Pharmacokinetics of inhaled anesthetics in green iguanas (Iguana iguana)

Robert J. Brosnan, DVM, PhD; Bruno H. Pypendop, Dr Med Vet, Dr Vet Sci; Linda S. Barter, MVSc; Michelle G. Hawkins, VMD

**Objective**—To test the hypothesis that differences in anesthetic uptake and elimination in iguanas would counter the pharmacokinetic effects of blood:gas solubility and thus serve to minimize kinetic differences among inhaled agents.

**Animals**—6 green iguanas (Iguana iguana).

**Procedures**—Iguanas were anesthetized with isoflurane, sevoflurane, or desflurane in a Latin-square design. Intervals from initial administration of an anesthetic agent to specific induction events and from cessation of administration of an anesthetic agent to specific recovery events were recorded. End-expired gas concentrations were measured during anesthetic washout.

**Results**—Significant differences were not detected for any induction or recovery events for any inhalation agent in iguanas. Washout curves best fit a 2-compartment model, but slopes for both compartments did not differ significantly among the 3 anesthetics.

**Conclusions and Clinical Relevance**—Differences in blood:gas solubility for isoflurane, sevoflurane, and desflurane did not significantly influence differences in pharmacokinetics for the inhalation agents in iguanas. (Am J Vet Res 2006;67:1670–1674)

Potent inhaled anesthetics behave differently in iguanas, compared with their behavior in mammals or birds. During a relatively short anesthetic episode achieved by administration of isoflurane, MAC, a measure of inhaled anesthetic ED50, is approximately 50% higher in iguanas than most other species. Although the pulmonary gas exchange units in iguanas are faveoli, rather than alveoli, the term MAC can still be used to define and compare potencies of inhalation agents. In addition, the LD50 of isoflurane is markedly decreased in MAC counteract changes in solubility; solubility for all anesthetics. In hypothermic mammals, decreases in MAC counteract changes in solubility; thus, the time to achieve 1 MAC for an anesthetic is unaltered. However, in some ectotherms, the ED50 of aqueous anesthetics may not be independent of temperature. If this is true for iguanas, it may be possible that their body temperature, which is generally lower than the body temperature of endotherms, could affect the time required to achieve 1 MAC for an anesthetic in the CNS.

Anesthetics with a low blood:gas partition coefficient typically provide more rapid induction and recovery. For example, in healthy pigs, anesthetic induction and washout are more rapid with the less-soluble agent desflurane than with sevoflurane, which, in turn, is more rapid than with the more-soluble agent isoflurane. Uptake of poorly soluble agents is expected to be impeded more by venous admixture than would uptake of extremely soluble agents. As a result, venous admixture should increase alveolar-arterial gradients for poorly soluble anesthetics more than for soluble anesthetics. Therefore, we hypothesized that venous admixture in iguanas would minimize kinetic differ-

**ABBREVIATIONS**

- MAC Minimum alveolar concentration
- ED50 Median effective dose
- FE End-tidal concentration of anesthetic agent measured at various time points during recovery
- F0 End-tidal concentration of anesthetic agent measured immediately prior to discontinuation of maintenance anesthesia
- AUC Area under the F_E:F0-versus-time curve
- t1/2 Half-life

distribution of anesthetic gases. First, reptiles have a much lower cardiac index than mammals and, probably, less flow per gram of vessel-rich tissues. This may slow movement of anesthetic gas from the faveoli to the CNS. Second, noncrocodilian reptiles have an incomplete intraventricular muscular ridge that allows right-to-left intracardiac shunting equal to 60% to 70% of venous return, which thus reduces the effective cardiac output available for distribution of anesthetic-rich blood. Third, the potential for large ventilation-perfusion mismatches and limitations in pulmonary diffusion in some reptiles may impede movement of inhaled anesthetics from the lungs to the blood and increase the alveolar-to-arterial anesthetic gradient. Finally, a decrease in core body temperature of iguanas could theoretically retard the increase in anesthetic partial pressure in tissues because of increased blood solubility for all anesthetics. In hypothermic mammals, decreases in MAC counteract changes in solubility; thus, the time to achieve 1 MAC for an anesthetic is unaltered. However, in some ectotherms, the ED50 of aqueous anesthetics may not be independent of temperature. If this is true for iguanas, it may be possible that their body temperature, which is generally lower than the body temperature of endotherms, could affect the time required to achieve 1 MAC for an anesthetic in the CNS.
ences among agents during induction and recovery. In addition, because venous admixture limits movement of anesthetic from the blood to the alveoli during recovery, we predicted that the alveolar washout for all anesthetic agents would appear to be more rapid in iguanas than has been reported for other species. However, if the anesthetic agents also have prolonged retention in the blood and tissues, there should be a diminished, yet prolonged, delivery of anesthetic to the alveoli. This would be reflected by a terminal washout period with a minimal slope for all anesthetic agents.

Thus, the objective of the study reported here was to characterize the pharmacokinetics of isoflurane, sevoflurane, and desflurane in green iguanas.

Materials and Methods

Animals and husbandry—Three male and 3 female mature green iguanas (Iguana iguana) that weighed (± SD) 1.2 ± 0.7 kg were obtained from a vendor approved by the Center for Laboratory Animal Science, University of California–Davis. The iguanas were included in a study that was approved by the Animal Care and Use Committee at the University of California–Davis.

Health status of each iguana was assessed on the basis of results of a physical examination, CBC, serum biochemical analysis, and lack of parasites detected during examination of fecal specimens. Iguanas were housed separately in humidified (> 60% relative humidity) cages with a temperature gradient of 27° to 37°C that was maintained by use of infrared lamps. Overhead and cage lights provided full-spectrum lighting with UVB; the light cycle was 12 hours of light and 12 hours of darkness. The diet consisted of leafy greens and vegetables supplemented with calcium powder. Iguanas were allowed to acclimate for at least 4 weeks before inclusion in the study. At the end of the study, iguanas were returned to the Center for Laboratory Animal Science and used to establish a colony for instructional purposes.

Induction of anesthesia—Each iguana was anesthetized with 3 inhalant anesthetics (isoflurane, sevoflurane, and desflurane). Anesthesia was accomplished by each of the inhalant anesthetics administered at 1 MAC.

Induction of anesthesia

Table 1—Mean ± SD interval from time of initial administration of an anesthetic agent to specific events during induction and from time of cessation of administration of an anesthetic agent to specific events during recovery in 6 green iguanas for 3 inhalation anesthetics administered at 1 MAC.

<table>
<thead>
<tr>
<th>Event</th>
<th>Isoflurane</th>
<th>Sevoflurane</th>
<th>Desflurane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction (min)</td>
<td>8 ± 3</td>
<td>8 ± 2</td>
<td>5 ± 1</td>
</tr>
<tr>
<td>Recumbency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss of righting reflex</td>
<td>8 ± 3</td>
<td>9 ± 1</td>
<td>7 ± 2</td>
</tr>
<tr>
<td>Intubation</td>
<td>10 ± 2</td>
<td>12 ± 2</td>
<td>9 ± 2</td>
</tr>
<tr>
<td>Recovery (min)</td>
<td>44 ± 33</td>
<td>46 ± 22</td>
<td>46 ± 25</td>
</tr>
<tr>
<td>Spontaneous ventilation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Movement</td>
<td>56 ± 29</td>
<td>62 ± 18</td>
<td>40 ± 23</td>
</tr>
<tr>
<td>Exhaltion</td>
<td>68 ± 29</td>
<td>64 ± 19</td>
<td>48 ± 25</td>
</tr>
<tr>
<td>Total anesthetic time (h)</td>
<td>11.0 ± 1.8</td>
<td>11.1 ± 1.5</td>
<td>10.2 ± 2.3</td>
</tr>
</tbody>
</table>

Where A and B are y intercepts; e is the base of the natural logarithm; α and β are the slope of the first and second compartments, respectively; and t is time. Initial and terminal 1/e2 values equaled the natural logarithm of 2 divided by the slope of the compartment. The AUC values were calculated by use of a trapezoid method. Differences between slopes of the compartments, AUCs, and intervals for induction and recovery events for isoflurane, sevoflurane, and desflurane were evaluated by use of a repeated-measures ANOVA followed by Dunn-Sidak tests, when appropriate. Normality for all variables was evaluated by inspecting box plots of the data and by calculating Shapiro-Wilk statistics. Values of P < 0.05 were considered significant.

Results

Anesthetic induction in all iguanas was unremarkable. We did not detect breath holding or an excitatory

Recovery from anesthesia—After anesthetic maintenance at approximately 1 MAC for 10 to 11 hours, the vaporizer was turned off, and the iguanas remained in dorsal recumbency but were mechanically ventilated with 100% oxygen at the same rate and tidal volume for 1 hour or until movement was detected. Samples for measurement of end-tidal gas concentrations were manually collected in ground-glass syringes at intervals of 2 to 4 minutes, and anesthetic agents were measured by use of an infrared gas analyzer that was calibrated daily against multiple certified gas standards that encompassed the range of measured concentrations for each anesthetic agent. When an iguana was still recumbent and immobile after 1 hour, ventilation was continued with room air at the rate of 1 breath/min until spontaneous respiration resumed. During this time, a toe pinch was performed on the iguana every 5 minutes until the righting reflex returned. Exhalation was performed once iguanas vigorously objected to the endotracheal tube. Intervals from discontinuation of inhalant anesthetic until specific recovery events were recorded, and the entire recovery was videotaped.

Data analysis—Anesthetic washout curves were generated for each iguana by dividing the F1 by the F0, which allowed us to make pharmacokinetic comparisons among agents with differing potencies (ie, MACs). Concentration-time data were fitted to compartment models. On the basis of visual inspection of raw data, logarithmic concentration-versus-time plots, and residual plots, data were best described by a 2-compartment model with the following equation:

\[ F_1/F_0 = A e^{-\alpha t} + B e^{-\beta t} \]

where A and B are y intercepts; e is the base of the natural logarithm; α and β are the slope of the first and second compartments, respectively; and t is time. Initial and terminal 1/e2 values equaled the natural logarithm of 2 divided by the slope of the compartment. The AUC values were calculated by use of a trapezoid method. Differences between slopes of the compartments, AUCs, and intervals for induction and recovery events for isoflurane, sevoflurane, and desflurane were evaluated by use of a repeated-measures ANOVA followed by Dunn-Sidak tests, when appropriate. Normality for all variables was evaluated by inspecting box plots of the data and by calculating Shapiro-Wilk statistics. Values of P < 0.05 were considered significant.
There were no significant differences between intervals for induction events (ie, recumbency, loss of righting reflex, or intubation) or for recovery events (spontaneous breathing, movement, or extubation) when iguanas were administered isoflurane, sevoflurane, or desflurane (Table 1). Although the mean value for desflurane did not differ significantly from the mean values for the other anesthetic agents, the interval to first movement and extubation following cessation of desflurane administration was only approximately 15 minutes in 2 iguanas. There was no association between $F_E:F_0$ and movement prior to the initial 1-hour washout with oxygen and mechanical ventilation. In fact, 2 iguanas anesthetized with desflurane were immobile with an $F_E:F_0$ of 0.02, whereas 2 other iguanas anesthetized with isoflurane were righting themselves with an $F_E:F_0$ of approximately 0.2.

Alveolar washout curves were plotted for each of the 3 anesthetic agents (Figure 1). Each agent could be described by use of a 2-compartment model (isoflurane, $F_E:F_0 = 0.745e^{-0.676t} + 0.259e^{-0.00853t}$; sevoflurane, $F_E:F_0 = 0.761e^{-0.691t} + 0.243e^{-0.00717t}$; and desflurane, $F_E:F_0 = 0.931e^{-0.494t} + 0.076e^{-0.00653t}$). For isoflurane, sevoflurane and desflurane, elimination $t_{1/2}^\alpha$ was 1.02, 1.00, and 1.40 minutes, respectively, and elimination $t_{1/2}^\beta$ was 81, 97, and 106 minutes, respectively. Evaluation of box plots and results of Shapiro-Wilk tests confirmed normal distributions for $\alpha$ and $\beta$ for each anesthetic agent. No significant differences were found among agents for the slope of the first or second compartment. A power analysis was performed in which we assumed the same SDs and statistical error rates from the study reported here. Those calculations revealed that 20 iguanas would be needed to detect a difference between sevoflurane and desflurane for the $\alpha$ value for the slope of the compartment and that 60 iguanas would be needed to detect a difference between isoflurane and desflurane for the $\beta$ value for the slope of the compartment. Nevertheless, final $F_E:F_0$ values were significantly lower for desflurane than for isoflurane or sevoflurane. Mean $\pm$ SD AUC for desflurane ($7 \pm 3$ [MAC•min]/dL) was also significantly less than the mean AUC for isoflurane ($25 \pm 8$ [MAC•min]/dL) or sevoflurane ($23 \pm 7$ [MAC•min]/dL).

**Discussion**

To our knowledge, the study reported here is the first in which pharmacokinetics have been described for inhalant anesthetics in reptiles. Washout kinetics for isoflurane, sevoflurane, and desflurane all fit a 2-compartment model. This stands in contrast to described washout kinetics for potent inhaled agents in mammals, for which 3- to 5-compartment models are necessary to adequately describe the data.

When ascribing anatomic equivalents to the model, the first compartment primarily represents rapid washout of the functional residual capacity of the lungs. The second compartment is equivalent to washout from vessel-rich tissues (eg, the brain, heart, and kidneys). Higher-order compartments in other
models probably correspond to washout from other tissue groups (eg, muscle or fat) and metabolism. Although differential washout as a function of the density of tissue vessels should be evident in iguanas, the small contribution of alveolar anesthetic from other model compartments is probably undetectable as a result of increased alveolar-arterial gradients.

Although the protracted duration of anesthesia in the study reported here should have prolonged alveolar washout, F1,F2,F0 values decreased rapidly for all agents. The significantly lower expired desflurane fractions at later time points may have been attributable to an increased gradient for gas diffusion early during elimination because desflurane has a higher MAC and, therefore, an increased gradient for diffusion. Values for F1,F2,F0 at equivalent time points in iguanas were much lower than those reported in studies of mammals that had considerably shorter anesthetic uptake times.

However, movement during anesthetic washout accomplished by the administration of oxygen and mechanical ventilation was not correlated with alveolar anesthetic concentration. Indeed, 2 iguanas anesthetized with desflurane were unresponsive even at an F1,F2,F0 of 0.02. For mammals, wakefulness and movement are typically observed at 20% to 30% of MAC, which would correspond to an F1,F2,F0 of 0.2 to 0.3 and an end-tidal anesthetic concentration at which most iguanas remained immobile. Most iguanas did not recover until after breathing room air for a few minutes. It is probable that hypoxemia caused a reduction in right-to-left intracardiac shunting that subsequently increased delivery of anesthetic to, and elimination of anesthetic from, the lungs. It is also possible that conscious iguanas may have remained immobile as a defensive response.

Similarities among washout curves mirrored similarities in induction and recovery characteristics for the 3 inhalation agents. In humans, blood:gas partition coefficients for isoflurane, sevoflurane, and desflurane are 1.4, 0.69, and 0.42, respectively. These solubility measurements are slightly higher than values reported in horses, similar to values reported in sheep, and slightly lower than values reported in rabbits and rats. To our knowledge, anesthetic partition coefficients have not been measured in iguanas, but the relative solubilities for these agents probably approximate relationships described in other species. This is supported by AUC calculations in the study reported here, which should be proportional to the total volume of anesthetic in an animal and, hence, a function of whole-animal anesthetic solubility. Therefore, the significantly lower AUC for desflurane suggests lower solubilities in blood, tissue, and fat for this agent than for isoflurane or sevoflurane. Because it is improbable that the anesthetics used in the study reported here have identical blood:gas partition coefficients in iguanas, it is similarly improbable that modest species differences of anesthetic solubility in blood can be used to explain the reason that the intervals to intubation and extubation were indistinguishable among anesthetic agents. However, it was not possible during anesthetic induction to deliver equivalent doses of all agents to the induction chamber by use of the temperature-compensated precision out-of-circuit vaporizers. Output from the isoflurane, sevoflurane, and desflurane vaporizers at maximal settings were equivalent to 2.8, 2.3, and 2.0 MAC, respectively.

In 1 study, investigators reported modest differences between isoflurane and sevoflurane for induction times in iguanas. However, the experiments in that study did not have an objective or clearly defined end point for induction, and the investigators were aware of the induction agents administered to each iguana. Any of those factors could have introduced substantial bias toward 1 anesthetic drug. Because elimination of inhaled anesthetics is inversely related to uptake of inhaled anesthetics, nonsignificant elimination kinetics suggest nonsignificant uptake kinetics. Thus, with 100% oxygen as a carrier gas and the use of conventional precision vaporizers, it may not be possible to substantially accelerate induction and recovery in iguanas through the selection of inhalant agents with low solubility. Rather, more favorable kinetics may be achieved by influencing determinants of shunt fraction, such as body temperature, cardiac preload, vagal tone, ventilation pattern, and the partial pressure of oxygen in blood.

Contemporary inhalant agents behave extremely differently in iguanas than in other commonly anesthetized species. This is not attributable to altered pharmacodynamic effects in iguanas, compared with results in other mammals. Rather, venous admixture from large anatomic shunts probably creates a pharmacokinetic limitation to movement of inhaled agents from the lungs to the CNS. Hence, safe and effective use of these drugs in iguanas will require special consideration of reptilian circulation and its profound effects on anesthetic uptake, distribution, and elimination.

References

5. Munson ES, Eger EI II. The effects of hyperthermia and


