

Minimum alveolar concentration of sevoflurane in spontaneously breathing llamas and alpacas

Tamara L. Grubb, DVM, MS, DACVA; John W. Schlipf, DVM, MS, DACVIM; Thomas W. Riebold, DVM, DACVA; Christopher K. Cebra, VMD, MS, DACVIM; Lisa Poland, BS; Xenia Zawadzka, BS; Nicole Mailhot, DVM

Objective—To determine the minimum alveolar concentration (MAC) of sevoflurane in spontaneously breathing llamas and alpacas.

Design—Prospective study.

Animals—6 healthy adult llamas and 6 healthy adult alpacas.

Procedure—Anesthesia was induced with sevoflurane delivered with oxygen through a mask. An endotracheal tube was inserted, and a port for continuous measurement of end-tidal and inspired sevoflurane concentrations was placed between the endotracheal tube and the breathing circuit. After equilibration at an end-tidal-to-inspired sevoflurane concentration ratio > 0.90 for 15 minutes, a 50-Hz, 80-mA electrical stimulus was applied to the antebrachium until a response was obtained (ie, gross purposeful movement) or for up to 1 minute. The vaporizer setting was increased or decreased to effect a 10 to 20% change in end-tidal sevoflurane concentration, and equilibration and stimulus were repeated. The MAC was defined as the mean of the lowest end-tidal sevoflurane concentration that prevented a positive response and the highest concentration that allowed a positive response.

Results—Mean \pm SD MAC of sevoflurane was $2.29 \pm 0.14\%$ in llamas and $2.33 \pm 0.09\%$ in alpacas.

Conclusions and Clinical Relevance—The MAC of sevoflurane in llamas and alpacas was similar to that reported for other species. (*J Am Vet Med Assoc* 2003;223:1167–1169)

Llamas, alpacas, and other camelids are obligate nasal breathers and prone to airway obstruction during recovery from general anesthesia.^{1,2} This is due in part to a slow return to consciousness and a delayed return of the swallow reflex. Thus, a more rapid return to consciousness and shorter time to restoration of airway reflexes following anesthesia could allow camelids to make the transition from endotracheal tube breathing to nasal breathing more rapidly and safely with less danger of severe airway obstruction.

Sevoflurane is a highly insoluble agent associated with rapid induction of and recovery from anesthesia.³ However, the potency of sevoflurane in camelids has not been established. The potency of inhalant anesthetic agents is described by the **minimum alveolar concentration (MAC)** that will result in no response to a painful stimulus in 50% of patients.⁴ The MAC must

be established in each species to determine the expected effective and safe dose of the agent for that species. The MAC for sevoflurane has been determined in human beings,⁵ dogs,⁶ horses,⁷ and cats⁸ but to our knowledge has not been determined in camelids. The purpose of the study reported here was to determine the MAC of sevoflurane in llamas and alpacas.

Materials and Methods

Animals—Six healthy adult female llamas and 6 healthy adult alpacas (3 males and 3 females) were used in the study. Mean \pm SD body weights were 167 ± 9 kg (367 ± 20 lb) for the llamas and 80 ± 17 kg (176 ± 37 lb) for the alpacas. Llamas ranged from 4 to 9 years old; alpacas ranged from 6 to 9 years old. The experimental protocol was approved by the Animal Care and Use Committee at Oregon State University.

Anesthetic procedure—On the day of anesthesia, body weight, heart rate, respiratory rate, and rectal temperature were recorded for each animal. Hair over an 8- to 10-cm portion of the right jugular vein was clipped, and the skin was aseptically prepared and anesthetized with 1 mL of 2% lidocaine administered SC. A 16-gauge, 12.5-cm polytetrafluoroethylene catheter was inserted into the jugular vein.

Anesthesia was induced with sevoflurane^a delivered with oxygen (6 L/min) through a facemask connected to a semi-closed circle system^b with an out-of-circle, agent-specific, precision vaporizer^c set at the highest available setting (8%). Once animals were recumbent and relaxed, they were placed in left lateral recumbency on an 8-cm-thick foam pad. The facemask was removed, and a cuffed endotracheal tube was inserted.

A connector port was attached between the endotracheal tube and the breathing circuit to allow constant monitoring of end-tidal gases. End-tidal and inspired sevoflurane concentrations and end-tidal partial pressure of CO₂ (PETCO₂) were measured continuously with commercial analyzers.^{d,e} The sevoflurane monitor was calibrated before and after each research period with a commercially prepared calibration gas.^f Soda lime was replaced after each animal.

After animals were intubated, the vaporizer setting was reduced to provide an end-tidal sevoflurane concentration of approximately 2.3% (ie, the MAC in other species). A pulse oximeter probe^g was placed on the tongue for noninvasive measurement of oxygen hemoglobin saturation (SpO₂). Body temperature was constantly evaluated with a temperature probe placed in the esophagus. Body temperature and PETCO₂ were maintained within ranges previously shown not to have significant effects on MAC in other species.^{9,10} A balanced electrolyte solution was administered through the jugular catheter at a rate of 5 mL/kg/h (2.3 mL/lb/h).

Determination of MAC—Once the ratio of end-tidal-to-inspired sevoflurane concentration was > 0.9 , the animal was allowed to equilibrate for 15 minutes. A 50-Hz, 80-mA electrical stimulus was then delivered^h to the medial aspect of the antebrachium until a response was achieved or for up to 1 minute. A response was defined as gross purposeful movement of the head or limbs. The stimulus was discontinued

From the Department of Clinical Sciences, College of Veterinary Medicine, Oregon State University, Corvallis, OR 97331. Dr. Grubb's present address is 2002 Schultheis Rd, Uniontown, WA 99179. Supported by a grant from the Morris Animal Foundation. Address correspondence to Dr. Grubb.

immediately if the animal responded. If a response was seen, the vaporizer setting was increased to increase end-tidal sevoflurane concentration by 10 to 20%. If no response was seen, the vaporizer setting was decreased to decrease end-tidal sevoflurane concentration by 10 to 20%. Once the ratio of end-tidal-to-inspired sevoflurane concentration was again > 0.9 , the animal was allowed to equilibrate for 15 minutes, and the stimulus was again administered. The MAC was defined as the average of the lowest end-tidal sevoflurane concentration that prevented a response and the highest concentration that allowed a response. These 2 values were determined twice in each animal. Animals were then disconnected from the anesthetic machine and allowed to recover quietly in a padded stall.

Results

Mean \pm SD MAC of sevoflurane in llamas was $2.29 \pm 0.14\%$. Mean MAC in alpacas was $2.33 \pm 0.09\%$. The SpO_2 was never $< 95\%$.

Discussion

The MACs of sevoflurane determined for llamas and alpacas in the present study were similar to MACs of sevoflurane reported for dogs (2.36%),⁶ cats (2.38%),⁸ horses (2.31%),⁷ goats (2.33%),¹¹ adult rats (2.29%),¹² neonatal rats (2.68%),¹² neonatal pigs (2.12%),¹³ rabbits (2.05%),¹⁴ and hamsters (2.31%).¹⁵ Although llamas and alpacas differ from other mammals in regard to sensitivity to some injectable anesthetic drugs,^h they do not appear to differ in regard to sensitivity to sevoflurane. This is not surprising, because the MACs of most inhalant anesthetic agents have proven to be consistent for most mammalian species.¹⁶

In this study, MAC was determined by evaluating responses to a 50-Hz, 80-mA electrical stimulus applied to the medial aspect of the antebrachium for up to 1 minute. Eger et al¹⁷ have shown that inconsistent responses to a stimulus and, thus, variability in the value assigned as the MAC may occur unless the stimulus is supramaximal. Electrical current has previously been used as a supramaximal stimulus in llamas¹⁸ and other species.^{4,7,19,20} A positive response to a stimulus is defined as gross purposeful muscular movement and usually entails movement of the head or limbs and does not include coughing, swallowing, chewing, or grimacing.¹⁷ As in a previous study¹⁸ of the MAC of isoflurane in llamas, the most common responses to the electrical stimulus in the present study were extension of the unstimulated forelimb and flexion of the hind limbs. Flexion of the stimulated forelimb was not considered a positive response, because the ulnar and median nerves and their branches course across the medial aspect of the antebrachium, and direct stimulus of these nerves by the electrical current could initiate a mechanical, rather than a reflex, response of the forelimb. Although responses were always determined by the same individuals in the present study, interpretation of responses can vary, resulting in some variability in the value assigned as the MAC. However, on the basis of the small SDs for MAC values in both groups of camelids in the present study, errors attributable to subjectivity appeared to be minimal.

In determining MAC, we assumed that following anesthetic equilibration, the partial pressures of sevoflu-

rane in all body tissues were equal, and the partial pressure of sevoflurane in the alveolus represented the partial pressure at the site of action, the brain. The time required for the alveolar partial pressure of an inhalant anesthetic agent to equilibrate with the partial pressure in the brain and other tissues is proportional to the blood-gas partition coefficient and brain volume and is inversely proportional to cerebral blood flow.²¹ Halothane has been shown to reach equilibration in 15 minutes in human beings.¹⁶ Because the blood-gas partition coefficient (Ostwald's coefficient) is significantly smaller for sevoflurane (0.69) than for halothane (2.36), sevoflurane should equilibrate in the tissues in a significantly shorter time than halothane. The ratio of end-tidal to inspired concentration has been used as an approximation of anesthetic equilibration. In dogs, the ratio of end-tidal to inspired sevoflurane concentration was 0.75 thirty seconds after the dogs had been breathing a constant inspired concentration of the gas.⁶ This ratio was approximately 3 times the ratio for halothane measured at the same time. Thus, allowing the camelids to equilibrate for 15 minutes at an end-tidal-to-inspired concentration ratio > 0.90 should have allowed adequate time for tissue equilibration of sevoflurane.

In the present study, we also assumed that end-tidal sevoflurane concentration was a reasonable approximation of alveolar partial pressure. However, anesthesia may cause or exacerbate ventilation-perfusion inequalities that exist in the lung, and this may affect the alveolar-arterial equilibration and the accuracy of end-tidal gas monitoring.^{22,23} This potential error is minimal when the measured ratio of end-tidal to inspired concentration is high (ie, > 0.90), as in our study, and when poorly soluble anesthetic agents, such as sevoflurane, are used.¹⁶ Furthermore, we chose to collect end-tidal gases from the end of the endotracheal tube. This is an established method of obtaining end-tidal gases in a clinical setting, but gas samples may be affected by mixing of inspired and expired gases in the trachea. This error can be minimized by collecting end-tidal gases from deep in the trachea, as close to the area of gas exchange (alveoli) as possible. However, we chose to measure MAC as it would be measured in the clinical setting. Because sevoflurane MACs determined in the present study were similar to sevoflurane MACs determined in other species, we feel that potential errors from the site of gas collection were minimal.

Methane gas, which is commonly produced by ruminants such as camelids, can interfere with end-tidal gas analyses when analyzers that incorporate infrared measurements are used.²⁴ However, analyzers used in the present study incorporated a piezoelectric crystal for measurement of end-tidal gas concentrations. Piezoelectric crystal technology should not be affected by methane.

One final limitation to MAC determinations in the present study is the fact that the end-tidal gas monitor was calibrated with isoflurane rather than sevoflurane. This monitor was designed by the manufacturer to use isoflurane as the calibration agent, with the other inhalant agents calibrated with cross-calibration factors determined at the time of manufacture and stored in the nonvolatile memory of the unit. The manufac-

turer claims an accuracy for sevoflurane of $\pm 0.1\%$.²⁵ Although this is an acceptable error, the accuracy of the monitor would ideally have been checked with a calibration gas containing a known sevoflurane concentration.

A multitude of factors can affect MAC, including any premedications given,^{26,27} PaCO₂,^{9,16} body temperature,^{10,16} and age.²⁸ To avoid the influence of other anesthetic drugs, anesthesia in the present study was induced with a mask, and animals were not given any premedications or induction agents. To avoid the influences of hypothermia and hypercarbia, heating blankets and lamps were available to maintain body temperature $> 32^{\circ}\text{C}$ (89.6°F), and a ventilator was available to provide intermittent positive-pressure ventilation to maintain PETCO₂ < 95 mm Hg. Body temperatures $< 32^{\circ}\text{C}$ ¹⁰ and PETCO₂ > 95 mm Hg⁹ have been shown to lower MAC in halothane-anesthetized dogs. However, neither body temperature nor PETCO₂ was altered to a degree that required intervention at any time in any of the animals in the present study. Hyperthermia ($> 42^{\circ}\text{C}$ [107.6°F]) has also been shown to decrease MAC²⁹; however, we did not encounter hyperthermia at any time during the study. Age was not a factor, as the camelids were adults of similar age. Severe hypoxemia (PaO₂ < 30 mm Hg or arterial oxygen saturation [SaO₂] $< 56.7\%$) may also affect the MAC.¹⁷ Although SaO₂ was not measured in these animals, hemoglobin saturation was measured with a pulse oximeter (SpO₂) and was $> 95\%$ at all times, which suggests that arterial partial pressures of oxygen were well above values that affect MAC.³⁰ Furthermore, in our experience, pulse oximetry has been shown to provide a reliable and repeatable measurement of SpO₂ in llamas. Although only female llamas were available for this study, Eger³¹ has reported that gender does not affect MAC. The MAC also varies with barometric pressure; therefore, for consistency, MAC is traditionally reported at the barometric pressure at sea level, and correction factors are available to determine MACs for higher elevations. However, the institution where this study was conducted is only 230 ft above sea level. Thus, a correction factor was not necessary.

^aSevoFlo, Abbott Laboratories, Abbott Park, Ill.

^bModulus I, Ohmeda, Madison, Wis.

^cSevotec 5, Ohmeda, Madison, Wis.

^dBCI 8100 anesthetic agent monitor, BCI Intl, Waukesha, Wis.

^eOhmeda 4700 OxiCap, Ohmeda, Louisville, Colo.

^fAnesthesia agent calibration gas, BCI Intl, Waukesha, Wis.

^gEZStim, Life-Tech Inc, Houston, Tex.

^hMama KR, Aubin ML, Johnson LW. Experiences with xylazine, butorphanol and ketamine for short-term anesthesia in llamas and alpacas, in *Proceedings. 7th World Cong Vet Anesth* 2000;104.

References

- Riebold TW, Kaneps AJ, Schmotzer WB. Anesthesia in the llama. *Vet Surg* 1989;18:400–404.
- Riebold TW, Engel HN, Grubb TL, et al. Orotracheal and nasotracheal intubation in llamas. *J Am Vet Med Assoc* 1994;204:779–783.
- Clarke KW. Desflurane and sevoflurane: new volatile anesthetic agents. *Vet Clin North Am Small Anim Pract* 1999;29:793–810.
- Saidman LJ, Eger EI II. Effect of nitrous oxide and of narcotic premedication on the alveolar concentration of halothane required for anesthesia. *Anesthesiology* 1964;25:302–306.
- Katoh T, Ikeda K. The MAC of sevoflurane in humans. *Anesthesiology* 1987;66:301–303.
- Kazama T, Ikeda K. Comparison of MAC and the rate of rise of alveolar concentration of sevoflurane with halothane and isoflurane in the dog. *Anesthesiology* 1988;68:435–437.
- Aida H, Mizuno Y, Hobo S, et al. Determination of MAC and physical response to sevoflurane inhalation in horses. *J Vet Med Sci* 1994;56:1161–1165.
- Doi M, Yunoki H, Ikeda K. The minimum alveolar concentration of sevoflurane in cats. *J Anesth* 1988;2:113–114.
- Eisele JH, Eger EI II, Muallem M. Narcotic properties of carbon dioxide in the dog. *Anesthesiology* 1967;28:856–865.
- Eger EI II, Saidman LJ, Brandstater B. Temperature dependence of halothane and cyclopropane anesthesia in dogs: correlation with some theories of anesthetic action. *Anesthesiology* 1965;26:764–770.
- Hikasa Y, Okuyama K, Kakuta T, et al. Anesthetic potency and cardiopulmonary effects of sevoflurane in goats: comparison with isoflurane and halothane. *Can J Vet Res* 1998;62:299–306.
- Kashimoto S, Furuya A, Nonaka A, et al. The minimum alveolar concentration of sevoflurane in rats. *Eur J Anaesthesiol* 1997;14:359–361.
- Lerman J, Oyston JP, Gallagher TM, et al. The minimum alveolar concentration (MAC) and hemodynamic effects of halothane, isoflurane, and sevoflurane in newborn swine. *Anesthesiology* 1990;73:717–721.
- Scheller MS, Saidman LJ, Partridge BL. MAC of sevoflurane in humans and the New Zealand white rabbit. *Can J Anaesth* 1988;35:153–156.
- Viven B, Langeron O, Coriat P, et al. Minimum alveolar anesthetic concentration of volatile anesthetics in normal and cardiomyopathic hamsters. *Anesth Analg* 1999;88:489–493.
- Quasha AL, Eger EI II, Tinker JH. Determinations and application of MAC. *Anesthesiology* 1980;53:315–334.
- Eger EI II, Saidman LJ, Brandstater B. Minimum alveolar anesthetic concentration: a standard of anesthetic potency. *Anesthesiology* 1965;26:756–763.
- Mama KR, Wagner AE, Parker DA, et al. Determination of the MAC of isoflurane in llamas. *Vet Anesth* 1999;28:121–125.
- Laster MJ, Liu J, Eger EI II, et al. Electrical stimulation as a substitute for the tail clamp in the determination of minimum alveolar concentration. *Anesth Analg* 1993;76:1310–1312.
- Steffey EP, Howland D. Cardiovascular effects of halothane in the horse. *Am J Vet Res* 1978;39:611–615.
- Smith AL, Wollman H. Cerebral blood flow and metabolism: effects of anesthetic drugs and techniques. *Anesthesiology* 1972;36:378–381.
- Eger EI II, Babad AA, Regan MJ, et al. Delayed approach of arterial to alveolar nitrous oxide partial pressures in dog and in man. *Anesthesiology* 1966;27:288–297.
- Eger EI II, Bahlman SH. Is the end-tidal anesthetic partial pressure an accurate measurement of the arterial anesthetic partial pressure? *Anesthesiology* 1971;35:301–303.
- Moens Y, Gootjes P, Lagerweij E. The influence of methane on the infrared measurement of halothane in the horse. *J Vet Anaesth* 1991;18:4–7.
- Operator's manual, BCI 8100 anesthetic agent monitor.* Waukesha, Wis: BCI Intl, 1992.
- Waters RM, Schmidt ER. Cyclopropane anesthesia. *JAMA* 1934;103:975–983.
- Robbins BH, Baxter JH Jr, Fitzhugh OG. Studies of cyclopropane. V. The effect of morphine, barbital, and amytal upon the concentration of cyclopropane in the blood required for anesthesia and respiratory arrest. 1939;65:136–142.
- Gregory GA, Eger EI II, Munson ES. The relationship between age and halothane requirements in man. *Anesthesiology* 1969;30:488–491.
- Steffey EP, Eger EI II. Hyperthermia and halothane MAC in the dog. *Anesthesiology* 1974;41:392–396.
- Banchero N, Grover RF, Will JA. Oxygen transport in the llama (*Lama glama*). *Respir Physiol* 1971;13:102–115.
- Eger EI II. Fundamentals of inhalation anesthesia. In: *Anesthetic uptake and action*. Baltimore: The Williams & Wilkins Co, 1974;103–116.