-Volume 0.5–10 μL; Thermo Fisher Scientific Inc, Waltham, MA, USA) with disposable tips (10 μL, Molecular Bioproducts Art 10, Thermo Fisher Scientific), leading to a final concentration of 0.2 mg/mL. The initial dose of lorazepam used was 0.25 mg/kg, based on the pilot study.

Physical examinations, including body weight, body condition, heart rate (HR), and respiratory rate (RR), were performed each morning of the experiment by a licensed veterinarian (I.Kh.). If considered unhealthy (eg, low body condition, presence of injury), the animals were excluded; only animals that were deemed healthy were used. The rest of the study was performed by a licensed veterinarian (I.Kh.) and a registered veterinary technician (I.Ka.). Observers were not blinded to the treatments and performed the same tasks on every bird to maintain consistency (ie, veterinarian administered drugs and technician restrained). The first randomly selected finch was physically restrained and the bird received the starting dose of 0.25 mg/kg lorazepam NAS by a laboratory grade micropipette. Volume was rounded to the nearest thousandth of a milliliter. After administration, the animal was placed in a 32 × 20 × 18-cm individual enclosure with a wired top, a solid bottom, and 1 perch. The lights were turned off and the observers left to an adjacent room to for 20 minutes. After 20 minutes, sedation was scored according to a predetermined scale (Table 1). Briefly, while in the enclosure, the bird was observed and determined to be recumbent or not. Recumbency for the observers was defined as sternal or lateral recumbency. If the bird was recumbent, a score of 0 was awarded; however, if it was not recumbent (eg, standing, moving), a score of 1 was given. Each bird's RR was visually determined by keel excursions. Afterwards, the animal was physically restrained and evaluated on ease of capture; a score of 0 was awarded if ≤1 attempt was required or a score of 1 was awarded if ≥2 attempts were required. The animal was then placed in dorsal recumbency and righting reflex (ie, ability to right itself ≤2 seconds) was determined to be absent (score = 0) or present (score = 1). Next, each bird's HR was estimated via auscultation. Once evaluated, the bird was placed back into the individual enclosure until it was considered recovered (ie, alert, standing, walking without ataxia, small flights from the perch to the bottom of the cage), at which time it was moved to its original enclosure. Throughout the study, flumazenil was readily available in case any bird displayed deep sedation that could lead to severe respiratory or cardiovascular depression. Total sedation score was calculated by adding the values of the 3 parameters. If the total score was 0 or 1, the bird was considered *sedated*, conversely, if a total score was 2 or 3, it was considered *not sedated.* If the first bird was sedated, the following random bird would receive a reduction by a factor of 2 of the previous dose (ie, 0.125 mg/kg). Conversely, if the first bird was not sedated, the following bird would receive an increase by a factor of 2 of the previous dose (ie, 0.5 mg/kg). Birds were used in a sequential manner and each bird was used only once. Crossover events, defined as contradictive responses between 2 sequential animals, were noted. These crossover events were defined as the first animal being classified as not sedated when the sequential animal was classified as sedated, and vice versa. Once an animal was part of a crossover event, its result was not used to assess against the next animal, meaning that the crossover events had to be observed in separate pairs of birds. The study was continued until 6 crossover events were identified. The authors elected to collect 6 crossover events because 6 or more crossovers reduce the likelihood of inaccurate ED_{50} when compared with 4 crossovers.[16,17] Although 4 crossovers may provide similar results, there is a higher risk for outliers.[17]

Statistical analysis

Data were recorded in a computerized spreadsheet and descriptive statistics were calculated (Microsoft

Table 2. Results of intranasal lorazepam sedation including dose assigned to each zebra finch (*Taeniopygia guttata*) (N = 15), sedation scores for each category, posture (recumbent versus nonrecumbent), ability to capture (first attempt versus not captured), and righting reflex (no reflex >2 seconds in dorsal recumbency versus reflex present <2 seconds). Total score is depicted on the right most column. Crossover events were defined as opposite effects observed in separate pairs of 2 sequential animals.

Finch no.	Dose, mg/kg	Posture (recumbent = 0; nonrecumbent = 1)	Capture (first attempt = 0; not captured = 1)	Righting reflex (no reflex >2 s = 0; reflex present <2 s = 1)	Total score	Crossover events
1	0.25	1	0	0	1	X
2	0.125	1	1	1	3	
3	0.25	0	0	1	1	X
4	0.125	1	1	1	3	
5	0.25	1	0	0	1	
6	0.125	1	0	0	1	X
7	0.0625	1	1	1	3	
8	0.125	1	0	1	2	X
9	0.25	1	0	0	1	
10	0.125	1	1	1	3	
11	0.25	1	1	1	3	X
12	0.5	1	0	0	1	
13	0.25	1	0	1	2	
14	0.5	1	0	1	2	X
15	1	0	0	0	0	

Excel, version 2008, Microsoft Corporation, Redmond, WA, USA). The ED_{50} was calculated by the Dixon up-and-down method.[18] With this method, the ED_{50} is defined as the mean dosage measured during crossover events.

RESULTS

Of the 31 zebra finches that were available, 2 animals were excluded due to abnormal health findings, including 1 with band constriction and another for a pectoral mass. All remaining birds were considered healthy. No mortality events occurred throughout the study or were associated with the administration of lorazepam. All birds recovered uneventfully to normal attitude and activity levels, and none required reversal with the benzodiazepine antagonist, flumazenil.

For the pilot study, the bird that received the lower dose (0.1 mg/kg) did not show signs of sedation (eg, standing, moving) and the bird that received the higher dose (0.2 mg/kg) appeared to show mild signs of sedation (eg, closed eyes, recumbency). Based on these results, the starting dose of 0.25 mg/kg was selected.

For the ED_{50} study, a total of 15 random finches were used. This subset consisted of 5 males and 10 females, weighing on average 15.09 g (range, 12.16–18.80 g). The maximum dose that was administered throughout the study was 1 mg/kg and the lowest dose was 0.0625 mg/kg. The range of volume of the medication administered was 4–81 μL. Seven birds were considered sedated, and 8 birds were considered not sedated (Table 2). A total of 6 crossover events were documented (Fig 1). By the Dixon up-and-down method,[18] the ED_{50} of NAS lorazepam was determined to be 0.3 mg/kg. Prior to drug administration, the HR and RR ranged from approximately 570 to >600 beats per minute (bpm) and 110 to 160 breaths per minute, respectively. At 20 minutes, the HR and RR ranged from approximately 500 to >600 bpm and 100 to 180 breaths per minute, respectively. Due to the very high HR and approximate calculation, no statistical analysis was performed on the cardiorespiratory function.

DISCUSSION

With a multitude of benzodiazepines crossing over into veterinary use, choosing the most effective and safe option can be difficult. Lorazepam, being an intermediate-acting benzodiazepine, has certain preferential uses in human medicine compared with shorter-acting midazolam and longer-acting diazepam. Lorazepam is not affected by route of administration in people, unlike diazepam.[14] In reviews of human seizure treatment, it is suggested that lorazepam is a superior benzodiazepine compared with diazepam as the first-line treatment of status epilepticus in adults.[19] This is supported by lorazepam's pharmacokinetic profile because it is less lipophilic than diazepam and has a smaller volume of distribution and a longer intracerebral half-life (12 hours)

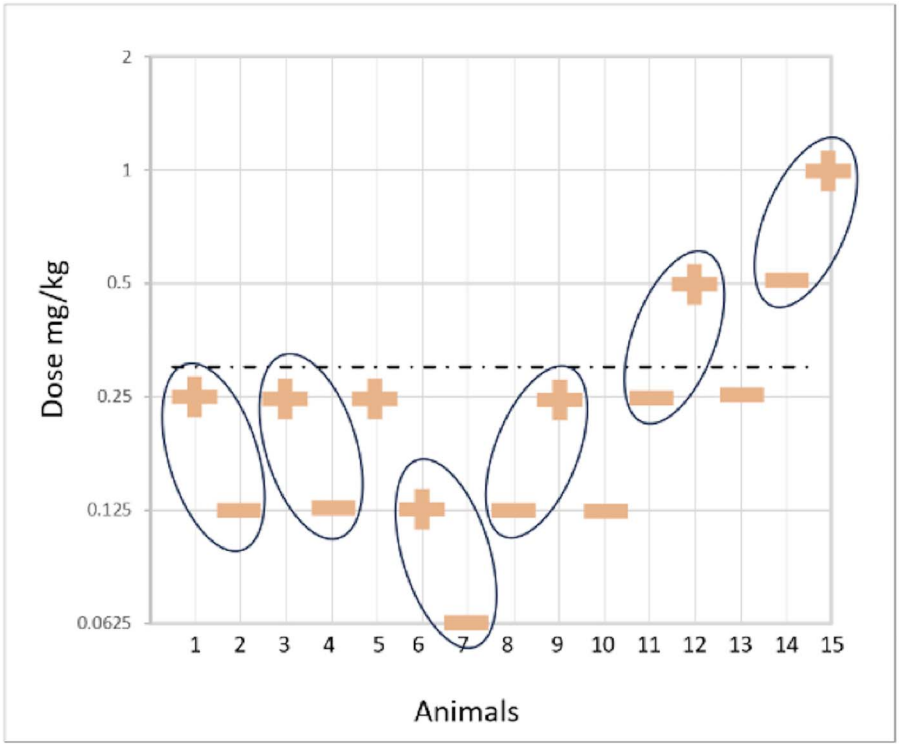

Figure 1. Effective dose 50 (ED_{50}) determination study by the Dixon up-and-down study design. Zebra finches (*Taeniopygia guttata*) were administered variable doses of intranasal lorazepam. Depending on sedation score of the preceding animal, the next animal's dose would increase or decrease by a factor of 2. "Sedated" animals (plus sign) had sedation scores of 0 or 1. "Not sedated" animals (minus sign) had sedation scores of 2 or 3. Crossover events (ovals) occurred when contradictory effects between separate pairs of sequential animals occurred. The ED_{50} of lorazepam, 0.3 mg/kg, is represented as the broken line horizontally across the graph.

than diazepam (15–30 minutes). These pharmacokinetic properties enable a longer-lasting antiepileptic effect.[19]

Although clinical studies have shown preferential use of lorazepam in human medicine, veterinary research has not supported the superiority of lorazepam compared with other benzodiazepines. Thus, outlining the variable effects these drugs can have across different species, including absorption, duration of effects, and safety, is necessary. Lorazepam has been investigated in canine veterinary patients for the treatment of seizures. Studies have found it less efficacious via rectal administration due to high first-pass effect,[20] and it is seen as equally effective as IV diazepam in dogs to stop and control seizures.[21] When administered IV, lorazepam maintains plasma concentrations above human anticonvulsant activity for 60 minutes in 100% of canine participants, but in only 50% of participants when administered NAS.[22] Although lorazepam can be an efficacious anticonvulsant in dogs, the lack of clinical trials in veterinary medicine has limited the clinical utilization of this benzodiazepine.

The study reported herein contributes to the paucity of information on lorazepam in veterinary patients. It provides the practitioner with a basis for a safe and effective dose, 0.3 mg/kg NAS, in at least 50% of zebra finches. Investigation into the use of lorazepam in other bird species is scarce. Lorazepam (1 mg/kg IM) has been compared with midazolam (1 mg/kg IM) on food intake in budgerigars, with no adverse effects or clinical difference from midazolam.[9] Although the purpose of the previous study was to evaluate the impact of benzodiazepines on food intake, the authors reported that both drugs produced sedation for 3 hours following administration.[9] Although our study reports a lower effective dose for sedation, via a different route of administration, it does support the lack of adverse effects in birds administered lorazepam.

In this study, sedation was determined by a sedation score. The sedation scoring method, involving 3 physical parameters of recumbency, capture, and righting reflex, complements clinical applications for avian procedures including restraint for exams, venipuncture, and radiographic positioning. Although this scale may mimic procedures performed routinely in veterinary practice, it may not be representative in certain research settings for which zebra finches are commonly used.

Further research is needed to fully assess the dependability of this method of sedation score in providing a consistent and reliable assessment of sedation. The results of this study show that lorazepam may be useful in a clinical setting for more minor procedures. Zebra finches are commonly used as a research model for avian behavioral and physiology studies. Although not evaluated in this study, the effects of lorazepam in, for example, stress markers (eg, corticosterone) should be evaluated and compared with other benzodiazepines.

There were several limitations to this study. A research population of zebra finches was used for this experimental protocol. This research population has a very similar genetic background. Additionally, although the overall population had similar number of males and females, the randomly selected animals were mainly females. With this lack of genetic variability and the female bias, there can be an impact on the results by providing possible standard reactions to the medication. This genetic similarity may also limit the interpretation and use of this protocol in other species. Furthermore, this study was performed in a controlled laboratory setting. A clinical setting may bring about different perceptions of sedation with this medication, including a lack of sedation due to overstimulation, leading to higher required doses. Throughout the study, a wide range of doses that induced sedation (0.0625–0.5 mg/kg) were administered. Although we believe this is the result of random effects across the population and representative of interindividual variability, other causes cannot be ruled out. As the study period progressed, it appears that the required doses increased. It is possible that this is a result of increased stress to the research population due to the presence of the observers. We tried to minimize this risk by not being present in the housing facility longer than strictly needed; however, its effect cannot be ruled out. It is important to note that 1 animal was considered sedated at a much lower dose (ie, 0.0625 mg/kg) than others. It is unclear if this animal had an underlying condition, heightened sensitivity to the drug, or another unknown cause. Indeed, all animals administered lorazepam were deemed healthy based on physical examination; however, the health status of these animals cannot be guaranteed. The safety and efficacy of the administration of lorazepam and the perception of sedation score in sick animals was not evaluated because they were outside the scope of this study, but the influence of underlying adverse physical conditions cannot be ruled out. Future studies would be needed to ensure no deleterious effects of this medication occur in a debilitated population. Although HR and RR were recorded prior to and 20 minutes after lorazepam administration, cardiovascular effects were not further analyzed in this study because HR was commonly >600 bpm and hindered appropriate data collection. Nevertheless, HR and RR were similar between the 2 time points. Another limitation to this study involved the size of our patients compared with the required volume of drug administered to them. To maintain consistency, 1 size of micropipette was used to administer the doses. Multiple animals required more than 1 administration with the micropipette to reach the required volume of lorazepam. This prolonged the administration of the medication compared with animals in which an entire dose could fit in 1 pipette. The higher volumes anecdotally bothered some animals, as sneezing and resistance to restraint were noticed. Future studies should consider either increasing the concentration of the medication to reduce volume or increasing the pipette size for a single administration. The micropipette used in this study was calibrated prior to its use in the experiment. Although unlikely, failure of accurate volume could have occurred during the experiment. Another aspect of the study to consider is the diluent used with lorazepam. Although lorazepam is labeled as compatible to dilute with sterile water, 100% certainty of a homogenous mixture cannot be guaranteed. Lorazepam also has limited stability outside of refrigeration. This led to making a fresh dilution of the medication each day of the study, which increases the possibility of error in calculation and differences in medication concentration. We limited possible errors by using calibrated laboratory-grade micropipettes that could set accurate volumes of medication and diluent needed to create our experimental solutions. In future studies, a controlled concentration without dilution may be beneficial for comparison of the efficacy of the medication.

Although this study was successful in determining the ED_{50} of lorazepam in zebra finches, future studies are needed to support the utility of this benzodiazepine in both clinical and laboratory settings. Prospective studies comparing lorazepam with other benzodiazepines such as midazolam and diazepam can be useful for knowing which is most effective for sedation in avian patients. Sedation in birds and other animals is most often achieved with a multidrug protocol, usually pairing the sedative with an opioid agent. Future studies should investigate the dose and effectiveness of lorazepam in combination with common opioid drugs in sedative protocols.

In conclusion, the ED_{50} of lorazepam administered NAS to zebra finches was determined to be 0.3 mg/kg via the Dixon up-and-down method. This result indicated that 0.3 mg/kg NAS lorazepam produces sedation in 50% of the zebra finch population. Future studies are

needed to determine if lorazepam can be used as a consistently reliable benzodiazepine in sedation protocols for avian patients.

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