The cardiac anesthetic index of isoflurane in green iguanas

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Objective—To determine the cardiac anesthetic index (CAI) of isoflurane in green iguanas and whether butorphanol affected the CAI.

Design—Prospective randomized controlled trial.

Animals—7 healthy mature iguanas.

Procedure—In 5 iguanas, CAI was determined after induction of anesthesia with isoflurane alone, and in 5 iguanas, CAI was determined after induction of anesthesia with isoflurane and IM administration of butorphanol (1 mg/kg [0.45 mg/lb]). Three iguanas underwent both treatments. Animals were equilibrated for 20 minutes at 1.5 times the minimum alveolar concentration (MAC) of isoflurane and observed for evidence of cardiovascular arrest. If there was no evidence of cardiovascular arrest, end-tidal isoflurane concentration was increased by 20%, and animals were allowed to equilibrate for another 20 minutes. This process was repeated until cardiovascular arrest occurred or vaporizer output could no longer be consistently increased. The CAI was calculated by dividing the highest end-tidal isoflurane concentration by the MAC.

Results—None of the iguanas developed cardiovascular arrest and all survived. Mean ± SD highest end-tidal isoflurane concentration during anesthesia with isoflurane alone (9.2 ± 0.60%) was not significantly different from mean concentration during anesthesia with isoflurane and butorphanol (9.0 ± 0.43%). The CAI was > 4.32.

Conclusions and Clinical Relevance—Results suggest that the CAI of isoflurane in green iguanas is > 4.32 and not affected by administration of butorphanol. Isoflurane appears to be a safe anesthetic in green iguanas. (J Am Vet Med Assoc 2003;222: 1565–1568)

The safety of inhalant anesthetics in animals is dependent on a number of factors, although the degree to which they depress respiratory and cardiovascular system function is of prime importance. Other factors include the extent of autonomic responses invoked, the degree of hepatic and renal impairment, and the vapor pressure and blood-gas partition coefficient as they relate to the minimum alveolar concentration (MAC) of the inhalant. Acute and chronic toxicoses associated with administration of halogenated anesthetics have been well described, but the most commonly used inhalant anesthetics are generally thought to have minimal toxic effects, even during long-term exposure.

Any inhalant anesthetic has the potential to lead to life-threatening respiratory or cardiovascular arrest if administered in sufficiently high doses. The necessary dose will vary among patients and agents and has been determined for only a small number of agents in a limited number of species. The values describing the doses necessary to cause respiratory and cardiovascular arrest are referred to as the respiratory anesthetic index and the cardiac anesthetic index (CAI), respectively. These values are comparable to the median lethal dose (ie, the dose of an agent that will result in death of 50% of subjects) commonly determined for most other medications. The respiratory anesthetic index represents the mean dose of an inhalant anesthetic necessary to cause a cessation of breathing for some time period, usually 30 to 60 seconds, divided by the MAC of that anesthetic. Similarly, the CAI is the mean dose necessary to cause cardiovascular arrest, as indicated by a lack of pulsatile blood flow, divided by the MAC of the anesthetic. For those agents for which these values have been determined, the CAI is greater than the respiratory anesthetic index.

The CAI represents an index of anesthetic safety but may also reveal inherent species differences in regard to tolerance of anesthetic overdoses, which may lead to a better understanding of the mechanisms by which anesthetics induce cardiovascular arrest. It has been determined directly by inducing cardiovascular arrest and by means of estimation on the basis of decreases in arterial blood pressure. Unfortunately, values determined by means of estimation may be inaccurate, and induction of cardiovascular arrest is the only reliable method to accurately determine CAI. The purpose of the study reported here was to determine the CAI of isoflurane in green iguanas and whether butorphanol affected the CAI.

Materials and Methods

Iguanas—Three male and 4 female healthy mature iguanas (Iguana iguana) were used in the study. Mean ± SD weight was 1.17 ± 0.53 kg (2.56 ± 1.17 lb). All iguanas were considered to be healthy on the basis of results of a general physical examination, CBC, and serum biochemical profile. The animals were group-housed in a large room at the University of Guelph Central Animal Facility. A temperature gradient of 26 to 35°C (79 to 95°F) was provided, along with a consistent photoperiod of 16 hours of light and 8 hours of darkness. Several ultraviolet-emitting lights and infrared spotlights were placed to provide basking areas in the room. The animals were fed a diet of 80% dark green leafy vegetables and 20% other vegetables and fruits with a light dusting of a calcium and phosphorus supplement. Iguanas were allowed to acclimate to the housing environment for at least 10 days.

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2 days prior to undergoing any study procedures. All experiments were performed at the Ontario Veterinary College, University of Guelph. The study was carried out with approval of the Animal Care Committee of the University of Guelph and in compliance with the guidelines of the Canadian Council of Animal Care.

Experimental design—A prospective randomized controlled study design was used. As iguanas became available for the study, they were randomly assigned to treatments consisting of determination of CAI after induction of anesthesia with isoflurane alone and determination of CAI after induction of anesthesia with isoflurane and IM administration of butorphanol. However, because we found that animals survived the experiments, 3 animals underwent both treatments with a minimum of 7 days between treatments. Thus, CAI for isoflurane alone was determined in 5 iguanas, and CAI for isoflurane in conjunction with IM administration of butorphanol was determined in 5 iguanas. All experiments were completed between 8:30 AM and 6:30 PM to reduce the impact of natural circadian rhythms on results.

Determination of CAI—On the day of each experimental trial, animals were transported from the Central Animal Facility to the Ontario Veterinary College. To minimize excitement, animals were transported in a secure carrier that prevented them from perceiving their surroundings. Transportation distance was approximately 100 m.

Following their arrival at the Ontario Veterinary College, the iguanas were placed on a warm water circulating blanket. Anesthesia was induced by administration of isoflurane through a mask connected to a Bain anesthetic circuit. Oxygen flow was set to 1 L/min, and the dial setting of the isoflurane vaporizer was set to 5%. Isoflurane was delivered with an out-of-circle, halothane-specific, pressure-compensated precision vaporizer. This vaporizer, although not specific for administration of isoflurane, was chosen because it was capable of reliably delivering high concentrations of isoflurane (approx 9%), which exceeded concentrations that could be delivered with commonly manufactured isoflurane-specific vaporizers. In addition, end-tidal isoflurane concentration was determined by analyzing airway gases, so it was not necessary that the dial setting accurately reflect the vaporizer's output. However, the vapor pressures of isoflurane and halothane are reasonably close, so the concentration of isoflurane delivered by a halothane-specific vaporizer is reasonably close to the percentage indicated on the vaporizer dial.

When the iguanas were sufficiently immobilized, an uncuffed endotracheal tube of the appropriate size (2 to 4 mm) was inserted. Intubation was facilitated with the use of 1 drop (1 to 2 mg) of lidocaine on the glottis. The seal around the tube was checked for leaks by inflating the lungs to a pressure of no more than 15 mm Hg. All animals were mechanically ventilated with a pressure-controlled ventilator; the ventilator was set to deliver a tidal volume of 30 mL/kg (14 mL/lb) at a rate of 4 breaths/min. Values for minute ventilation were selected on the basis of results of a previous study of the respiratory mechanics of green iguanas. The volume of each breath was measured with a respirometer.

Following induction of anesthesia, heart rate and rhythm were monitored continuously with a lead II ECG. The ECG leads were attached to stainless steel wires placed SC in the right and left axilla and left groin. A cloacal thermometer was used to measure body temperature; a forced warm air blanket was used to maintain body temperature between 30 and 32°C (86 and 90°F). A gas analyzer was connected between the Bain circuit and the endotracheal tube with a standard gas sampling line connector, and fractional concentration of oxygen in inspired gas, fractional concentration of oxygen in expired gas, end-tidal partial pressure of CO₂, and end-tidal isoflurane concentration were measured continuously. The gas analyzer also displayed a continuous capnogram. The gas analyzer was calibrated with the manufacturer's recommended calibration gas prior to each experiment. A 3-F feeding tube was fed down the endotracheal tube to a level near the bifurcation of the trachea for gas sampling. During the instrumentation period, animals were maintained at an end-tidal isoflurane concentration of between 1 and 1.5 times MAC, with the MAC of isoflurane in green iguanas considered to be 2.1%.

Once instrumentation was complete and animals had achieved a stable body temperature, a dose of saline (0.9% NaCl) solution (0.1 mL/kg [0.045 mL/lb]) or butorphanol tartrate (1 mg/kg [0.45 mg/kg]) was given IM in the forelimb. An individual not otherwise involved in the study prepared the injection, and the individual determining CAI did not know whether saline solution or butorphanol had been given during any particular experimental trial. Injections were given at least 30 minutes prior to the initiation of testing.

Animals were allowed to equilibrate for 20 minutes at each anesthetic concentration; this equilibration time was chosen on the basis of results of a previous study of MAC. The mean ± SD inspired and end-tidal percentages of isoflurane at MAC were 2.2 ± 0.7 and 2.1 ± 0.7, respectively. The inspired to end-tidal difference was 7.4 ± 3.8%. Anesthetic concentration was initially set at 1.5 times MAC for 20 minutes, and the iguana was observed for cardiovascular arrest, as evidenced by a rapid decline or loss of exhaled CO₂ on the capnogram and confirmed with auscultation. The ECG was observed for changes but was not considered a sensitive indicator of cardiac arrest because of the possibility of electromechanical dissociation. If there was no evidence of cardiac arrest, the end-tidal isoflurane concentration was increased by 20%, and the animal was allowed to equilibrate for another 20 minutes while being observed for evidence of cardiovascular arrest. This process was repeated until cardiovascular arrest occurred or until the maximum output of the vaporizer was achieved. The end-tidal isoflurane concentration at which arrest occurred was recorded. If arrest did not occur, the highest end-tidal concentration achieved was recorded. The CAI was calculated by dividing the end-tidal isoflurane concentration at which arrest occurred (or the highest concentration recorded) by the MAC of isoflurane in green iguanas.

If cardiovascular arrest did not occur, administration of isoflurane was discontinued, and the animals were ventilated until they moved in response to stimulation. At this time, they were extubated and observed until spontaneous respiration returned. Recovery was completed in an enclosed quiet area in the group-housing room.

Data analysis—A Student t-test was used to determine whether CAI was significantly different between treatments. Standard software was used; a value of P < 0.05 was considered significant. Data are given as mean ± SD.

Results

None of the iguanas had any signs of cardiovascular arrest, and all survived the experimental treatments. Mean ± SD highest recorded end-tidal isoflurane concentration with isoflurane alone was 9.2 ± 0.6%; mean highest recorded end-tidal isoflurane concentration with isoflurane and butorphanol was 9.0 ± 0.4%. These values were not significantly different. Therefore, the CAI was calculated by combining data for both treatments and was found to be > 4.32. There was a significant (P = 0.003) difference in the time required to achieve the maximum end-tidal isoflurane concentration...
tion between treatments. Mean times were 160 ± 10 minutes with isoflurane alone and 197 ± 15 minutes with isoflurane and butorphanol.

Discussion

Although it was our goal in the present study to induce cardiovascular arrest by administering high concentrations of isoflurane, we were unable to do so. We attempted to increase vaporizer output by warming the vaporizer, as it was not temperature compensated, but this was associated with fluctuations in output. A more precise warming method could have been developed, but we did not believe that there was practical value in further pursuing this, because we were already delivering isoflurane at concentrations twice the highest concentration attainable with most properly functioning isoflurane-specific vaporizers. Our results show that despite achieving end-tidal isoflurane concentrations > 4 times the MAC, we were unable to induce cardiovascular arrest. This suggests that the CAI of isoflurane in green iguanas is greater than values for similar indices in swine (3.02) and dogs (4.11). However, a higher CAI than these has been reported in rats (5.7). In the study involving dogs, a circulatory anesthetic index was estimated by extrapolating the linear relationship between anesthetic concentration and mean arterial pressure to zero. Strictly speaking, however, this value is not equivalent to the CAI. In the study involving rats, the CAI was calculated by determining tissue concentrations of isoflurane in the brain at the time of respiratory and cardiovascular arrest and dividing these concentrations by the concentration of isoflurane in the brain when rats were at an appropriate anesthetic depth. This represents a method of determining CAI different from the technique used in the present study. Although this technique should theoretically produce the same result as our method, it is not clear whether the concentration of isoflurane in the brain when rats were at an appropriate anesthetic depth is equivalent to the MAC. A study of the CAI of isoflurane and desflurane in swine used a method similar to that used in the present study, except that the authors were able to induce cardiovascular arrest. Values for isoflurane and desflurane were 3.02 and 2.45, respectively. The authors also provided the linear equation for the relationship between end-tidal anesthetic concentration and mean arterial pressure. Solving the equation for a mean arterial pressure of zero yields an estimate of the CAI of isoflurane of 4.12 versus the actual value of 3.02. Thus, extrapolation overestimates the CAI and, consequently, the safety margin of isoflurane. Similarly, extrapolation overestimates the CAI of desflurane, although to a lesser degree. This suggests that techniques based on extrapolation may not be as accurate as those based on inducing cardiovascular arrest. From our study, it appears that green iguanas may be more resistant to the cardiovascular depressant effects of isoflurane than swine, with a CAI for isoflurane > 4.32.

The effects of intracardiac shunting are an additional consideration that may affect the validity of our results. Reptilian cardiopulmonary physiology is vastly different from the mammalian system. Intracardiac shunting is common, and the direction and magnitude of the shunting cannot be predicted nor accounted for in our studies. The impact of intracardiac shunting on anesthetic uptake and distribution within the body cannot be predicted, because even mammalian models of intracardiac shunting cannot approximate the complexity and sophistication of the reptilian system. The green iguana has a 3-chambered heart and 3 outflow tracts (1 pulmonary and 2 systemic). The quantity and quality of blood (oxygenated vs unoxygenated) may vary not only between the pulmonary and systemic outflow tracts but also between the 2 systemic outflow tracts. Further, each outflow tract contributes differently to cranial and caudal systemic perfusion. The brain and hind limbs can potentially receive blood with different PaO2 values. The stimulus to respire and the determinants of intracardiac shunting remain elusive to reptile physiologists. Our ability to directly apply our mammalian understanding of anesthetic uptake and distribution to reptiles should be done cautiously. It is unknown whether end-tidal inhalant concentrations in reptiles accurately reflect concentrations in the brain or heart. However, until such research is done, we are left using the methods and techniques developed for mammals. Clinicians cannot measure partial pressures of inhalant anesthetics in the brain or even blood but can only obtain estimates by knowing the percentage delivered, inspired, or exhaled. Thus, although we cannot with certainty state the validity of our results, we can say that on the basis of available methods, we have determined values that are clinically useful and relevant.

In conclusion, results of the present study suggest that the CAI for isoflurane in green iguanas is greater than values for swine and dogs and, possibly, similar to the value for rats. It is important to recognize that there are differences in methodology for determining these indices among researchers. The true CAI in green iguanas could not be calculated in this study, because we were unable to induce cardiovascular arrest with the highest concentration that could be delivered with the vaporizer we were using. The CAI was > 4.32, and exceeding an end-tidal concentration of isoflurane higher than 4.32 times MAC would seem unlikely when using a properly functioning isoflurane-specific precision vaporizer. However, this does not imply that iguanas could not be overdosed with isoflurane, as the CAI is likely to be lower in sick or debilitated animals and may vary among individuals.

Although our sample size was small, it does appear that there is a substantial safety margin associated with isoflurane anesthesia in healthy green iguanas. Thus, practitioners can use this anesthetic technique with confidence despite the limited monitoring available. Reasonable errors in anesthetic depth should be well tolerated in this species. It should also be stressed that the use of butorphanol as an analgesic in green iguanas does not appear to increase the risk associated with isoflurane anesthesia.

8Reptisun 5.0 UVB, Zoo Med Laboratories Inc, San Luis Obispo, Calif.
9Sage London Industries Inc, Cambridge, ON, Canada.
References


