The Efficacy of Intranasal Administration of Dexmedetomidine and Ketamine to Yellow-Bellied Sliders (*Trachemys scripta scripta*)

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Abstract: The purpose of this study was to evaluate the efficacy of dexmedetomidine and ketamine and reversal with atipamezole administered intranasally to *Trachemys scripta scripta*. Eight healthy adult turtles received 0.2 and 10 mg/kg of dexmedetomidine and ketamine, respectively. Heart rate, respiratory rate, temperature, and sedation (on a scale of 0–4) were measured. Blood was collected 45 min post induction for drug plasma levels from both the subcarapacial and tail veins, followed by intranasal atipamezole administration (0.5 mg/kg). The most frequent sedation scores (2 and 3) provided a level of sedation deep enough to perform a thorough physical exam and minor clinical procedures. All of the turtles became active in 18.9 ± 7 min after atipamezole administration. No adverse effects were observed and all measured cardiopulmonary parameters were within normal limits. Plasma levels of both dexmedetomidine and ketamine indicated adequate absorption and distribution with no difference in the levels obtained from either the subcarapacial or the tail venipuncture sites. A combination of dexmedetomidine–ketamine can be used intranasally to induce moderate to heavy sedation for physical examination, venipuncture, and other minor procedures in the yellow-bellied slider without adverse effects. In addition, the intranasal administration of atipamezole appears efficacious for reversal of dexmedetomidine. Intranasal administration of anesthetic agents holds promise for sedating and anesthetizing chelonians, which are often difficult to thoroughly examine and restrain for biological sample collection, both in the clinic and in the field.

Key Words: Dexmedetomidine, field anesthetic, intranasal anesthetic, ketamine, *Trachemys scripta scripta.*

Introduction

Freshwater turtles are popular pets and present for veterinary care with increasing frequency. They are also the subjects of numerous field studies. As a result, there is a growing need for physical or chemical restraint methods for complete physical examinations, biological sample collection, and therapeutic procedures. However, these turtles are often difficult to fully examine and collect biological samples from because of their tendency to withdraw completely into their shell. Due to their unique physiology, chemical immobilization of aquatic turtles presents challenges such as unpredictable absorption and metabolism of anesthetics, inconsistent depth of anesthesia and muscle relaxation, prolonged recovery periods, and anesthetic drug distribution variability associated with the renal portal system (Mosley, 2005). Despite the fact that a number of anesthetic gases are routinely used in chelonians, each has its limitations, particularly for field studies. Inhalation anesthetics such as volatile gases are commonly used in chelonian species (Bennett, 1991; Bennett, 1996; Rooney *et al*., 1999; Mosley, 2005). However, chelonians can hold their breath for long periods of time and exhibit cardiac shunting, rendering anesthetic induction from inhalant agents impractical. Modern IV anesthetics, such as propofol, offer a rapid induction period and appropriate relaxation for short procedures in reptiles but consistent, reliable access of an intravenous site in a conscious turtle can be difficult. Therefore,

most practitioners and field biologists typically rely on intramuscular agents such as N-methyl-D-aspartate (NMDA) antagonists (e.g., ketamine), alpha-2 (α_2) agonists, paralytic agents, benzodiazepines, and opioids (Mosley, 2005). For example, various doses of medetomidine (0.1–0.2 mg/kg, IM) combined with ketamine (5–10 mg/kg, IM), a popular combination among clinicians, have been tested in red-eared sliders, *Trachemys scripta elegans*, and found to provide anesthetic levels adequate for performing physical examinations, minor procedures, and endotracheal intubation (Greer *et al*., 2001). Oral, rectal, intracoelomic, and subcutaneous routes of anesthetic administration have also been used; however, these alternative routes are fraught with disadvantages, primarily related to unreliable absorption (Bennett, 1996; Sladky and Mans, 2011).

Intranasal (IN) administration of anesthetics has been utilized as a safe and effective route for short-term sedation and restraint in children (Malinovsky *et al*., 1996; Weber *et al*., 2003). The advantage this administration route offers over others is that it is generally less technically demanding than IV administration, it avoids the pain and anxiety associated with IM injections, and it circumvents the hepatic first-pass metabolism (Malinovsky *et al*., 1996). The nasal mucosa is a highly permeable port of entry for different drugs, which should translate to rapid drug absorption and short induction periods. In addition, IN drug studies have demonstrated that this route also produces a more rapid induction due to the relatively large potential surface area of absorption and its proximity to the brain (Louon and Reddy, 1994; Klein *et al*., 2011). Recently, several studies in domestic dogs (*Canis lupus familiaris*), elk (*Cervus canadensis)*, European rabbits (*Oryctolagus cuniculus*), ring-necked parakeets (*Psittacula krameri*), and canaries (*Serinus canaria domestica*) have shown that administration of IN agents (i.e., midazolam, sufentanil, diamorphine, and midazolam with ketamine) is both safe and efficacious (Robertson and Eberhart, 1994; Vesal and Eskandari, 2006; Vesal and Zare, 2006; Moghadam *et al*., 2009; Cattet *et al*., 2004).

The objective of this study was to determine if IN administration of dexmedetomidine (0.2 m/kg) combined with ketamine (10 mg/kg), and the partial reversal of this combination with intranasal administration of atipamezole (2 mg/kg), would result in a safe and useful protocol to achieve a plane of anesthesia appropriate for a thorough physical exam and minor clinical procedures in yellow-bellied sliders. If successful, this protocol would provide both practitioners and field veterinarians an alternative route of administration for chelonians that would result in both a rapid induction and recovery.

Materials and Methods

Animals: In February 2012, eight adult yellow-bellied sliders were obtained from the Savannah River Ecology Laboratory (SREL), a research unit of the University of Georgia located at the U.S. Department of Energy's Savannah River Site near Aiken, South Carolina. All animals originated from outdoor artificial ponds at SREL where they are maintained year-round under seminatural conditions. One week prior to this study, turtles were captured and maintained indoors in individual plastic containers at 26°C (80°F) and fed aquatic turtle pellets (Mazuri Fresh Water Turtle Diet, PMI Nutrition, Richmond, IN) *ad libitum*. The turtles were transported to the College of Veterinary Medicine at the University of Georgia (Athens, GA) in insulated containers and were housed in a large, heated enclosure at 26°C (80°F) for one night. All animals were fasted for 24 h prior to the procedure. The morning of the trial we collected morphological measurements (body weight to the nearest 1 g, carapacial width and length to nearest 1 mm) and performed a complete physical exam. Additionally, we obtained a cloacal body temperature, a baseline heart rate with a Doppler, and the respiratory rate. For the duration of the study, all animals were housed individually in plastic containers placed on top of a heated table or heating pads to maintain their body temperatures at 26°C (80°F). All procedures performed were in accordance with the University of Georgia Institutional Animal Care and Use Committee-approved protocol: A2011 10-007-Y1-A1.

Administration: Dexmedetomidine (0.2 mg/kg) was administered in the right naris, immediately followed by administration of ketamine (10 mg/kg) in the left naris. To ensure adequate dosing, drugs were delivered into the nares using a micropipette (Varipet 4810; Eppendorf, Hamburg, Germany) while the turtle was held vertically (Fig. 1). To minimize drug loss and allow the maximum drug volume to run down the nasal cavity, drugs were infused slowly over approximately 30 sec. Immediately after drug administration, each turtle was placed in sternal recumbency in its plastic container where noise, movement, and other stimuli were minimized.

Quality of anesthesia: To understand the effects of the anesthetics on the turtles, we measured four response variables: the speed of induction, the depth of sedation, and the speed and quality of recovery. The depth of sedation was evaluated just prior to and at 5, 15, 30, and 45 min post administration and every 15 min thereafter until recovery by subjectively assessing 1) the ease with which we could manipulate the head and extremities, 2) palpebral and corneal reflexes, 3) patient response to a deep toe pinch, 4) resistance to opening the mouth, and 5) whether endotracheal intubation was possible. The same two examiners throughout the study ascertained the sedation of each turtle, and the resulting sedation score was the average of their individual assessments. The sedation score consisted of a score of 1) 0—which meant no sedation (fully conscious, moving all limbs normally, examiner unable to pull the limbs away from the body), 2) 1—mildly sedated (delayed retraction of the limbs when manipulated, but examiner is able to extend the limbs minimally, with fast return to the tucked position), 3) 2—moderately sedated (head and limbs flaccid, unresponsive to a deep toe pinch or other external stimuli, and palpebral reflexes still intact but slow), 4) 3—heavily sedated (as for score 2, but without palpebral reflex and slight jaw tone), and 5) 4—light anesthesia (as for score 3, but without jaw tone and animal could be intubated without resistance) (Table 1).

Reversal: Forty-five minutes post drug administration, animals were held vertically to administer 2 mg/kg atipamezole (Antisedan, Pfizer Animal Health, New York, NY) IN divided between both nares. Turtles were considered fully recovered once they returned to a sedation score of 0. Visual monitoring was continued for the next 24 h to observe for any adverse reactions or signs of resedation.

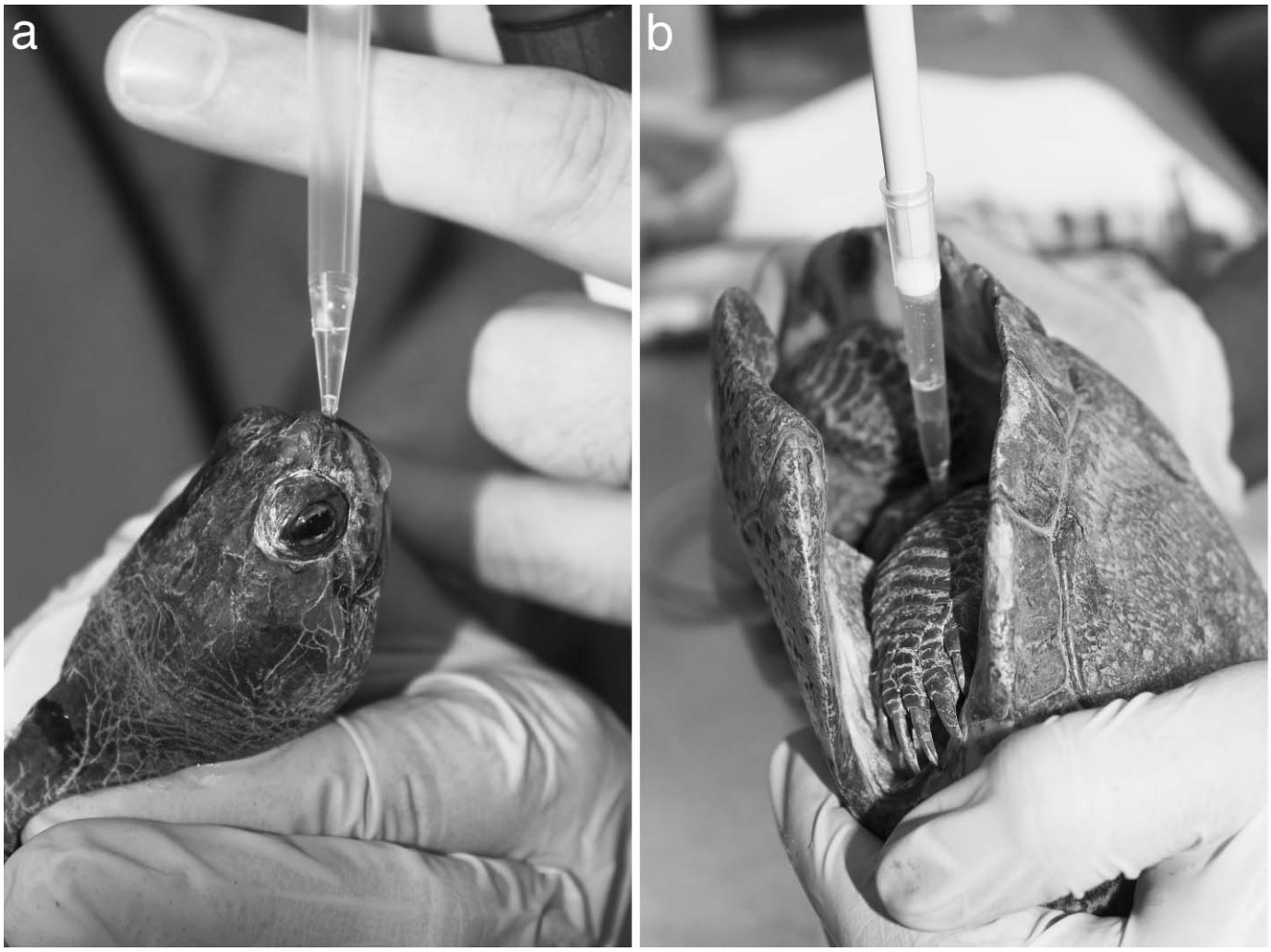

Figure 1. A combination of dexmedetomidine and ketamine was administered to yellow-bellied turtles ($N = 8$) intranasally with the use of a micropipette (a). This technique was also successfully accomplished without the need to restrain the head (b).

Table 1. Yellow-bellied turtles ($N = 8$) were administered dexmedetomidine and ketamine, intranasally, and sedation scores subjectively determined at 5 min after initial drug administration and every 15 min thereafter until recovery. Sedation scores were used to assess ease of physical examination.

Sedation scores	Score description
0—No sedation	Animal is fully awake and alert, all limbs and head retracted
1—Mild sedation	Limbs weak, delayed retraction
2—Moderate sedation	Head out, limbs flaccid, not responsive to stimulus, palpebral reflexes still intact but slow
3—Heavy sedation	No palpebral reflex, head and limbs out, no response to stimulus, slight jaw tone
4—General anesthesia (light)	No jaw tone, animal can be intubated without struggling

Monitoring: Heart and respiratory rates and cloacal and ambient temperatures were measured immediately prior to administration of the anesthetics and at 5, 15, 30, and 45 min post administration and again every 15 min following reversal drug administration until the turtles were fully responsive and had a sedation score of 0. Heart rate was monitored using an ultrasonic Doppler flow detector (Model 811, Parks Medical Electronics, Aloha, OR) placed at the thoracic inlet, and respiratory rates were measured by observing pumping movements of the thoracic limbs and neck. Cloacal and ambient temperatures were measured with a digital thermometer (RMR202A, Oregon Scientific, Cannon Beach, OR).

Pharmacokinetic analyses: Forty-five minutes after drug administration, 1 ml of blood was collected from both the subcarapacial and dorsal tail veins and stored in tubes lined with lithium heparin (Microtainer, Sarstedt Inc., Newton, NC) to measure ketamine and dexmedetomidine plasma concentrations. Samples with visible lymph contamination were discarded and the venipuncture repeated. Blood was

immediately centrifuged at 8,000 *g* for 5 min, and the plasma was harvested and stored at −80°C (−112°F) until analysis.

Quantification of ketamine and dexmedetomidine was achieved using liquid chromatography–tandem mass spectrometry using an Agilent 1100 high performance liquid chromatography (Agilent Technologies, Inc., Santa Clara, CA) which consisted of a degasser, a binary pump, an autosampler, and a thermostated column compartment coupled with an Agilent XCT Ultra Plus ion-trap mass spectrometer (MS) with an electrospray ionization (ESI) source. Nitrogen gas was used as desolvation gas (flow rate of 9 L/min at 350°C [662°F]) and as nebulizer gas (40 psi), and helium was used as a collision gas. The MS was operated in positive ionization mode with an ion source voltage (V) of 4500 V, a skimmer voltage of 40 V, and the cap exit was set at 120.6 V. Thirty microliters of plasma were mixed with 70 µl of an extraction solvent comprised of 0.1% (v/v) formic acid and acetonitrile (1:9 v/v) followed by centrifugation (10,000 *g* for 12 min) at 4°C (39.2°F). The supernatant (20 µl) was injected onto a reverse-phase C18 column (Agilent Eclipse Plus 3.5 mcg, 4.6 × 100 mm) protected by a C18 guard column (Phenomenex column 4.0 × 3.0 mm) and the column temperature was maintained at 20°C (68°F). Analytes were eluted from the column using an isocratic mobile phase composed of 0.1% (v/v) formic acid and ACN (35:65 v/v) at a flow rate of 0.250 ml/min. Mass spectra were acquired in positive-ion mode and mass transitions were monitored using multiple-reaction monitoring. The mass to charge (*m*/*z*) ion transitions monitored were *m*/*z* 201 → 95 and *m*/*z* 238 → 220 for quantification of dexmedetomidine and ketamine, respectively. A final concentration range of 3.9 to 1,000 ng/ml of both drugs mixed together in turtle plasma was used to construct the standard curve by plotting the peak area of analytes versus their theoretical concentration. A calibration curve was fit using a weighted least squares; the inverse of the variance ($1/y^2$) of the observed data was used as the weighting factor. The calibration curve was deemed acceptable if all the values were within 15 of their nominal values and the coefficient of variation (CV%) was ≤15%. The lower limit of quantification (LLOQ) was determined by analyzing blank rat plasma spiked with dexmedetomidine standard solution. The LLOQ was determined based on the following criteria: accuracy and CV of the response were within ±20% of the theoretical concentration, and the response was at least five times higher than the baseline noise (signal to noise >5).

Statistical analyses: All analyses were performed using SAS V 9.2 (SAS, Cary, NC). Descriptive statistics were performed on time periods in minutes (15 min intervals) to reach sedation levels 1, 2, or 3 and time to reversal (from 45 min time point) and time to recovery (from reversal). A repeated measures model that recognized multiple measurements as belonging to the same turtle was used to test for differences in heart rate, respiration, temperature, and sedation between time points. Multiple comparisons were adjusted for by using Tukey's test. An unstructured covariance structure was used in the repeated measures models. All hypothesis tests were 2-sided and the significance level was $\alpha = 0.05$. Correlations between sedation scores and drug plasma levels and drug volume were tested using Pearson's correlation. Subcarapacial and tail plasma levels were compared by a paired *t*-test.

Table 2. Yellow-bellied turtles ($N = 8$) were administered dexmedetomidine and ketamine, intranasally. Intranasal absorption likely depends on the anesthetic drug having direct contact with the nasal mucosa; thus, drug volumes and administration speeds, which overwhelm the mucosa's capacity to absorb, may influence its efficacy and subsequent sedation.

Descriptive parameters	Mean and Standard Deviation
Body weight (kg)	1.75 ± 0.11
Dexmedetomidine (ml)	0.70 ± 0.11
Ketamine (ml)	0.17 ± 0.03
Atipamezole (ml)	0.77 ± 0.07
Total anesthesia time (min)	83 ± 5.7
Core body temperature (°C; °F)	26.8 ± –17 80.3 ± 1

Results

Descriptive statistics are reported in Table 2. After 15 min, a significant increase in heart rate was documented when compared to all other time points (at 30 min, $P = 0.0032$; at 45 min $P = 0.0014$). No significant difference in respiratory rate was observed between any of the time points. No significant correlations between heart rate, temperatures, respiration, and sedation scores were found. Sedation scores were significantly different between all time point comparisons except the 0 and 5 min time points (at 5 min, $P = 1.0$; at all other time points $P < 0.01$) (Fig. 2). The mean time to a sedation score of 1 was 21 ± 8 min, a score of 2 was 35.6 ± 8 min, and a score of 3 was 45 min. The mode sedation score was 2 (4 out of 8 animals) and 3 (4 out of 8 animals), which was a level of anesthesia deep enough to perform a thorough physical examination and minor clinical procedures. At 45 min post induction, ketamine and dexmedetomidine plasma concentrations measured were 1,014.5 ± 620 ng/ml/kg (K) and 17.3 ± 8.6 ng/ml/kg (D) from the tail vein, respectively, and 2,390.6 ± 2,966 ng/ml/kg (K) and 24.6 ± 23.9 ng/ml/kg (D) from the subcarapacial vein, respectively. There were no significant differences in the plasma concentrations of dexmedetomidine ($P = 0.4683$) or ketamine ($P = 0.3227$) in the blood collected from the tail and subcarapacial veins. The average volume of both dexmedetomidine and ketamine administered to each animal was 0.87 ± 0.14 ml (Table 2). A significant negative relationship was observed between drug volume and sedation scores ($R = -0.87202$, $P = 0.0048$); thus, as the volume of the drug administered increased, the sedative effects decreased. After atipamezole administration, the average return time to pre-anesthetic activity was 18.9 ± 7 min.

Discussion

Ketamine, an NMDA receptor antagonist, has been part of anesthetic protocols used for reptiles for many years due to its relatively wide margin of safety and sedative and anesthetic effects (Sladky and Mann, 2012). The appropriate dose of ketamine in reptiles varies depending on a number

of different factors including the level of sedation desired and the body temperature of the animal. In the past, ketamine was often used by itself; however, high doses were required to reach sufficient muscle relaxation for handling, which typically resulted in prolonged recovery periods. For example, ketamine was administered IM at dosages ranging from 60–90 mg/kg in tortoises, and full recovery took as long as 24 h at an ambient temperature of 22°C (72°F) (Green *et al.*, 1981).

Studies of chelonians, where medetomidine was used alone, have shown that it did not provide sufficient sedation (Sleeman and Gaynor, 2000). As a result, multimodal therapy in which ketamine is combined with an α_2 adrenergic agonist is appealing because the α_2 agonist provides analgesia, improves muscle relaxation, and can be reversed, and the combination with ketamine allows for a lower dose of the α_2 agonist, minimizing its negative side effects (Mosley, 2005). Medetomidine and ketamine combinations have proven to be a safe and effective form of anesthesia in reptiles, including chelonians such as gopher tortoises (*Gopherus polyphemus*), red-eared sliders, map turtles (*Graptemys geographica*), and box turtles (*Terrapene carolina carolina*) (Lock *et al.*, 1998; Sleeman and Gaynor, 2000; Greer *et al.*, 2001). Medetomidine at 50–300 μg/kg and ketamine at 4–15 mg/kg, administered IM, produced moderate to heavy sedation in both squamates and chelonians (Bennett, 1996; Greer *et al.*, 2001). The doses for IN administration chosen in this study were based on a previous study of red-eared sliders in which the anesthetics were administered IM and produced similar results (Greer *et al.*, 2001).

Dexmedetomidine and ketamine are highly lipid-soluble compounds, which makes them ideal agents for IN administration (Anttila *et al.*, 2003). The nasal mucosa offers a highly permeable port of entry for some drugs and has been shown to reduce first-pass metabolism (Malinovsky *et al.*, 1996). Rapid onset of sedation and analgesia has been reported following IN administration of α_2 agonists and dissociative agents in multiple species (Robertson and Eberhart 1994; Cattet *et al.*, 2004; Vesal and Eskandari, 2006; Vesal and Zare, 2006; Moghadam *et al.*, 2009).

Intranasal route of anesthetic drug administration has been meticulously investigated in humans. A study performed in adults demonstrated that an IN dose of 1 μg/kg and 1.5 μg/kg of dexmedetomidine produced a mild to moderate level of sedation within 45–60 min, with sedation levels peaking between 90–105 min (Yuen *et al.*, 2007). In children, IN ketamine at 1–6 mg/kg has been shown to produce enough sedation to decrease pre-operative anxiety, allowing for catheterization and facemask placement (Malinovsky *et al.*, 1996). Another study comparing IV, rectal, and IN methods of dosing ketamine in people demonstrated that IN administration provided systemic bioavailability of 50%, twice the absorption when compared to rectal administration at 25% (Malinovsky *et al.*, 1996). As in this turtle study, the administration of ketamine dosed in the human studies did not produce general anesthesia, and other drugs such as inhalants were needed to induce the patients fully.

Intranasal administration has only recently become applicable in veterinary medicine. Studies in canaries, pigeons (*Columba livia domestica*), and ring-necked parakeets showed that IN administration of xylazine produced only mild to moderate levels of sedation (Vesal and Eskandari, 2006; Vesal and Zare, 2006). However, lateral recumbency was achieved when administering IN detomidine and ketamine or xylazine and ketamine in ring-necked parakeets (Vesal and Eskandari, 2006). In New Zealand white rabbits (*Oryctolagus cuniculus*), a combination of IN xylazine and ketamine produced similar results compared to IM administration. All animals experienced good muscle relaxation and most of the animals did not respond to a painful stimulus for at least 15 to 30 min after IN administration (Robertson and Eberhart, 1994).

The IN administration of other anesthetic drugs, such as midazolam, has been evaluated in humans, dogs, cats, birds, and rabbits (Walbergh *et al.*, 1991; Robertson and Eberhart 1994; Cattet *et al.*, 2004; Vesal and Eskandari, 2006; Vesal and Zare, 2006; Moghadam *et al.*, 2009; Mans *et al.*, 2012). Although midazolam in those studies produced adequate levels of sedation, analgesia was not achieved. We initially aimed to test the efficacy of IN administration of midazolam in the yellow-bellied sliders; however, 1–2 mg/kg midazolam IN to six yellow-bellied turtles yielded poor results. The sedation scores of two animals at 15 min was 1 and the score for the other four turtles was 0. Most importantly, 66.7% (4/6) of the turtles produced a frothy white discharge from their oral cavity 5 min after being dosed (Fig. 3). The authors attributed this discharge as a sign of irritation either within the nasal or oral cavity and, thus, terminated that portion of the study. Humans occasionally report mild side effects after IN administration of midazolam, including transient burning sensation and lacrimation. These symptoms may be a result of the acidity of midazolam (pH 3.0–3.5) (Lugo *et al.*, 1993). Yet IN irritation has not been reported in any other animal models to authors' knowledge. Furthermore, similar complications have not been reported with the IN use of dexmedetomidine and ketamine.

This study is the first to evaluate IN administration of dexmedetomidine and ketamine to sedate aquatic turtles. The onset and peak of sedation were similar to IM administration of dexmedetomidine–ketamine in chelonians. Comparatively, a study performed on red-eared sliders where ketamine was administered at 10 mg/kg combined with low (0.1 mg/kg) and high doses of medetomidine (0.2 mg/kg) IM showed that most animals reached an adequate level of muscle relaxation to withdraw the fore and hind limbs at 30 min and the neck at 45 min, although in that study tracheal intubation was achieved (Greer *et al.*, 2001). In contrast, turtles in our study recovered faster (18.9 ± 7 min) than in the aforementioned study (30 to 60 min). Although we did not evaluate this, we speculate that the faster recovery was either due to the higher dose we administered (2 mg/kg compared to 1 mg/kg) or could be attributed to a faster absorption of atipamezole from the nasal mucosa (Greer *et al.*, 2001).

There was high variability in the mean drug plasma concentrations among individual turtles. This variation may be attributed to differences in the metabolic rates of individuals or inconsistent drug administration. Such high variability in bioavailability is not unusual when unmodified IV preparations are used for IN drug administration (Malinovsky *et al.*, 1996). In this study, a negative relationship between drug volume and sedation scores was found. The average volume of drugs administered was 0.87 ± 0.14 ml, which is a considerable amount for such small animals. Thus, it is likely that the drug ran down from the nasal

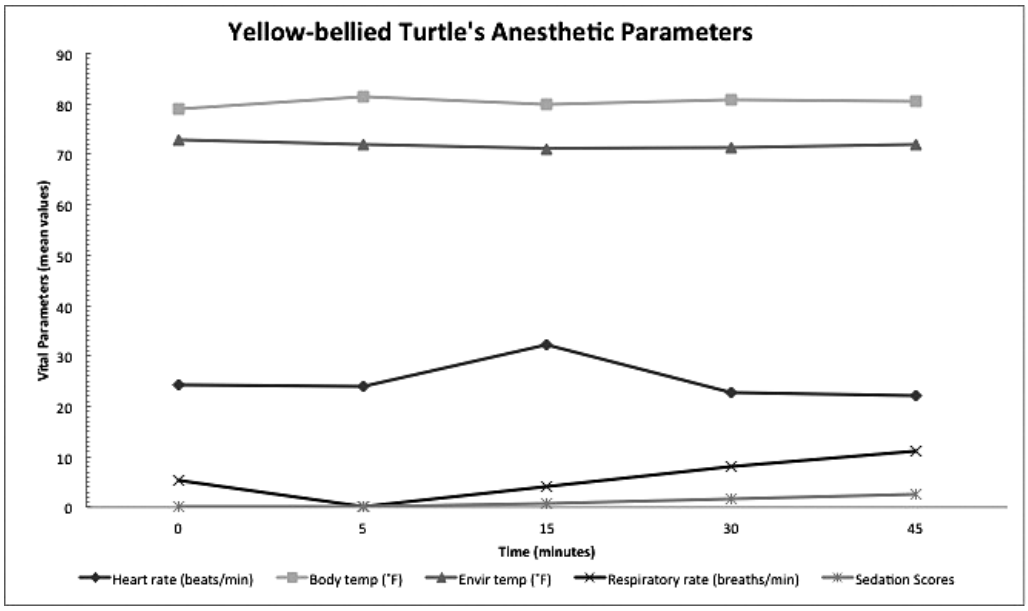

Figure 2. The heart rate, respiratory rate, body temperature, and sedation score of eight yellow-bellied turtles was monitored before and after intranasal administration of dexmedetomidine–ketamine for up to 45 min post administration.

cavity into the oropharynx or esophagus, affecting drug absorption and metabolism.

The interpretation of the drug plasma levels obtained in this study is challenging because pharmacokinetic studies of dexmedetomidine and ketamine in reptiles do not exist. However, when comparing plasma levels obtained in these turtles with pharmacokinetic trials in humans, there were some interesting correlations. In a human study, adults were administered 1 μg/kg of dexmedetomidine and achieved mean plasma levels of 0.18 ng/ml at 45 min (Scheinin *et al.*, 1992). In this study, turtles received a dose of 0.2 mg/kg dexmedetomidine, equivalent to 200-times the above dose, and achieved plasma levels that ranged from 17 to 26 ng/ml, which is consistent with scaling of plasma levels between the species.

In an IN ketamine study of children, patients received 9 mg/kg of ketamine, and the mean ketamine plasma concentration was 2,104 ng/ml at 20 min and 632 ng/ml at

Figure 3. Midazolam was administered to six yellow-belied turtles intranasally; however, turtles immediately developed a white foamy discharge from the mouth, possibly indicating nasal or oral irritation, and the rest of the experiment was aborted.

45 min (Malinovsky *et al*., 1996). In this study, the mean plasma concentration of ketamine in the turtles ranged between 1,014 and 2,319 ng/ml at 45 min. The authors suspect the differences in the plasma levels of ketamine between children and chelonians are likely related to the higher metabolic rate of the former.

Intranasal administration of dexmedetomidine and ketamine provided a mode sedation score of 2 and 3. This level of sedation and muscle relaxation meant the limbs and the head of the animals were flaccid and unresponsive to external stimuli, which would allow field biologists and veterinarians to perform thorough physical examinations, diagnostic sample collection, and minor clinical procedures. Although in this pilot study it was not possible to intubate the animals, the authors have since used the concentrated forms of medetomidine and ketamine (20 mg/ml and 200 mg/ml, respectively) at the same doses to intubate an African spurred-thighed tortoise (*Geochelone sulcata*) and two eastern box turtles. The highly concentrated formulations allowed for administering a smaller volume, which may have resulted in less drug running down the oropharynx. It is also possible there are interspecies differences that were not tested in this study.

The IN administration of dexmedetomidine and ketamine did not cause any significant changes in heart rate, temperature, or respiration in relation to sedation scores. Throughout the experiment the heart rate, respiratory rate, and temperature remained within normal values for chelonians (Sleeman and Gaynor, 2000; Sladky and Mans, 2012). Although within normal limits, there was a significant decrease in the respiratory rate during the 5 min period immediately following drug administration. This was likely due to the turtles holding their breath for a brief period due to handling and drug administration.

Although the protocol was effective at causing moderate to heavy sedation with minimal changes to vital parameters, the authors were not able to determine the safety of this protocol decisively. Both dexmedetomidine and ketamine can have significant effects on blood pressure and cardiac output, yet these parameters were not monitored in this initial study. All animals recovered from the procedure without adverse effects. Furthermore, although no observable discomfort was detected with the administration of IN dexmedetomidine–ketamine, the authors did not assess microscopic effects of the nasal–upper respiratory mucosae. Depending on the formulation used, the pH of dexmedetomidine and ketamine can range from 4.5–7.0 and 3.5–5.5, respectively, which may cause irritation or inflammation, although in this study clinical signs consistent with these changes were not observed.

The results of this trial show that there was adequate absorption of both drugs when administered IN, proving that IN administration could be a suitable route of anesthetic drug administration in chelonians. Although α_2 adrenergic agonists and NMDA receptor antagonists are not the preferred analgesic drugs in reptiles, this study can provide a model for the IN administration of other analgesics, such as mu opioid agonists. The IN route may reduce the pain associated with multiple injections needed for the treatment of chronic pain and may allow owners to administer these drugs at home. Further studies need to be conducted to determine if other analgesic drugs are tolerated and are adequately absorbed from the IN mucosa.

Although IN delivery of anesthetics drugs has been shown to be effective, it has some limitations. Rapid administration, or a large volume of drugs, can result in runoff out through the nares or down the nasopharynx, which can decrease the bioavailability and efficacy of the drugs. In this study, animals tolerated IN administration very well; however, the authors did note a miniscule amount of drug running out of the nares post administration. Ideally, if this study were repeated, a double-crossover design would allow for more-robust comparisons with IM or other types of drug administrations. Additionally, the observer(s) would not be privy to the drug administration route to avoid bias.

Conclusion

Intranasal administration of dexmedetomidine and ketamine resulted in adequate sedation of yellow-bellied sliders for physical examination, venipuncture, and other minor procedures. Intranasal administration provided a faster and more effective sedation and recovery than other medetomidine and ketamine studies that administered the drugs IM. The results of this study suggest that IN drug administration appears to be an acceptable, minimally invasive alternative method of drug delivery for aquatic turtles. This method requires no special technical skills, and only brief physical restraint is needed to deliver the drugs into the nares. Intranasal drug administration has the potential to become a viable clinical option in exotic animal medicine and may replace conventional IM or subcutaneous injections. In addition, this route of administration would be extremely useful for biologists and field veterinarians when sedation of chelonians is needed. Further studies are necessary to evaluate different doses, their safety in compromised patients, and their usefulness in other reptilian species.

Acknowledgments: The authors would like to thank the various veterinary and graduate students who helped with animal handling, sample collection, and processing. Manuscript preparation by author TDT was partially supported by the Department of Energy under Award Number DE-FC09-07SR22506 to the University of Georgia Research Foundation.

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