In information about reptile analgesia has advanced substantially during the past 10 years, and veterinarians who work with reptiles should strive to ameliorate pain whenever possible.1–4 Reptiles have the requisite neuroanatomic structures and neurophysiologic mechanisms to detect pain5–7; therefore, stimuli considered painful to mammals should be assumed to be painful to reptiles. However, effective analgesic drugs, proper dosages, and frequency of administration continue to be a challenge in reptile pain management, and analgesic drugs that appear to be efficacious in one class of reptiles are not necessarily efficacious in another. For example, µ-opioid receptor agonists (eg, morphine) appear to provide analgesia in turtles8–10 and bearded dragons11 but not in corn snakes.11 Strikingly, we found no difference in the noxious thermal stimulus withdrawal response of ball pythons regardless of whether saline (0.9% NaCl) solution or fentanyl was administered, which was unexpected given that other reptile species consistently respond to µ-opioid receptor agonists.12 However, ball pythons express a similar amount of µ-opioid receptor mRNA in the brain and spinal cord as do turtles,12 which suggests that µ-opioid receptor agonists should be effective in ball pythons. Thus, antinociception in snakes represents a conundrum with respect to determining analgesic drug efficacy in both clinical and research conditions.

It is worth evaluating drugs with known antinociceptive properties in mammalian species for use in reptiles. The α2-adrenergic receptor agonists have anesthetic and antinociceptive properties and are commonly administered to mammals.13,14 In reptiles, administration of an α2-adrenoceptor agonist (medetomidine) in combination with ketamine induces reversible anesthesia in crocodiles,15 alligators,16 and chelonian species.17,18 Similarly, dexmedetomidine combined with ketamine can induce anesthesia in chelonian species.19–21 In 2 studies,22,23 intrathecal administration of clonidine decreased nociceptive behaviors in 2 chelonian species.

Antinociceptive efficacy and respiratory effects of dexmedetomidine in ball pythons (Python regius)

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OBJECTIVE
To determine antinociceptive efficacy, behavioral patterns, and respiratory effects associated with dexmedetomidine administration in ball pythons (Python regius).

ANIMALS
12 ball pythons.

PROCEDURES
Antinociception was assessed by applying an infrared heat stimulus to the cranioventral surface of snakes during 2 experiments. Thermal withdrawal latency was measured at 0, 2, and 24 hours after SC injections of dexmedetomidine (0.1 or 0.2 mg/kg) or saline (0.9% NaCl) solution and at 0 to 60 minutes after injection of dexmedetomidine (0.1 mg/kg) or saline solution. Behaviors were recorded at 0, 2, and 24 hours after administration of dexmedetomidine (0.1 mg/kg) or saline solution. Tongue flicking, head flinch to the approach of an observer’s hand, movement, and righting reflex were scored. Respiratory frequency was measured by use of plethysmography to detect breathing-related movements after injection of dexmedetomidine (0.1 mg/kg) or saline solution.

RESULTS
Mean baseline withdrawal latency was 5 to 7 seconds; saline solution did not alter withdrawal latency. Dexmedetomidine increased withdrawal latency by 18 seconds (0.2 mg/kg) and 13 seconds (0.1 mg/kg) above baseline values at 2 hours. Increased withdrawal latency was detected within 15 minutes after dexmedetomidine administration. At 2 hours after injection, there were few differences in behavioral scores. Dexmedetomidine injection depressed respiratory frequency by 55% to 70%, compared with results for saline solution, but snakes continued to breathe without prolonged apnea.

CONCLUSIONS AND CLINICAL RELEVANCE
Dexmedetomidine increased noxious thermal withdrawal latency without causing excessive sedation. Therefore, dexmedetomidine may be a useful analgesic drug in ball pythons and other snake species. (Am J Vet Res 2018;79:718–726)
Because ketamine and the $\alpha_2$-adrenoceptor agonist drugs were coadministered in most of these studies, it is not clear whether $\alpha_2$-adrenoceptor agonist drugs induce antinociception in reptiles.

The objective of the study reported here was to evaluate whether $\alpha_2$-adrenoceptor agonists induce antinociception in a snake species. Ball pythons (Python regius) were used to determine whether dexmedetomidine has antinociceptive properties; a noxious thermal stimulus was used for testing. Snake responses (tongue flicking, head flinching, movement, and righting reflex) after administration of dexmedetomidine or saline solution were evaluated by use of video recordings. Finally, because administration of medetomidine to desert tortoises causes profound bradypnea, whole-body closed-chamber plethysmography was used to quantify the effects of dexmedetomidine on breathing frequency of ball pythons.

**Materials and Methods**

**Animals**

Twelve ball pythons (7 females and 5 males) were obtained from commercial suppliers. Snakes were housed individually in standard laboratory cages (width, 26 cm; depth, 48 cm; and height, 20 cm). Snakes had ad libitum access to drinking water, and each cage had a hide chamber. Temperature of the housing room was maintained at 25° to 29°C. Snakes were fed frozen-thawed mice or juvenile rats, as appropriate for each snake's body size, once weekly (Friday). All tests were performed the following week on Monday through Thursday; feeding had no obvious effects on testing results. All snakes were examined regularly by a veterinarian and were considered healthy throughout the study. All procedures were approved by the Animal Care and Use Committee at the University of Wisconsin School of Veterinary Medicine (protocol No. V005710).

**Thermal antinociception experiments**

Two randomized complete crossover double-blind experiments were used to evaluate changes in thermal antinociception after administration of dexmedetomidine or saline solution. Both antinociception experiments were conducted at an ambient temperature of 26°C to 28°C. Before the first experiment was conducted, snakes were allowed to acclimate for a minimum of 3 days to the testing chamber, stimulus apparatus, and presence of an observer. On the basis of our experience with this species, there were no obvious indications that snake behavior was affected by the presence of an observer.

The testing chamber consisted of 3 contiguous and attached clear plastic boxes placed on top of an elevated glass surface. Sides of the boxes were clear to provide visual access for the observer, but panels between each box were opaque so that the snakes were unable to see each other. On each test day, snakes were allowed a 2-hour acclimation period in the chamber prior to data collection.

Nine snakes (mean ± SEM body weight, 186 ± 16 g) were used in the first experiment. Snakes were arbitrarily assigned to initially receive 1 of 3 treatments: dexmedetomidine (0.1 or 0.2 mg/kg) or an equal volume of saline solution (approx 200 µL). Dexmedetomidine and saline solution were injected in the cranial half of the body in the subcutaneous tissues overlying the epaxial muscles. The observer was not aware of the treatment administered to each snake.

Antinociception was assessed by measuring the latency (time from onset of stimulus to movement) of body withdrawal reflexes in response to a noxious heat stimulus with a standard apparatus and established methods. An infrared heat source was applied directly beneath the glass surface under the cranioventral surface of a snake's body 5 to 12 cm caudal to the tip of the nose, which located the infrared device as close to the snake’s head as possible. The stimulus was applied in approximately the same location on the rostral third of each snake's body regardless of the snake’s length. Optimal intensity was set to induce a baseline withdrawal latency of 5 to 10 seconds, thereby allowing a dynamic range sufficient to detect increases or decreases in withdrawal latency. The apparatus automatically quantified withdrawal latency via a motion-sensitive timer, which measured latency in seconds when the snake moved its body from the heat stimulus. As a precaution to prevent tissue damage, the apparatus was set to allow a maximum exposure latency of 32.6 seconds.

Thermal withdrawal latency was obtained immediately before injection (time 0) and 2, 4, 6, 8, and 24 hours after injection of dexmedetomidine or saline solution. Two measurements of withdrawal latency were obtained 15 minutes apart at each time point. Mean withdrawal latency for each time point was the mean of the 2 measurements. When the 2 values differed by > 10 seconds, a third measurement was obtained; the mean for the 3 values was then calculated.

After a minimum washout period of 7 days, the procedures were repeated. Each snake was arbitrarily administered another of the 3 treatments, and antinociception testing was performed. The procedures were repeated a final time 7 days later, when each snake received the third treatment.

A second experiment was conducted to measure withdrawal latency during the first 60 minutes after injection. The second experiment was conducted a minimum of 9 days after conclusion of the preceding antinociception experiment. Nine snakes (8 from the first experiment and 1 new snake; mean ± SEM body weight, 181 ± 14 g) were used in this experiment. Snakes were injected SC with dexmedetomidine (0.1 mg/kg) or saline solution, and antinociception testing was conducted as described previously. After a minimum washout period of 7 days, snakes received the other treatment, and the procedures were repeated.

**Behavior experiment**

A randomized complete crossover experiment was conducted to evaluate the effects of saline solu-
tion and dexmedetomidine injections on ball python behaviors (tongue flicking, head flinching, movement, and righting reflex). The behavior experiment was conducted at an ambient temperature of 26°C to 28°C during late morning and early afternoon hours.

Eight snakes (mean ± SEM body weight, 381 ± 23 g) were used in this experiment; 6 of these snakes had been used in the antinociception experiments. Each ball python received an SC injection of dexmedetomidine (0.1 mg/kg) or saline solution. Snakes were individually filmed with a digital video-recording program on a laptop computer. Behaviors were recorded immediately before injection (time 0) and 2 and 24 hours after injection of dexmedetomidine or saline solution. Each snake was placed on a soft paper pad on a laboratory benchtop; snakes were allowed 1 minute to acclimate. At each time point (0, 2 and 24 hours), a video recording of unimpeded behavior was obtained for approximately 1 minute and used to assess spontaneous movement and tongue flicking. The observer (LGB), who recorded the behavior and was unaware of the treatment administered to each snake, then made a hand movement toward the head of the snake to induce a head flinch, which is a typical behavior for this species. Approximately 30 seconds after the head flinch test was performed, each snake was placed in dorsal recumbency to assess the righting reflex. Video recording was again obtained for approximately 1 minute. Recordings were uploaded to a computer and labeled with identifying information for the snake.

After behaviors for all snakes were recorded, a second observer (KKS, who was also unaware of the treatment administered to each snake) scored the videos with respect to 4 behaviors. Tongue flicking frequency was scored as 0 (normal or regular tongue flicking for the species [> 10 flicks/min], 1 (diminished [1 to 10 flicks/min]), or 2 (rare or absent [≤ 1 flick/min]). Head flinching was scored as 0 (present) or 1 (absent). Movement was scored as 0 (normal for the species [purposeful movement for the entire duration of video recording]), 1 (diminished [purposeful movement for < 50% of the duration of the video recording]), or 2 (no movement [no movement for the entire duration of the video recording]). Righting reflex was scored as 0 (normal for the species [1 to 2 seconds]), 1 (2 to 5 seconds), or 2 (> 5 seconds). Snakes receiving saline solution were expected to have values near 0 for this scoring system. After a washout period of 7 days, snakes were administered the other treatment, and the procedures were repeated.

**Respiratory experiment**

A complete crossover experiment was conducted to evaluate dexmedetomidine effects on changes in breathing. The respiratory experiment was conducted at an ambient temperature of 26°C to 28°C. Seven snakes (mean ± SEM body weight, 255 ± 14 g) were used in this experiment (5 snakes had been used in the antinociception experiments, and 6 had been used in the behavior experiment). Snakes were allowed to acclimate to the test chamber with airflow for up to 8 h/d for the 3 days prior to testing. On the day of testing, snakes were placed in the chamber with airflow and allowed a 90-minute period of acclimation.

Snakes were placed in an opaque, airtight chamber (inner dimensions, 10 × 20 cm) with constant airflow (approx 0.2 L/min). Inflow and outflow ports were closed, and a pressure transducer was attached to a separate port, which converted pressure changes to voltage signals. Upward deflections indicated increased pressure (expiration), and downward deflections indicated decreased pressure (inspiration). These signals were digitized and summarized with a data acquisition system and analyzed offline with computer software. Snakes remained in the box for a total of 9 to 10 h/d on testing days. Breathing frequency data were collected immediately before SC injection of dexmedetomidine (0.1 mg/kg) or saline solution (baseline [time 0]) and hourly for 8 hours after injection. Respiratory data were recorded continuously during sequential 20-minute sessions (closed chamber) that were separated by 2-minute episodes when airflow was used to flush the chamber (open chamber). This cycle between opening and closing continued for the entire 9 to 10 hours of testing. Preliminary experiments revealed that breathing frequency was unchanged when the chamber was closed for 20 minutes. Thus, it was unlikely that there was marked CO₂ accumulation or hypoxia during a 20-minute recording session. Breathing frequency was measured by counting downward inspiratory deflections during periods of quiet breathing. Obvious irregular movement artifacts were not counted. Mean value for breathing frequency was calculated within each specific time point.

Snakes were returned to their housing cages overnight. The next day, they were again placed in the testing chamber and allowed an acclimation period of 90 minutes, which was followed by recording of data at 24 hours after injection. After a minimum washout period of 7 days, the other treatment was administered to each snake and the procedures were repeated. The 7-day washout period was considered adequate because there were no changes in baseline breathing frequency. Snakes were monitored daily during and after the respiratory experiment.

**Data analysis**

Commercially available software was used to analyze data with a 2-way repeated-measures ANOVA. For the antinociception and behavior data, normality and equal variance assumptions were met. For the respiratory data, square root transformation of data was needed to meet normality and equal variance assumptions. Post hoc comparisons were conducted with the Student-Newman-Keuls test. Comparison of the mean thermal withdrawal latency at 2 hours after injection was conducted with a Mann-Whitney rank
sum test because the data did not have equal variance. All data were reported as mean ± SEM. Values were considered significant at $P < 0.05$

**Results**

**Thermal antinociception experiments**

Dexmedetomidine increased noxious thermal withdrawal latency in a dose-dependent manner. When snakes were injected with saline solution (control treatment), mean ± SEM thermal withdrawal latency at baseline was 7.0 ± 0.8 seconds, and it did not change over time (Figure 1). Mean thermal withdrawal latency ranged between 5.8 and 6.5 seconds during the period from 2 to 24 hours after injection of saline solution. Baseline mean thermal withdrawal latency when snakes received dexmedetomidine at 0.1 and 0.2 mg/kg was 6.7 ± 0.5 seconds and 6.7 ± 0.5 seconds, respectively, which was similar to the baseline value for the snakes after injection of saline solution. At 2 hours after administration of dexmedetomidine, mean thermal withdrawal latency significantly ($P < 0.001$) increased to peak values of 20.2 ± 2.3 seconds (0.1 mg/kg) and 24.9 ± 2.6 seconds (0.2 mg/kg). During the next 6 hours, mean thermal withdrawal latency decreased; mean values were still significantly different from the baseline value at the 8-hour time point (12.0 ± 2.1 seconds for 0.1 mg/kg [$P < 0.001$] and 15.7 ± 2.6 seconds for 0.2 mg/kg [$P = 0.006$]). At 24 hours after dexmedetomidine administration, mean thermal withdrawal latency had decreased further and did not differ significantly ($P = 0.746$) from the baseline value. There was a significant ($P < 0.001$) effect of dexmedetomidine at both dosages. The 7-day washout period was adequate because there were no changes in baseline withdrawal latency during the study.

Because the peak increase in thermal withdrawal latency was at 2 hours after injection with dexmedetomidine at both doses, dexmedetomidine (0.1 mg/kg) or saline solution was administered during a second experiment, and thermal withdrawal latency was evaluated at 15, 30, and 60 minutes after injection to determine the rapidity of dexmedetomidine effects on thermal withdrawal latency. Baseline mean ± SEM thermal withdrawal latency was similar for snakes when injected with dexmedetomidine (5.3 ± 0.4 seconds) or saline solution (5.8 ± 0.6 seconds; Figure 1). Similar to results for the first antinociception experiment, mean thermal withdrawal latency did not change over time when saline solution was administered. When dexmedetomidine was administered, mean thermal withdrawal latency increased significantly ($P < 0.001$) to 23.5 ± 0.9 seconds at 15 minutes, and it remained elevated at 20.8 ± 1.5 seconds at 60 minutes. There was a significant ($P < 0.001$) effect of dexmedetomidine.

**Behavior experiment**

In general, there were no consistent differences in behavior between snakes when they received sal-
line solution or dexmedetomidine. For tongue flicking, mean ± SEM baseline preadministration score was similar when snakes were injected with saline solution (1.0 ± 0.4) and dexmedetomidine (0.5 ± 0.2; Figure 2). At 2 hours after saline solution administration, mean tongue flicking score (1.6 ± 0.3) was higher, but not significantly so (P = 0.076), and it decreased to 0.5 ± 0.3 by the 24-hour time point. In contrast, the mean tongue flicking score after dexmedetomidine administration was significantly increased, compared with the baseline value, at 2 (1.9 ± 0.1; P = 0.001) and 24 (1.3 ± 0.5; P = 0.056) hours; however, there was not a significant (P = 0.626) overall drug effect. For head flinching, there was no difference in the mean baseline scores after injection of saline solution (0.1 ± 0.1) and dexmedetomidine (0.3 ± 0.2), and there were no significant changes in scores over time or for drug effects (P = 0.451). For movement, there was no significant difference in the mean baseline score after injection of saline solution (1.1 ± 0.4) and dexmedetomidine (0.6 ± 0.3). For saline solution injection, mean movement score was higher (19 ± 0.1), but not significantly so (P = 0.055), at 2 hours, and it decreased at 24 hours (0.5 ± 0.3) to values that were less than, but not significantly (P = 0.106) different from, baseline values. In contrast, mean movement score after dexmedetomidine injection increased significantly (P = 0.033) to 1.6 ± 0.3 at 2 hours and remained significantly higher at 24 hours (1.5 ± 0.3; P = 0.027 compared with the baseline dexmedetomidine value and P = 0.037 compared with the 24-hour value for saline solution). There was not a significant (P = 0.79) overall drug effect for movement. For righting reflex, there were no differences in the baseline score for saline solution (0.9 ± 0.4) and dexmedetomidine (0.3 ± 0.2), and there was not a significant effect of changes over time or drug-dependent changes (P = 0.185).

At the 2-hour time point, mean thermal withdrawal latency was significantly (P < 0.001) higher for snakes after dexmedetomidine injection (22.1 ± 2.2 seconds), compared with the value for snakes after saline solution injection (6.9 ± 0.8 seconds). This confirmed that results for the behavior tests performed at the 2-hour time point were consistent with the maximal thermal withdrawal latency.

**Respiratory experiment**

Dexmedetomidine administration depressed breathing frequency, but the snakes continued to breathe throughout the experimental period. Mean ± SEM baseline breathing frequency was similar when snakes were injected with saline solution (6.4 ± 0.5 breaths/min) and dexmedetomidine (6.7 ± 0.8 breaths/min; Figures 3 and 4). After saline solution was administered, breathing frequency decreased during the next 4 hours and plateaued at a significantly (P = 0.029 to 0.032) higher value of 3.7 to 4.0 breaths/min at 6 to 8 hours, compared with the baseline value. Breathing frequency at 24 hours after saline solution administration was 5.2 ± 0.5 breaths/min, which was lower than, but not significantly (P = 0.339) different from, the baseline value. In contrast, breathing frequency decreased significantly (P < 0.001) after dexmedetomidine administration to a mean of 2.1 ± 0.7 breaths/min at the 1-hour time point and remained significantly lower (1.5 to 2.2 breaths/min) for the next 7 hours, compared with the baseline value. Breathing frequency remained significantly (P = 0.011) lower at 24 hours. There was a significant (P = 0.002) effect of dexmedetomidine. Although tidal volume could not be accurately quantified with the technique used, inspiratory traces were generally increased in amplitude, whereas breathing frequency was depressed by dexmedetomidine, which suggested that tidal volume was increased and breathing frequency was depressed.

![Figure 2](image-url)
Discussion

To the authors' knowledge, the study reported here was the first in which the antinociceptive, behavioral, and respiratory effects of dexmedetomidine in ball pythons have been evaluated. Results of the present study indicated that SC administration of dexmedetomidine increased thermal withdrawal latency with minimal changes in behavior, which suggested that dexmedetomidine provided antinociception with few indications of potential sedative effects. Although dexmedetomidine clearly caused respiratory depression, all ball pythons continued to breathe regularly and did not have periods of sustained apnea. Because dexmedetomidine caused reproducible and robust increases in thermal withdrawal latency in this snake species, it and other \(\alpha_2\)-adrenoceptor agonists may have clinical applications for providing analgesia in snakes.

The \(\alpha_2\)-adrenoceptor agonist drugs are commonly used in veterinary medicine because they provide short-term, reversible sedation (to facilitate physical examinations, clinical procedures, and minor surgical procedures), analgesia, muscle relaxation, and anxiolysis.26 The \(\alpha_2\)-adrenoceptor agonists are also useful because of their potent anesthetic-sparing effects for other injectable and inhalation anesthetics.14,26 In mammals, the antinociceptive effects of \(\alpha_2\)-adrenoceptor agonist drugs are likely attributable to activation of \(\alpha_2\)-adrenoceptors in the dorsal portion of the spinal cord,27,28 but the underlying mechanisms are complex because \(\alpha_2\)-adrenoceptors are abundantly expressed at presynaptic and postsynaptic sites in dorsal horn spinal neurons.29 However, the antinociceptive effects of \(\alpha_2\)-adrenoceptor agonists in reptiles are poorly understood. In studies that involved formalin-induced nociception, clonidine administration reduced hind limb withdrawal in marsh terrapins22 and Speke’s hinged tortoises.23 Antinociceptive effects of dexmedetomidine in any reptile species or class are unknown. In the present study, dexmedetomidine without other coadministered drugs significantly increased the noxious thermal withdrawal latency in a consistent, dose-dependent manner that lasted for at least 8 hours. Onset of the dexmedetomidine effects was rapid (within 15 minutes after injection), which would be a clear benefit in clinical settings.

Application of noxious thermal stimuli to an animal’s limb is an established method for assessing nociception and analgesic efficacy in mammals,25 birds,30 and reptiles.8,10,11,31 This experimental approach is a valuable screening tool because it can be performed rapidly, is reproducible and quantifiable, and does not cause temporary or permanent tissue damage. It is recognized that this experimental approach does not simulate the multidimensional aspects of nociception in clinical situations.32 Nevertheless, candidate analgesic drugs can be identified with this method and then subsequently tested and validated for clinically relevant painful conditions (e.g., after surgery). Although snakes may have distinct differences in

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**Figure 3** — Representative respiratory-related traces obtained with whole-body closed-chamber plethysmography illustrating breathing movements in a ball python at various times after SC injection of saline solution (A) and dexmedetomidine at 0.1 mg/kg (B). Breathing frequency was assessed before administration (time 0; baseline), hourly for 8 hours after administration, and 24 hours after administration. Downward deflections represent inspiratory movements, and upward deflections represent expiratory movements. Analysis of the patterns indicates that dexmedetomidine decreases breathing frequency to a greater extent than does saline solution. In panel B, notice that the traces at 2 and 8 hours after administration were obtained at half the gain of all other traces.

**Figure 4** — Mean ± SEM breathing frequency during a 24-hour period for ball pythons \((n = 7)\) after SC injection of saline solution (white circles) or dexmedetomidine at 0.1 mg/kg (black squares) in accordance with a complete crossover design. Breathing frequency was assessed by use of whole-body closed-chamber plethysmography before administration (time 0), hourly for 8 hours after administration, and 24 hours after administration. There was a significant \((P < 0.05)\) drug effect for dexmedetomidine. See Figure 1 for remainder of key.
thermal nociceptive pathways as opposed to other somatic nociceptive sensations (eg, noxious incisional stimuli), the large increase in thermal withdrawal latency in the present study suggested that dexmedetomidine was altering nociception to a substantial degree and warrants further study with other clinically relevant evaluations of nociception.

The $\alpha_2$-adrenoceptor agonist drugs are used extensively as sedatives in veterinary medicine, but they often are coadministered with other anesthetic drugs, which makes it difficult to determine the extent to which the sole use of $\alpha_2$-adrenoceptor agonists causes sedation. The combination of dexmedetomidine and ketamine rapidly induces sedation and anesthesia in yellow-bellied sliders,$^{19}$ diamondback terrapins,$^{20}$ and hatching leatherback sea turtles.$^{21}$ To the authors’ knowledge, there has been only 1 study$^{24}$ in which medetomidine was administered alone to desert tortoises; it caused reversible anesthesia within 20 minutes after injection. Results of that study$^{24}$ of desert tortoises suggest that $\alpha_2$-adrenoceptor agonists can cause sufficient anesthesia and sedation in some reptile species, but there have been no studies that involved the use of snakes. Accordingly, it was important to determine whether the dexmedetomidine-dependent increase in thermal withdrawal latency in ball pythons was a result of antinociception or sedation. Thus, behavior was observed after saline solution or dexmedetomidine was administered SC to ball pythons. If dexmedetomidine were increasing thermal withdrawal latency as a result of sedation, one would expect to see dramatic increases in the scores for all 4 behaviors assessed, especially the movement and righting reflex scores. For example, medetomidine-induced sedation in desert tortoises caused significant slowing of leg and neck reflexes, and half the tortoises urinated copiously during that study,$^{24}$ which likely reflected loss of bladder sphincter muscle tone. In the study reported here, there were no dexmedetomidine-induced gross deficits in motor function or bowel control. It was possible that circadian rhythm-dependent changes in snake activity and responsiveness increased variability in the responses, but the experiment was performed at approximately the same time of day for all snakes, and there were no obvious effects of time of day on activity during preliminary studies on ball python behavior. In the present study, ball pythons retained the flinch reflex, which indicated a functional visual system, and the righting reflex was not altered, which indicated a functional vestibular response. Dexmedetomidine administration decreased tongue flicking and caused a modest decrease in movement, which suggested that that there were mild sedative effects on some aspects of motor function. Breathing frequency was significantly decreased after administration of dexmedetomidine, but the ball pythons were able to continue breathing (in some cases with large respiratory efforts), which suggested that respiratory motor function may not have been impaired by dexmedetomidine. Considered together, these data suggested that dexmedetomidine had substantial analgesic effects and mild sedative properties on some motor behaviors.

The $\alpha_2$-adrenoceptor agonists generally cause respiratory depression in mammals. For example, breathing frequency decreases in dogs after administration of medetomidine$^{35}$ or dexmedetomidine$^{34}$ and in cats after administration of dexmedetomidine.$^{35}$ Similarly, dexmedetomidine increases Pa$^{2}$CO$_{2}$ and decreases PaO$_{2}$ in adult sheep.$^{36}$ Substantially less is known concerning the effects of activation of $\alpha_2$-adrenoceptors on breathing in ectothermic vertebrates. Application of clonidine-soaked pledgets on the ventral medullary surface of cane toad brainstems increases respiratory activity at low doses and decreases respiratory activity at high doses.$^{37}$ In desert tortoises, medetomidine induces significant respiratory depression that lasts > 2 hours.$^{21}$ Little is known for snakes with regard to respiratory rhythm generation and modulation by adrenoceptor regulation. Snakes typically breathe with single breaths at a rate of 1.8 to 4.3 breaths/min.$^{38-40}$ Mean ± SD breathing frequency is 1.8 ± 0.3 breaths/min in 1 python species (Python molurus).$^{21}$ In those studies, a number of methods was used to measure total ventilation, breathing frequency, and tidal volume in awake snakes, but several of these methods constrained normal snake behavior (eg, snakes were secured to a flat surface,$^{38}$ or a mask was attached with epoxy glue$^{41}$). In the present study, whole-body closed-chamber plethysmography was used because this allowed the unrestrained ball pythons to coil up within the chamber and breathe normally. Although this noninvasive technique did not allow accurate quantification of tidal volume, breathing frequency was easily measured. Ball pythons breathed at approximately 6.5 breaths/min during the preinjection baseline period, which decreased to approximately 4 breaths/min over the next 8 hours, which is similar to breathing frequencies previously reported for snakes. Results of the present study indicated that breathing frequency decreased after administration of dexmedetomidine, but there appeared to be a compensatory increase in tidal volume, which may have allowed for sufficient oxygenation and regulation of arterial CO$_{2}$ content. The decrease in breathing frequency suggested that dexmedetomidine was altering the respiratory rhythm generator in the brainstem directly or indirectly. For example, dexmedetomidine may have been directly decreasing synaptic excitation or augmenting synaptic inhibition within the respiratory central pattern generator of the snakes, which thereby decreased respiratory frequency. On the other hand, dexmedetomidine may have been indirectly altering respiratory frequency by decreasing peripheral or central chemosensory stimulation or by altering excitatory neuromodulatory inputs to the respiratory rhythm generator. Although there was significant dexmedetomidine-induced depression of breathing frequency, all snakes recovered from multi-
ple drug administrations without obvious deleterious or lingering adverse effects.

Results of the study reported here suggested that dexmedetomidine may provide antinociception in snakes for at least 8 hours with minimal sedative effects and modest respiratory depression. This would be a major step forward in research on snake analgesia because we are aware of no other studies for which there have been antinociceptive effects of a drug without additional evidence of sedation. The main limitation of dexmedetomidine as an analgesic appeared to be substantial respiratory depression. It may be possible to use a lower dexmedetomidine dose to minimize respiratory depression but still provide some degree of antinociception. Alternatively, it may be possible to coadminister a respiratory stimulant along with dexmedetomidine to prevent respiratory depression while maintaining antinociception. Other snake species (eg, corn snakes and boas) may respond differently to dexmedetomidine, which is similar to the varied responses of reptiles to opioid-receptor activation.8–11 Although it is not possible to predict how other snake species will respond to dexmedetomidine, opioid-receptor activation does not alter the thermal withdrawal latency in corn snakes,10 ball pythons,12 and boa constrictors (KKS and SMJ; unpublished observations). Thus, we hypothesize that several snake species will respond to dexmedetomidine administration in a manner similar to the response of ball pythons.

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Footnotes

a. Reptile Rapture, Monona, Wis.

b. PetSmart West Madison, Madison, Wis.


d. Ugo Basile plantar analgesia instrument, model 37370, Ugo Basile Co, Comerio, Italy.

e. Dexcomitror, 0.5 mg/mL, Orion Corp, Espoo, Finland.

f. Photo Booth, version 8.0, Apple Inc, Cupertino, Calif.

g. MacBook Pro, Apple Inc, Cupertino, Calif.

h. Model DP45-14, Validyne Engineering Corp, Northridge, Calif.

i. DiGiData 1200, Axon Instruments, Sunnyvale, Calif.

j. pClamp software, Axon Instruments, Sunnyvale, Calif.


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27. Pertovaara A, Kauppila T, Tukeva T. The effect of medetomi-


