Respiratory and antinociceptive effects of dexmedetomidine and doxapram in ball pythons (Python regius)

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OBJECTIVE  
To determine the effects of dexmedetomidine, doxapram, and dexmedetomidine plus doxapram on ventilation (V\text{e}) breath frequency, and tidal volume (V\text{t}) in ball pythons (Python regius) and of doxapram on the thermal antinociceptive efficacy of dexmedetomidine.

ANIMALS  
14 ball pythons.

PROCEDURES  
Respiratory effects of dexmedetomidine and doxapram were assessed with whole-body, closed-chamber plethysmography, which allowed for estimates of V\text{e} and V\text{t}. In the first experiment of this study with a complete crossover design, snakes were injected, SC, with saline (0.9% NaCl) solution, dexmedetomidine (0.1 mg/kg), doxapram (10 mg/kg), or dexmedetomidine and doxapram, and breath frequency, V\text{e}, and V\text{t} were measured before and every 30 minutes thereafter, through 240 minutes. In the second experiment, antinociceptive efficacy of saline solution, dexmedetomidine, and dexmedetomidine plus doxapram was assessed by measuring thermal withdrawal latencies before and 60 minutes after SC injection.

RESULTS  
Dexmedetomidine significantly decreased breath frequency and increased V\text{t} but did not affect V\text{e} at all time points, compared with baseline. Doxapram significantly increased V\text{e}, breath frequency, and V\text{t} at 60 minutes after injection, compared with saline solution. The combination of dexmedetomidine and doxapram, compared with dexmedetomidine alone, significantly increased V\text{e} at 30 and 60 minutes after injection and did not affect breath frequency and V\text{t} at all time points. Thermal withdrawal latencies significantly increased when snakes received dexmedetomidine or dexmedetomidine plus doxapram, versus saline solution.

CONCLUSIONS AND CLINICAL RELEVANCE  
Concurrent administration of doxapram may mitigate the dexmedetomidine-induced reduction of breathing frequency without disrupting thermal antinociceptive efficacy in ball pythons. (Am J Vet Res 2021:82:11–21)

Untreated pain and causes of stress in reptiles are associated with immunocompromise, negative energy balance, and delayed wound healing.\(^1\) Well-defined guidelines exist regarding pain assessment and management in mammals,\(^2\)–\(^4\) but not for reptiles, for which the neural mechanisms of pain are poorly understood and effective analgesic drugs are frequently lacking.\(^5\)–\(^9\) Consequently, analgesia may infrequently be provided to reptilian patients in practice.\(^5\)

Opioids are effective analgesics in turtles and lizards,\(^10\)–\(^15\) but opioids are inconsistently effective analgesics in snakes, with many opioids failing to provide adequate antinociception in laboratory models of pain.\(^11,16,17\) Nonsteroidal anti-inflammatory drugs are commonly used in practice to mitigate signs of postoperative pain in reptiles; however, the few studies\(^9\) with reptiles, including snakes, reveal that NSAIDs have minimal efficacy.

Given the questionable efficacy of opioids and NSAIDs in snakes, we recently investigated and demonstrated that dexmedetomidine, an \(\alpha_2\)-adrenoceptor agonist, is a candidate analgesic for ball pythons (Python regius).\(^18\) \(\alpha_2\)-Adrenoceptor agonists are commonly used as an analgesic or anesthetic induction agent in veterinary medicine, particularly for mammals.\(^19\)–\(^22\) Several \(\alpha_2\)-adrenoceptor agonists provide sedative and antinociceptive effects in turtles and lizards.\(^23\)–\(^26\) Dexmedetomidine provides thermal antinociception for at least 8 hours in ball pythons, but it also significantly decreases breath frequency.\(^18\) \(\alpha_2\)-Adrenoceptor agonists acting at brainstem and peripheral \(\alpha_2\)-adrenoceptors\(^27\) cause inhibition of breathing in mammals,\(^28\)–\(^32\) amphibians,\(^33\) and reptiles.\(^23\)–\(^26\) Because respiratory depression in reptiles
may alter arterial blood gases and reduce hypoxic ventilatory responses, leading to hypoxemia and tissue hypoxia.\textsuperscript{33} Dexametomidine-induced respiratory depression in snakes could have similar physiologic effects. Reptiles are generally more tolerant of hypoxia than mammals,\textsuperscript{35-42} with many adaptations to cope with hypoxia.\textsuperscript{35-42} However, respiratory depression could negatively impact snakes, especially if they are already compromised by respiratory disease, hemorrhage, hypovolemia, or cardiac disturbances (eg, congenital heart defects, endocarditis, or heart failure). Respiratory depression induced by an \( \alpha_2 \)-adrenoceptor agonist could also prolong the time to recover from trauma or surgical procedures, as well as prolong the time to expel volatile anesthetics in the postoperative period. Therefore, counteracting respiratory depression induced by dexametomidine is ideal, and doxapram, a respiratory stimulant, may do this.

Doxapram is a potassium channel blocker that acts on central respiratory centers and peripheral chemoreceptors to stimulate breathing in a dose-dependent manner.\textsuperscript{43,44} Doxapram is efficacious in crocodiles\textsuperscript{45} and, in anecdotal reports,\textsuperscript{46} stimulates breathing in reptilian patients in emergency settings, but no studies have yet specifically included an evaluation of doxapram in snakes. However, because reptiles have central respiratory centers and peripheral chemoreceptors similar to mammals,\textsuperscript{47-49} doxapram is expected to similarly stimulate breathing in snakes.

The primary goal of the study presented here was to determine whether the combination of dexametomidine and doxapram could effectively provide adequate nociception (dexametomidine) and simultaneously mitigate dexametomidine-induced respiratory depression (doxapram). First, dexametomidine-induced respiratory depression was confirmed. Then, the respiratory effects of doxapram alone and in combination with dexametomidine were determined. Lastly, the antinociceptive effects of dexametomidine alone and combined with doxapram were determined.

Materials and Methods

Animals

Fourteen ball pythons with mean (SEM; range) body weight of 243 g (35 g; 55 to 430 g) were obtained from multiple commercial vendors through the course of the study. The sex of each snake was not determined. All snakes were housed in the Animal Resource Center at the School of Veterinary Medicine, University of Wisconsin-Madison. Snakes were kept in standard laboratory enclosures (width, 26 cm; depth, 48 cm; height, 20 cm) and provided with a hideaway and a water source at all times. Snake enclosures were cleaned at least weekly by animal care technicians but more frequently when the enclosures were wet or soiled. Environmental temperature was maintained between 25°C and 29°C, and snakes were subjected to a 12-hour light cycle. Snakes were fed thawed mice or neonatal rats once weekly (Friday afternoons). All tests were performed Monday through Friday, and no tests were performed < 60 hours after feeding. The study was approved by the Institutional Animal Care and Use Committee (protocol No. V5710).

Dose selection

A dose of 0.1 mg of dexametomidine/kg was used for the present study on the basis of results of a previous study\textsuperscript{48} of ball pythons, in which this dose was effective for thermal antinociception and associated with decreased breath frequency. A dose of 10 mg of doxapram/kg was selected on the basis of a previous study\textsuperscript{45} with alligators, in which an increase in breathing frequency was noted after its administration.

Respiratory experiment

A complete crossover-design experiment was conducted to evaluate the effects of dexametomidine alone, doxapram alone, and the 2 drugs in combination on changes in breathing. Respiratory function was measured in snakes (\( n = 11 \)) through unstrained, whole-body, closed-chamber plethysmography in a room maintained between 26°C and 28°C (measured by a thermometer next to the chamber). Snakes that weighed < 300 g were placed in a small air-tight chamber (inner dimensions, 10 X 20 X 5 cm) and snakes > 300 g were placed in a large air-tight chamber (inner dimensions, 22 X 11 X 7 cm) with a transparent lid (Figure 1). The chambers were large enough such that the snakes could move freely. Room air (21% O\textsubscript{2}) was supplied at a rate of approximately 0.10 L/min into one port of the chamber, verified with a flowmeter,\textsuperscript{4} and room air was removed from another port at the same verified rate with the facility’s vacuum system. The chamber was connected via a different port to a differential pressure transducer.\textsuperscript{4} The pressure transducer was also connected to a similarly sized chamber (reference chamber). The reference chamber helped to minimize artifacts resulting from changes in ambient barometric pressure or noise, as noted in previous studies\textsuperscript{50,51} involving whole-body plethysmography. A visual barrier was placed around the chamber to minimize visual cues to the snake that could induce its movement (and therefore artifacts) or alter its breathing. The valves that controlled airflow for the flowmeter and vacuum were separate from the chamber, outside of the visual barrier, so that movements and vibrations resulting from adjusting the valves would not startle the snake (eg, a light tap on the chamber markedly increased breathing frequency for several minutes). Key improvements from our previously published\textsuperscript{18} method were a transparent chamber lid, so a snake did not sleep or enter a torpor-like state that can affect its breathing pattern during the 12-hour light cycle\textsuperscript{52,53}; the airflow control valves were located away from the
and increase $\dot{V}_e$ and $V_t$ were calculated from a linear calibration curve that was generated by making expiratory traces with known volumes of a syringe, that mimicked snake breathing, attached to the recording chamber. This technique allowed for reasonable estimation of $\dot{V}_e$ and $V_t$.

Prior to the respiratory experiment, the snakes were conditioned to the chamber and portions of the experimental protocol for at least 6 hours on 2 or more days. Conditioning was conducted by placing a snake into the chamber and alternating between 20 minutes of airflow and 10 minutes of no airflow (ie, air inflow and outflow ports closed), with data recorded during the 10-minute period of no airflow. Alternating periods of airflow and no airflow prevented accumulation of CO$_2$ in the chamber, which can stimulate breathing.$^{54}$ Increase $V_t$, increase breath frequency, and increase $\dot{V}_e$ and allowed for nearly continuous recording for > 8 hours.$^{58}$ When the inflow and outflow ports were closed, the pressure transducer detected pressure changes attributable to breathing movements. An amplifier converted these pressure changes to voltage signals, which were subsequently recorded by a data acquisition system$^6$ and later analyzed with computer software.$^h$ On the digital tracing produced by the pressure transducer, upward deflections indicated increased pressure (expiration) and downward deflections indicated decreased pressure (inspiration).

For the experiment, snakes were placed in the chamber for approximately 2 hours to allow the snake to reach a steady rate and quality of breathing. For the time-control part of the experiment, the breathing of non-sedated snakes was recorded for 10 out of every 30 minutes (20 minutes of airflow and 10 minutes of no airflow, when breathing recorded) for 4 to 6 hours. For the treatment part of the experiment, the snakes were allowed to reach steady baseline breathing, then the chamber was opened, and the snakes randomly received the first of 4 treatments: SC injection of saline (0.9% NaCl) solution (isovolumetric to doxapram dose), dexmedetomidine$^i$ (0.1 mg/kg), doxapram$^j$ (10 mg/kg), or dexmedetomidine plus doxapram.

Treatments were injected SC into the cranial one-third of the body at the approximate level of the heart to avoid the hepatic first-pass effect. Breathing data were collected for 240 minutes after injection. A minimum 7-day washout period was maintained between treatments.

Thermal antinociception study

A blinded, randomized, within-subjects complete crossover-design experiment was conducted to determine whether doxapram would alter the antinociceptive efficacy of dexmedetomidine. This experiment included use of a modified Hargreaves plantar thermal limb withdrawal latency apparatus,$^k$ with the original designed to assess nociception and thermal antinociception in rodents$^59$ and which our laboratory had previously adapted for use with reptiles.$^{10-15}$ The testing enclosure was comprised of 3 contiguous chambers on an elevated glass surface (allowing 3 snakes to be tested simultaneously), through which a noxious thermal stimulus could be applied from below. An opaque panel separated each chamber, such that the snakes

Figure 1.—Drawing of the whole-body, closed-chamber plethysmography apparatus used for the respiratory experiment with 11 ball pythons (Python regius). A—The snake was placed into an air-tight chamber with a transparent lid. Airflow into and out of the chamber was manually controlled with valves located approximately 20 cm from the chamber to minimize chamber disturbances. An opaque barrier (visual barrier) surrounded the chamber to minimize visual stimulation or disturbance of the snake. The chamber was connected to a reference chamber of similar size via plastic tubing and a differential pressure transducer, which detected pressure changes attributable to breathing movements. An amplifier converted the pressure changes into voltage signals that were subsequently recorded by a data acquisition system to be later analyzed with computer software. B—A representative respiratory-related voltage trace (created by voltage signals) shows waveforms consistent with normal breathing plus an area of movement artifact. Downward deflections represent inspiratory movements, and upward deflections represent expiratory movements.
could not see each other but could see the observer. The experiment was conducted at an ambient temperature of 26°C to 28°C. In the modified version, the Har-greaves apparatus was used to apply a noxious thermal stimulus, via an infrared beam, to the cranoventral one-third of the snake’s body. Following activation of the infrared heat source, TWLs were measured automatically with a motion-sensitive timer. Stimulation strength of the infrared beam was adjusted to produce baseline latencies of 8 to 12 seconds. To minimize thermal injury, the heating apparatus automatically turned off at 32.6 seconds.

Three snakes were used for the thermal antinociception study, under 3 experimental conditions. Prior to the day of testing, snakes were conditioned to the test chamber and the presence of an observer for 2 to 4 hours, with intermittent exposure to a beam from the infrared heat source to minimize the snakes’ anticipatory behaviors during testing. On the day of testing, snakes were acclimated to the test chamber for at least 30 minutes. Baseline TWLs were then recorded every 5 minutes for at least 2 trials. If the 2 TWLs differed by > 10 seconds, a third trial was performed. Mean baseline TWL was calculated from these trials. A blinded observer then administered a randomly assigned, SC injection to each snake. Thermal withdrawal latencies were measured 60 minutes after injection, the time of peak dexmedetomidine effects. A 7-day washout period was maintained between treatments.

### Data analysis

Within each 10-minute data acquisition period for the respiratory experiment, all upward-deflecting (expiration), respiratory-related voltage traces (without obvious motion artifacts) were marked for analysis with commercially available software. The area of the upward deflections was added and divided by the total number of breaths (breath frequency) to obtain the area per breath. Area per breath was then converted to volume per breath by comparison to a linear calibration curve generated by making similar expiratory traces (duration and shape) with known volumes of a syringe attached to the recording chamber. Separate calibration curves were generated for the small and large recording chambers. The calibration curve permitted calculation of VE (mL/min/kg) and VT (mL/breath/kg) by using the breath frequency data (VE = VT X breathing frequency). Mean values for respiratory variables were calculated for each snake within each 10-minute period and then mean values of all snakes for each 10-minute period of data acquisition were averaged. Whole-body plethysmography is an indirect and qualitative method to evaluate respiratory function because of the inherent pressure variability within the chamber. Thus, determination of actual values for VE and VT was not possible, so VE and VT data were regarded as estimates of their actual values. Nevertheless, this method provided information noninvasively with awake snakes behaving normally during a 12-hour light cycle.

Respiratory and thermal antinociception data were analyzed with a 2-way repeated-measures ANOVA with commercially available software. Normality and equal assumption tests were not always satisfied, despite data transformation. Given that a 2-way repeated-measures ANOVA is not applicable for non-parametric data, the statistical results were interpreted cautiously. Post hoc comparisons were conducted with the Student-Newman-Keuls test. All data were reported as mean ± SEM, and values of P < 0.05 were considered significant.

### Results

#### Respiratory experiment

Variability in the shape of voltage traces recorded by the plethysmograph was considerable, likely because of each snake’s posture in the chamber and variability in each snake’s movements during breathing (Figure 2). Nevertheless, rhythmic upward and downward traces indicated that breathing was observed and could be differentiated from movement...
artifacts. For the time-control and saline solution and dexmedetomidine treatment parts of the experiment, baseline $\dot{V}_e$, breath frequency, and $V_t$ were similar, which indicated that all snakes were breathing similarly prior to the start of the experiment (Figure 3).

For the time-control part of the experiment, $\dot{V}_e$ was not altered through 240 minutes from baseline (mean ± SEM, 1.22 ± 0.22 mL/min/kg; Figure 3), but breath frequency was significantly ($P < 0.036$) different between baseline and all other time points (mean ± SEM; baseline, 5.59 ± 1.33 breaths/min vs 240 minutes, 2.56 ± 0.45 breaths/min). No significant differences were noted between $V_t$ at baseline (0.31 ± 0.07 mL/breath/kg) and all other time points.

Saline solution significantly ($P < 0.001$) increased $\dot{V}_e$ at 30 (2.93 ± 0.64 mL/min/kg) and 60 minutes (2.11 ± 0.40 mL/min/kg), compared with baseline (1.21 ± 0.31 mL/min/kg), without significantly affecting $V_t$ (Figure 3). A concurrent significant ($P < 0.005$) increase in breath frequency was noted (baseline, 4.85 ± 0.90 breaths/min vs 30 minutes, 9.26 ± 0.79 breaths/min or 60 minutes, 7.36 ± 0.85 breaths/min). Breath frequency decreased thereafter and achieved a value near baseline at 120
minutes through 240 minutes. Breath frequency increased with saline solution \( (P < 0.001) \) but not with time-control or dexmedetomidine.

Dexmedetomidine caused large expiratory and inspiratory deflections and irregular breathing patterns, compared with time-control and saline solution, starting at 30 minutes after administration.

Compared with baseline \( (1.34 \pm 0.31 \text{ mL/min/kg}) \), \( \dot{V}_E \) did not significantly differ throughout the experiment (Figure 3). Breath frequency at all time points was significantly \( (P < 0.001) \) decreased from baseline \( (5.76 \pm 1.49 \text{ breaths/min vs } 2.09 \pm 0.57 \text{ breaths/min [240 minutes]}) \). Overall, \( \dot{V}_E \) and \( V_t \) with doxapram were significantly \( (P = 0.002 \text{ and } P < 0.001, \text{ respectively}) \) increased versus saline solution.

Thirty and 60 minutes after doxapram administration, \( \dot{V}_E \) was significantly \( (P < 0.001) \) increased, compared with baseline \( (1.23 \pm 0.20 \text{ mL/min/kg}) \), and added doxapram, compared with dexmedetomidine alone, prevented a significant \( (P = 0.016) \) decrease in breath frequency at 30 and 60 minutes. Dexmedetomidine plus doxapram significantly \( (P = 0.041) \) increased \( \dot{V}_E \) from 0.25 \pm 0.04 mL/breath/kg at baseline to 0.61 \pm 0.11 mL/breath/kg (maximum value) at 30 minutes, but baseline \( V_t \) did not significantly differ from other time points. Tidal volume overall and at 120 minutes through 210 minutes for dexmedetomidine plus doxapram was significantly \( (P = 0.013 \text{ and } P < 0.023, \text{ respectively}) \) decreased, compared with dexmedetomidine alone.

**Thermal antinociception experiment**

Sixty minutes after injection of saline solution, TWL \( (\text{mean } \pm \text{ SEM}, 9.5 \pm 1.5 \text{ seconds}) \) did not signifi-
Snakes and other reptiles breathe with a distinct pattern of active inspiration, active expiration, and a breath-holding period. A dramatic change in the overall respiratory pattern of active inspiration, active expiration, and a breath-holding period can be achieved by the administration of dexmedetomidine or doxapram.
tion vary in duration and amplitude throughout the entire 240-minute respiratory experiment. These changes may have been attributable to dexmedetomidine’s effect on the respiratory rhythm–generating neurons in the brainstem. Disrupted breathing patterns caused by dexmedetomidine could have negative consequences (eg, increased arterial hypoxia and hypercapnia) for healthy and unhealthy snakes. Although $\dot{V}E$ was not altered by dexmedetomidine, breathing disruptions may cause moment-by-moment fluctuations in $P_{aO_2}$ and $P_{aCO_2}$. Switching from regularly spaced breaths to episodic breaths (ie, clusters of breaths) increases CO$_2$ retention and subsequent acidemia in turtles, thereby illustrating the importance of breath patterns to blood gas homeostasis.

In reptiles, hypoxia and hypoxemia induce compensatory hypothermia and reduced metabolic rate. Reduced body temperature and metabolism could prolong recovery from sedation or anesthesia and could negatively impact wound healing. However, veterinarians frequently use supplemental heat sources to keep reptiles within the optimal temperature range. Alternatively, increased body temperature is associated with increased respiratory rate, oxygen uptake, $\dot{V}E$, and metabolic rate. Yet, a snake administered dexmedetomidine may not be able to respond accordingly to increased temperature. Ultimately, the effects of dexmedetomidine on hypoxic and hypercapnic responses in snakes are unknown; however, for snakes affected by trauma or disease, dexmedetomidine may exacerbate compromised respiratory function and prolong recovery from anesthesia.

The present study findings of doxapram-induced increase of $\dot{V}E$ and, in some situations, of $Vt$ were consistent with those previously reported for mammals and crocodilians. However, unlike previous studies, breath frequency after doxapram administration to the ball pythons of the present study did not significantly increase. Instead, the results aligned with those observed with people, in which doxapram’s primary action on respiration is through...
changes in \( V_t \) and \( V_e \). Unexpectedly, doxapram did not increase breath frequency similar to that observed immediately after injection of saline solution. Possibly, breath duration increased secondary to a 3-fold, doxapram-induced increase in \( V_t \), such that breath frequency did not significantly increase concurrently.

In mammalian studies\(^{15,44,75,76} \) of doxapram, the effects of single doses are short-lived, typically lasting only 5 to 15 minutes. In a study\(^{45} \) of alligators, however, a measurable effect of doxapram on respiration was detected for hours after intra-arterial administration. In the present study of ball pythons, doxapram had respiratory stimulant effects for the first 60 minutes after injection. Doxapram’s increased duration of action in alligators and snakes may be because of the lower metabolic rate of reptiles and subsequent slower drug metabolism.\(^{71} \)

In the present study, results obtained after administration of the combination of dexmedetomidine and doxapram suggested that doxapram may counteract the respiratory disturbances caused by dexmedetomidine. With the addition of doxapram, the dexmedetomidine-induced decrease in breath frequency and irregular breathing pattern were blunted (ie, breath frequency was unchanged from baseline during the first 60 minutes after injection). Tidal volume was likely stable secondary to doxapram’s blunting of the dexmedetomidine-induced decrease in breath frequency. However, the exact mechanism by which these drugs caused these changes is unknown, but we speculated that the stimulus to breathe induced by doxapram may have overridden the decreased breath frequency and stabilized the breathing pattern to reduce the disturbances caused by dexmedetomidine.

We did not anticipate any interference with the antinociceptive efficacy of dexmedetomidine by the addition of doxapram on the basis that they act on different types of receptors in the CNS.\(^{27,43} \) The thermal antinociception experiment showed that combined dexmedetomidine and doxapram did not block the antinociceptive efficacy of dexmedetomidine. Results of the respiratory and thermal antinociception experiments indicated that doxapram may effectively ameliorate respiratory disturbances induced by dexmedetomidine, while preserving its thermal antinociceptive effects. Our findings were similar to those of previous animal\(^{79} \) and human\(^{78} \) studies that indicate doxapram can counteract the respiratory depressive effects of morphine without disrupting its thermal antinociceptive efficacy. However, in contrast to one of those studies\(^{76} \) in which only transient improvement of opioid-induced respiratory depression was detected after doxapram administration, we observed persistent improvement of dexmedetomidine-induced respiratory depression in the present study. When combined with dexmedetomidine, doxapram maintained a more normal respiratory rate, \( V_t \), and breathing pattern over several hours. After the initial respiratory stimulation (ie, increased \( V_e \)) from doxapram waned, breath frequency was unchanged, compared with baseline, and snakes never demonstrated the decreased frequency or aberrant respiratory patterns observed when dexmedetomidine was administered alone. The snakes’ slow metabolic rate and subsequent slow doxapram metabolism may have permitted sustained mitigation of dexmedetomidine-induced respiratory abnormalities.

Dexmedetomidine may be an important analgesic option for snakes, and doxapram may mitigate respiratory disturbances caused by dexmedetomidine, while also preserving its antinociceptive function. The results reported here may be applicable to other reptiles, such as chelonians and lizards, in which breath frequency also decreases after administration of \( \alpha_2 \)-adrenoceptor agonists.\(^{23,26} \) However, doxapram is associated with decreased cerebral blood flow in dogs and goats\(^{79,80} \) and increased cardiac work in dogs,\(^{81} \) which may limit the usefulness of doxapram in reptiles. Yet, whether doxapram has these same effects in snakes is unknown. A clinically relevant model of pain for snakes needs to be developed before the analgesic effects of dexmedetomidine alone and combined dexmedetomidine and doxapram can be fully understood.

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The authors declare that there were no conflicts of interest.

**Footnotes**

a. Reptile Rapture, Monona, Wis.
b. Pet Supplies Plus, Madison, Wis.
c. LLI Reptile, Oceanside, Calif.
e. Mass flow meter, model 4140, TSI Incorporated, Shoreview, Minn.
f. Model DP45-14, Validyne Engineering Corp, Northridge, Calif.
g. DigiData 1200, Axon Instruments, Sunnyvale, Calif.
h. pClamp, Axon Instruments, Sunnyvale, Calif.
i. Dexamitorm, 0.5 mg/mL, Iron Corp, Espoo, Finland.
j. Dopram, West-Ward, Eatontown, NJ.
k. Ugo Basile plantar analgesia instrument, model 37370, Ugo Basile Co, Comerio, Italy.

**References**


Additionally, the text includes references to various studies on reptilian physiology, behavior, and pharmacology, highlighting the importance of understanding these factors in reptile medicine and surgery. The references cover a range of topics from the effects of analgesics on reptilian behavior to the respiratory responses of various species to different stimuli. This comprehensive approach provides a solid foundation for the practice of reptile medicine and surgery.


