Clinical and histologic effects of intracardiac administration of propofol for induction of anesthesia in ball pythons (Python regius)

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Objective—To assess the clinical differences between induction of anesthesia in ball pythons with intracardiac administration of propofol and induction with isoflurane in oxygen and to assess the histologic findings over time in hearts following intracardiac administration of propofol.

Design—Prospective randomized study.

Animals—30 hatching ball pythons (Python regius).

Procedures—Anesthesia was induced with intracardiac administration of propofol (10 mg/kg [4.5 mg/lb]) in 18 ball pythons and with 5% isoflurane in oxygen in 12 ball pythons. Induction time, time of anesthesia, and recovery time were recorded. Hearts from snakes receiving intracardiac administration of propofol were evaluated histologically 3, 7, 14, 30, and 60 days following propofol administration.

Results—Induction time with intracardiac administration of propofol was significantly shorter than induction time with 5% isoflurane in oxygen. No significant differences were found in total anesthesia time. Recovery following intracardiac administration of propofol was significantly longer than recovery following induction of anesthesia with isoflurane in oxygen. Heart tissue evaluated histologically at 3, 7, and 14 days following intracardiac administration of propofol had mild inflammatory changes, and no histopathologic lesions were seen 30 and 60 days following propofol administration.

Conclusions and Clinical Relevance—Intracardiac injection of propofol in snakes is safe and provides a rapid induction of anesthesia but leads to prolonged recovery, compared with that following induction with isoflurane. Histopathologic lesions in heart tissues following intracardiac injection of propofol were mild and resolved after 14 days. (J Am Vet Med Assoc 2011;239:803–807)

Reptiles have continued to increase in popularity as pets in the United States, and veterinarians who treat reptiles are faced with situations that require immobilization or anesthesia. Performing anesthesia in reptiles can be challenging because of anatomic and physiologic differences from mammals, variable responses to anesthetic drugs, and patient size.

Induction of anesthesia with inhalant anesthetics is commonly used in many reptile species. The use of less tissue-soluble anesthetics such as isoflurane, sevoflurane, or desflurane is preferred, as solubility is inversely related to induction and recovery times. Induction of anesthesia with inhaled anesthetics can be prolonged in some reptiles because of breath holding or limited access to the head (chelonians). Induction of anesthesia with intracardiac injection of propofol is generally easier in lizards and snakes, but these species are capable of prolonged breath holding as well.

Many injectable agents have been used for anesthetic induction in reptiles, with varying results. Most effective in prolonged induction and recovery times, with some exceeding 24 hours. Propofol has gained popularity for anesthesia in reptiles because of the rapid induction and recovery and limited toxic effects on organs. A major disadvantage of propofol is the need for IV administration, which can be challenging in reptile patients. For species in which venous access is difficult to obtain, propofol has been administered intraosseously, into the coelomic cavity, intracardially, and transdermally, and in the supravertebral sinus. The purpose of the study reported here was to examine the efficacy and safety of propofol administered by intracardiac injection into hatching ball pythons (Python regius), to evaluate histologic changes in the heart caused by the intracardiac injection of propofol, and to evaluate induction and recovery times, compared with anesthetic induction with 5% isoflurane, in oxygen administered by direct endotracheal intubation in fully conscious snakes. We hypothesized that administration of propofol via intracardiac injection would provide rapid anesthetic induction and recovery, have minimal adverse effects during anesthesia, and lead to minimal histopathologic lesions in the heart.

Materials and Methods

This study was approved by the University of Illinois Institutional Animal Care and Use Committee.
Animals—Thirty hatching ball pythons (16 males and 14 females) obtained from a commercial source and undergoing anesthesia for a study investigating suture reactions were used in this study. The ball pythons were housed in a commercially available rack system specifically designed to house small snakes of this species. Mean body weight was 80.2 ± 17.7 g (0.18 ± 0.04 lb; range, 48 to 117 g [0.11 to 0.26 lb]), and mean length was 45.3 ± 2.01 cm (range, 40.6 to 49.5 cm). Snakes were maintained within their preferred optimum temperature zone (ambient daytime temperature, 23° to 28°C [78° to 82°F]; ambient night temperature, 24° to 25°C [75° to 78°F]; basking temperature, 32° to 35°C [90° to 93°F]), proper humidity (50% to 60%), and 12-hour light-to-dark cycles. Snakes were offered a thawed frozen mouse of appropriate size for their body diameter every 7 to 10 days. All ball pythons were physically examined on arrival and allowed to acclimate for 7 days prior to initiation of the study.

Anesthesia—Prior to induction of anesthesia, food was withheld for a minimum of 48 hours. Twenty minutes prior to induction of anesthesia, all snakes received butorphanol (1 mg/kg [0.45 mg/lb], IM). Snakes were assigned to 1 of 2 anesthesia induction groups randomly by use of a lottery selection method. Group A received propofol (10 mg/kg [4.54 mg/lb]) by intracardiac injection for induction of anesthesia, and group B received 5% isoflurane delivered in 100% oxygen via a Bain nonrebreathing circuit after intubation while fully conscious. Snakes receiving propofol by intracardiac injection were manually restrained in dorsal recumbency, and the beating heart was observed at the caudal aspect of the cranial third of the body. By use of digital pressure, the heart was gently pushed cranially and stabilized to prevent movement during injection. Propofol was administered with a 25-gauge, 5/8-inch needle directed in a craniodorsal direction. Aspiration of blood prior to injection was used to ensure proper placement of the needle. Snakes were immediately intubated after induction of anesthesia. For anesthetic induction with isoflurane, the snakes were physically restrained and the mouth opened manually. An endotracheal tube created from a 14- or 16-gauge catheter was lubricated with water-soluble gel and passed through the open glottis during inspiration. Physical restraint was continued until muscle tone was lost, then the tube was secured in place with adhesive tape and the snake was allowed to breathe spontaneously.

In both groups, general anesthesia was maintained with isoflurane delivered in 100% oxygen. Anesthetic depth was monitored by evaluating righting reflex, ECG, heart rate, and response to painful stimuli (tail pinch or movement during surgery). Positive pressure ventilation was manually performed in snakes that had respiratory rates < 1 breath/min. Ball pythons were placed on circulating water blankets set at 40.5°C (105°F) as a supplemental heat source. Induction time was defined as the time from administration of the anesthetic until the righting reflex was lost. Total time of anesthesia was defined as the duration of isoflurane administration. Recovery time was defined as the time from discontinuing isoflurane until the snake was ventilating spontaneously and had regained the righting reflex and further monitoring was deemed unnecessary, allowing for safe return to its enclosure.

Histologic evaluation of heart tissues—Five snakes each were euthanized (pentobarbital sodium, 100 mg/kg [43.5 mg/lb], administered into the coelomic cavity) at 3, 7, 14, 30, 60, and 90 days following surgery; hearts from 13 of the 18 snakes given propofol by intracardiac injection were submitted for histologic evaluation. The hearts from snakes that received intracardiac administration of propofol and were euthanized at 90 days were not evaluated histologically. Tissues were processed by use of standard methods, embedded in paraffin, trimmed at 3 levels, sectioned at 5-μm thickness, placed on slides, and stained with H&E. No gross lesions were identified; therefore, multiple longitudinal sections at each level of the heart were evaluated. All slides were examined histologically by a single pathologist (DRR) with extensive experience in exotic animal pathology.

Statistical analysis—All data are expressed as mean ± SD. Significant differences in induction time, total time of anesthesia, and recovery time were evaluated between the groups by use of a t test. Significant differences in heart rate between groups were evaluated by use of a repeated-measures ANOVA. Post hoc analyses were performed with the least significant difference test. A commercially available software program was used for statistical testing. Values of P ≤ 0.05 were considered significant.

Results

Eighteen snakes received propofol by intracardiac injection. In 16 of 18 snakes, induction times were < 10 seconds with rapid loss of consciousness, loss of muscle tone, and loss of the righting reflex. Orotracheal intubation was possible in all snakes receiving propofol. In 2 of 18 snakes, complete loss of righting reflex and muscle tone did not occur until administration of isoflurane; data from these 2 snakes were excluded from statistical analysis.

Snakes in which anesthesia was induced with direct intubation and administration of isoflurane had significantly longer induction times (425.4 ± 249.5 seconds), compared with those of snakes in which anesthesia was induced by intracardiac injection of propofol. Anesthetic episodes were considered uneventful in all snakes. Arrhythmias were not detected in any snake on ECG evaluation. Maintenance anesthesia was not standardized and was adjusted as needed to maintain a surgical plane of anesthesia for the unrelated study; however, there was no difference in total time of anesthesia between groups (21 ± 6.4 minutes in the propofol group; 25 ± 8.6 minutes in the isoflurane group). The mean recovery time was significantly longer for snakes receiving propofol (68.5 ± 27.9 minutes), compared with snakes in which anesthesia was induced with 5% isoflurane in oxygen (45.9 ± 14.1 minutes).

Heart rate between groups was not different over time (63.8 ± 5.1 beats/min in the propofol group; 59.5 ± 6.4 beats/min in the isoflurane group). For all snakes, the preoperative heart rate was significantly higher, compared with 10, 15, and 20 minutes following induction of anes-
theia. Heart rates were significantly lower at 15 minutes following anesthetic induction, compared with 5, 25, 30, 35, 40, and 45 minutes. Overall, there was a significant decrease in heart rate in all snakes between 10 and 25 minutes following induction of anesthesia (Figure 1).

At day 3 following anesthesia, 2 of the 3 snakes that received intracardiac administration of propofol had mild acute inflammation and some degenerative changes of the myocardium that were more prominent in the ventricle, which was most likely the site of injection. The degenerative changes were characterized by vacuolization of the cells with a loss of cross striations. One snake also had a local aggregate of macrophages with cytoplasmic pigments (hemosiderin) present in the epicardium of the atria. At day 7 following anesthesia, a very mild lesion of myocardial degeneration with minimal heterophilic infiltrates was observed in heart tissue of 1 snake, with no lesions observed in tissues of 2 snakes. In the 3 hearts evaluated at 14 days after anesthesia, the lesions were minimal to mild in the same location. The inflammation was primarily heterophilic. No histopathologic lesions were found in any heart tissues from snakes at 30 to 60 days after anesthesia.

**Discussion**

Although propofol is labeled for IV use in dogs, it has been administered IM, into the coelomic cavity, IV, intraosseously, as a bath, and intracardially in exotic species because of the difficulty or inability to establish venous access.6–8,11,12,14–16

When propofol was administered IM to rats, most did not develop substantial sedation and none became anesthetized. Histologically, there was substantial inflammation and necrosis at the injection sites.15 Administration of propofol into the coelomic cavity leads to rapid absorption, but accidental injection into organs, fat bodies, or other undesirable locations (air sacs in birds) can occur, which can affect drug absorption.2 Administration of propofol into the coelomic cavity of White’s tree frogs (*Pelogyas caerulea*) resulted in varied dose-dependant responses (from loss of righting reflex to death) and prolonged recovery times up to 16 hours.11 Intracoelomic administration of propofol in green iguanas caused mild sedation or induced light anesthesia in 5 of 6 iguanas, and endotracheal intubation was possible in only 1 of 5. One iguana had no measured effect after intracoelomic administration of propofol.17 Intraperitoneal administration of propofol to mice caused inconsistent results among mice given the same dose.14

The use of anesthetic agents IV can vary among species depending on size and anatomy. In snakes, the most commonly used vein for phlebotomy and drug administration is the coccygeal vein; however, in small snakes, it is technically difficult to maintain the needle’s
position within the vein during drug administration. This can result in perivascular leakage and decreased effectiveness.\(^2,16\) In addition, manipulation of the tail for probing or venous access in some young, small snakes can cause deformations of the caudal vertebrae.\(^18\)

Intraosseous administration of propofol has been used successfully in lizards and chelonians\(^6,13\) but is not applicable to snakes. Intracardiac sampling and drug administration have been used successfully in snakes that have limited vascular access and in which intraosseous administration of drugs is not possible.\(^2,18\) A previous report\(^7\) on intracardiac administration of propofol in brown tree snakes (Boiga irregularis) resulted in smooth, uncomplicated anesthesia in all cases with minimal cardiopulmonary effects. These snakes were administered 5 mg of propofol/kg (2.27 mg/lb) intracardially, intubated, allowed to breathe room air, monitored, and allowed to recover without any additional administration of anesthetics. Two of 9 snakes failed to achieve a surgical level of anesthesia, and overall, the mean duration of anesthesia (time from loss of righting reflex until the return of the righting reflex) was 24 minutes (range, 10 to 47 minutes). Snakes were euthanatized 7 months following the procedure, and only mild hemosiderosis in the epicardial or pericardial tissues was noted. One snake had focal, mild, myocardial atrophy and fibrosis. The investigators did not evaluate induction times, recovery times, or the short-term histologic effects on heart tissues.

When repeated cardiocentesis (39 blood samples from each snake) was performed to collect blood samples from ball pythons in a pharmacokinetic study,\(^6,13\) no clinically apparent complications were noted. Histologic evaluation of heart tissues following repeated cardiocentesis revealed primary lesions involving the epicardium, with fibrosis extending into the myocardium at the site of epicardial fibrosis. These chronic lesions were noted 73 days after the last blood sample was collected via cardiocentesis. Despite the successful use of this route for blood sample collection, some authors recommend its use only in larger snakes (> 200 g (> 0.44 lb)) and for emergency situations.\(^3,4,16,20\)

In this study and the previous report\(^7\) in brown tree snakes, intracardiac injection of propofol did not have any immediate effects on cardiovascular function. When propofol was administered IM in rats, there was moderate to severe inflammation and necrosis at the injection sites 24 hours later.\(^3\) It is possible that intraosseous administration of propofol could have caused similar local inflammatory changes that may not be evident during anesthetic monitoring. Anderson et al\(^7\) evaluated the hearts of the tree snakes 7 months following intracardiac injection, and only mild lesions were noted. More severe inflammatory changes may have occurred but could have resolved by the time the hearts were examined histologically 7 months later. In the present study, injection of propofol into the heart did result in some inflammation and changes to the endocardium and myocardium. Overall, the changes were mild, consisting of focal areas of myocardial degeneration and endocarditis in the early samples, but unlike the previous report, no lesions were noted 30 or 60 days following intracardiac propofol administration. Comparing these snakes with those in a study\(^19\) evaluating multiple episodes of cardiocentesis, the trauma caused by repeated injections may be responsible for the lesions in the heart.

In this study, mean induction time with direct intubation and administration of isoflurane was 7 minutes, with a maximum of nearly 20 minutes. This is consistent with other reports\(^3\) of induction of anesthesia in other reptiles with inhalant anesthetics. Airway irritation caused by inspiration of the inhalant anesthetic during induction of anesthesia can lead to breath holding and increased induction times.\(^21\) Our snakes were intubated while awake, and manual ventilation could have been used to reduce the effects of breath holding during induction of anesthesia. Alternatively, sevoflurane could have been used to decrease breath holding and induction time.\(^22\)

Recovery in snakes that received propofol by intracardiac injection was significantly longer than in the snakes in which anesthesia was induced with isoflurane. Although the anesthesia protocol following induction was not standardized, there was no significant difference in total time of anesthesia between groups. Snakes in both groups were intermittently manually ventilated; therefore, if there were prolonged episodes of apnea in one group as opposed to the other as a result of propofol administration, they could not be assessed. Subjectively, in snakes receiving propofol, anesthesia was maintained with lower isoflurane concentrations, compared with snakes in the isoflurane group. The longer recovery time in the snakes that received propofol may be associated with propofol metabolism or may be due to the dose of propofol that was used. In mammals, recovery from propofol anesthesia is through redistribution and metabolism by conjugation of the drug. The rapid clearance of propofol from the plasma is greater than hepatic blood flow, suggesting extrahepatic sites for metabolism.\(^23\) In reptiles, the method of metabolism and elimination of propofol is unknown and may play a role in prolonged recoveries. The dose of 10 mg/kg was selected on the basis of several references for propofol in reptiles.\(^24-26\) Doses from 3 to 15 mg/kg (1.4 to 6.8 mg/lb) are commonly referenced. A lower dose of propofol may have been effective by this route and may also have decreased the recovery time.

There was no significant difference in heart rates between groups. No arrhythmias were noted, and subjectively, there were no differences in findings during ECG monitoring throughout the procedure. With both groups, there was a significant decrease in heart rate between 10 to 20 minutes following induction of anesthesia. As this occurred in both groups, it is unlikely to be associated with the method of induction of anesthesia. The decrease in heart rates was seen during the time the snakes received isoflurane. Once the isoflurane was discontinued, the heart rates returned to preoperative values.

The main limitation of this study is that the anesthesia following induction of anesthesia was not standardized; however, this represents a realistic clinical situation because isoflurane was adjusted on the basis of the snake's response to the surgical stimuli. In conclusion, it appears that propofol administered by
intracardiac injection in snakes is safe, provides a rapid induction of anesthesia, and does not cause immediate electromyocardial dysfunction or changes in heart rate; however, it does prolong recovery (at 10 mg/kg intracardially), compared with induction of anesthesia with isoflurane, and leads to minor inflammatory changes in the myocardium. The difference in recovery time is acceptable (20 minutes), and the inflammatory changes noted in the myocardium had resolved by 30 days following injection. Further studies could evaluate administration of different doses of propofol to evaluate their effectiveness and to evaluate the effect of a lower dose on recovery time.

References