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RESEARCH PAPER

Comparison of subcutaneous dexmedetomidine–midazolam *versus* alfaxalone–midazolam sedation in leopard geckos (*Eublepharis macularius*)

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Abstract

Objective To compare dexmedetomidine–midazolam with alfaxalone–midazolam for sedation in leopard geckos (*Eublepharis macularius*).

Study design Prospective, randomized, blinded, complete crossover study.

Animals Nine healthy adult leopard geckos.

Methods Geckos were administered a combination of dexmedetomidine (0.1 mg kg^{-1}) and midazolam (1.0 mg kg^{-1}; treatment D–M) or alfaxalone (15 mg kg^{-1}) and midazolam (1.0 mg kg^{-1}; treatment A–M) subcutaneously craniodorsal to a thoracic limb. Heart rate (HR), respiratory rate (f_R), righting reflex, palpebral reflex, superficial and deep pain reflexes, jaw tone and escape response were assessed every 5 minutes until reversal. Conditions for intubation and response to needle prick were evaluated. Antagonist drugs [flumazenil (0.05 mg kg^{-1}) ± atipamezole (1.0 mg kg^{-1})] were administered subcutaneously, craniodorsal to the contralateral thoracic limb, 45 minutes after initial injection, and animals were monitored until recovery.

Results HR, but not f_R, decreased significantly over time in both treatments. HR was significantly lower than baseline at all time points in D–M and for all but the 5 and 10 minute time points in A–M. HR was significantly higher in A–M at all time points after drug administration when compared with D–M. Sedation scores between protocols were similar for most time points. All animals in A–M lost righting reflex compared with seven out of nine (78%) geckos in D–M. Geckos in A–M lost righting reflex for significantly longer time. Mean ± standard deviation time to recovery after antagonist administration was 6.1 ± 2.2 minutes for D–M and 56 ± 29 minutes for A–M, and these times were significantly different.

Conclusions and clinical relevance Combination D–M or A–M provided sedation of a level expected to allow physical examinations and venipuncture in leopard geckos. A–M provided a faster onset of sedation compared with D–M. Recovery was significantly faster following antagonist reversal of D–M, compared with A–M.

Keywords alfaxalone, dexmedetomidine, midazolam, sedation, Squamata.

Introduction

Sedation or light anesthesia is required for a variety of clinical procedures in reptiles, such as diagnostic sample collection, imaging or minor surgical procedures. However, systematically derived anesthetic and sedation efficacy data are absent for many reptile species, so that drug dosages must be extrapolated from information about other, frequently unrelated, species. Consequently, drug administration may result in ineffective sedation or anesthesia, prolonged induction and recovery times, and potentially harmful side effects, including death. Availability of species-specific data is essential, especially in commonly encountered reptile species. Leopard geckos (*Eublepharis macularius*) are widely available in the pet trade and are often kept in zoological

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collections and educational facilities. However, anesthetic efficacy studies in this species are scarce.

Both α_2-agonists and benzodiazepines were described as effective sedatives in reptiles (Schnellbacher et al. 2012; Olsson & Phalen 2013a). These agents are commonly used in veterinary medicine to induce sedation, and α_2-agonists may provide analgesia. Dexmedetomidine and midazolam have been incorporated in protocols for reptile anesthesia (Bienzle & Boyd 1992; Schnellbacher et al. 2012; Olsson & Phalen 2013a; Schumacher & Mans 2014). An advantage of the use of dexmedetomidine and midazolam is that they can be antagonized with atipamezole and flumazenil, respectively, conferring control over the duration of the recovery period and facilitating correction of adverse effects.

Alfaxalone is a promising option for sedation and anesthesia in reptiles, as it can be administered through various routes, including intramuscular (IM) and intravenous (IV) routes (Shepard et al. 2013; Olsson et al. 2013). Alfaxalone is a neuroactive steroid molecule that potentiates $GABA_A$ receptors, resulting in centrally mediated muscle relaxation and anesthesia that is not reversible.

The goal of this study was to develop protocols incorporating dexmedetomidine–midazolam or alfaxalone–midazolam that could be administered subcutaneously and would result in clinically applicable quality of sedation in leopard geckos. Our hypotheses were that: 1) both sedative combinations would result in rapid immobilization and 2) recovery following administration of antagonist drugs would be faster for the dexmedetomidine–midazolam combination.

Materials and methods

Animals

This study was approved by the University of Wisconsin-Madison School of Veterinary Medicine Institutional Animal Care and Use Committee (number V005068). Nine adult leopard geckos (five males and four females) of unknown age were used in this project and considered healthy based on serial physical examinations throughout the study period. The mean ± standard deviation (SD) body weight was 58.6 ± 10.8 g for males and 45.5 ± 8.4 g for females. Animals were housed individually, and provided hiding areas and *ad libitum* water. The ambient room temperature was maintained at 26.0–28.0 °C. Geckos were fed appropriately sized mealworms and a commercial insect-based gel diet (Grub Pie; Repashy Ventures, CA, USA). Mealworms were maintained on a high-calcium gut-loading formula (High Calcium Cricket Feed; Fluker Farms, LA, USA) and were dusted with calcium (Rep-Cal Research Labs, CA, USA) and multivitamin (Herptivite; Rep-Cal Research Labs) supplements prior to feeding.

Pilot study

An initial pilot study involving all nine geckos was performed using two drug combinations to determine clinically effective dosages without adverse effects. Combinations of dexmedetomidine (Dexdomitor, 0.1 mg mL^{-1}; Pfizer Animal Health, NY, USA) and midazolam (West-Ward Pharmaceuticals Corp., NJ, USA) were tested based on protocols reported in the relevant literature (Mans et al. 2013; Selleri et al. 2013) and dosages used successfully in the authors' institution. Initial dosages of alfaxalone (Alfaxan; Jurox Pty Ltd, NSW, Australia) were chosen based on previous studies (Bertelsen & Sauer 2011; Kischinovsky et al. 2013; Shepard et al. 2013). Lower dosages of drugs were evaluated initially; however, if the sedation quality was deemed inadequate, then drug dosages were increased by 33–100%. Physiological variables were monitored, and reflexes and behavioral parameters evaluated as described below. Various combinations of midazolam and alfaxalone were investigated to identify the best sedative effect, and high dosages of dexmedetomidine were combined with low dosages of midazolam, and *vice versa*, to find a protocol with the desired sedative effects and acceptable recovery time. Each of the different combinations was tested in two to four animals: alfaxalone (10–30 mg kg^{-1}) alone or in combination with midazolam (0.5–1.0 mg kg^{-1}), and dexmedetomidine (0.05–0.10 mg kg^{-1}) with midazolam (0.5–1.0 mg kg^{-1}). All drugs were administered subcutaneously.

Study design

A washout period of at least 7 days was allowed prior to the final study. For the final study, the same nine healthy adult leopard geckos were administered two treatments in a randomized crossover study with ≥7 days between treatments. Randomization was performed using free, online software (Research Randomizer Version 4.0; www.randomizer.org). The treatments were dexmedetomidine (0.1 mg kg^{-1}) and midazolam (1.0 mg kg^{-1}) (treatment D–M) or alfaxalone (15 mg kg^{-1}) and midazolam (1.0 mg kg^{-1}; treatment A–M). These treatments

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