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Determination of the minimum alveolar concentration of isoflurane in donkeys

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OBJECTIVE
To determine the minimum alveolar concentration (MAC) of isoflurane in donkeys and characterize recovery from anesthesia.

ANIMALS
7 healthy castrated male adult donkeys.

PROCEDURES
Anesthesia was induced with propofol and maintained under mechanical ventilation with 1.3% isoflurane end-tidal concentration (ETiso). The MAC of isoflurane was determined after a 60-minute propofol washout period using the bracketing method. A continuous noxious electrical stimulation was applied to the oral mucosa for 1 minute or until the donkey moved. The ETiso was increased or decreased by 10% depending on the response, and MAC was defined as the average of 2 ETiso values allowing and preventing movement in response to stimulation. Arterial blood gases were measured during anesthesia and the recovery period. Unassisted recovery was timed, and a quality score was assigned from 1 (very poor) to 5 (excellent).

RESULTS
The mean dose of propofol required for induction was 3.0 ± 0.6 mg/kg. The MAC of isoflurane was 1.44 ± 0.13%. One donkey was excluded from the study because it was still responsive when stimulated at ETiso of 2.8%. Immediately after extubation, the median (range) partial pressure of oxygen in the arterial blood was 63 (minimum to maximum, 46 to 72) mm Hg and 3 donkeys were hypoxemic (partial pressure of arterial oxygen < 60 mm Hg). The median time to standing was 13 (7 to 38) minutes, while the recovery score was 3 (2 to 5).

CLINICAL RELEVANCE
The MAC of isoflurane in donkeys is similar to that reported in other species. Oxygen support should be provided to donkeys during recovery from isoflurane anesthesia to prevent hypoxemia.

Inhalant anesthetics are dosed based on the minimum alveolar concentration (MAC), defined as the percent of anesthetic agent in alveolar gas required to prevent movement in 50% of patients exposed to a noxious stimulus at sea level.[1] This allows comparison of anesthetic agents by potency and the ability to determine the MAC-sparing effects of other classes of drugs. Although isoflurane MAC among species is relatively consistent, deviations as high as 40% have been reported for some carnivores.[2,3] The MAC of isoflurane has been shown to be higher in horses[4,5] than in ponies;[6,7] however, it has not been studied in donkeys.

The humane treatment of donkeys must include adequate veterinary care, which includes appropriate anesthesia and analgesia. Donkeys may be undertreated for pain due to their stoic nature,[8] although there is evidence that pain processing is the same as in ponies.[9] This underscores the mistakes that may occur if we attempt to treat donkeys as small horses. While there are a handful of publications examining injectable anesthetic protocols in donkeys,[10–14] these protocols would only be useful in short field procedures such as castration. Inhaled anesthetics are generally required for procedures lasting longer than an hour, which would include most nonelective surgeries. While isoflurane is in routine clinical use for donkey anesthesia, its MAC and recovery characteristics have not been fully defined yet. This information, in addition to MAC-sparing studies, would improve anesthetic and analgesic care of this species.

The aim of this study was to determine the minimum alveolar concentration of isoflurane and its recovery pattern in donkeys. We hypothesized that the MAC of isoflurane in donkeys would be similar to that of horses.

Materials and Methods

Animals

Seven healthy male castrated donkeys weighing 137 ± 17 kg and 7 (minimum to maximum, 6 to 8) years old were used in the study. The donkeys were housed in pens at the Ross University School of Veterinary Medicine with fresh Guinea grass, and water was provided ad libitum. A minimum of 7 days of acclimation was allowed before the study. Animals were considered healthy based on physical examination and evaluation of packed cell volume and total protein. Food was not withheld before the study. This study was performed at sea level and approved by the Institutional Animal Care and Use Committee (protocol No. 19.12.36).

Experimental design

A 14-gauge, 5.5-inch catheter was aseptically inserted into the right jugular vein and anesthesia induced with propofol (2.5 mg/kg) administered intravenously over 5 seconds. An additional bolus of propofol (0.5 mg/kg, IV) was administered every 60 seconds thereafter if animals were still moving or could not be intubated. The total dose of propofol used for each donkey was recorded and the quality of induction was evaluated by the same observer **(BTD; Appendix 1)**. Animals were placed in left lateral recumbency on a padded mat and trachea intubated with a 16-mm internal diameter endotracheal tube that was then connected to a circle system (Universal F; King Systems) with an oxygen flow rate of 6 L/min and isoflurane vaporizer set at 2%. Intermittent positive pressure ventilation was started with a respiratory rate (RR) of 8 breaths/min and a maximum peak inspiratory pressure of 20 cm H_2O to maintain the partial pressure of end-tidal carbon dioxide (P_{ETCO_2}) between 35 and 40 mm Hg. The isoflurane end-tidal concentration (ETiso) and P_{ETCO_2} were measured by a gas analyzer (Datascope Gas Module SE; Mindray), and gas samples were collected via a sampling line with the tip located in the distal end of the endotracheal tube. The vaporizer setting was subsequently adjusted to target an ET_{iso} of 1.3% and maintained constant for at least 20 minutes. The accuracy of the gas analyzer was verified with room air and 2 standard (1% and 3%) isoflurane concentrations (gas mixture: isoflurane/sevoflurane/carbon dioxide/nitrous oxide/oxygen; Airgas Healthcare) before each anesthetic procedure. The ET_{iso} values were corrected using a linear regression equation obtained by using the calibration gas values as comparative standards.[15]

An insulating blanket was placed over the donkeys to minimize heat loss with the aim of avoiding a decrease in body temperature at the time of MAC determination. The ambient temperature was maintained at approximately 23 °C. A thermistor (Surgivet Advisor Vital Signs Monitor; Smiths Medical) was calibrated before the study against a mercury thermometer and placed in the esophagus for temperature monitoring. Lactated Ringer's solution was administered intravenously at a rate of 5 mL/kg/h. A 20-gauge catheter was inserted into the right or left auricular artery from which arterial blood pressures were measured and blood samples for gas analyses collected. The arterial pressure transducer was zeroed while positioned at the level of the xiphoid process. Heart rate, RR, P_{ETCO_2}, systolic arterial pressure (SAP), mean arterial pressure (MAP), diastolic arterial pressure (DAP), and peripheral saturation of oxygen (Spo_2) were continuously monitored (Surgivet Advisor Vital Signs Monitor; Smiths Medical) and recorded at MAC determination times. In case the MAP was below 70 mm Hg, a continuous infusion of dobutamine was administered and the mean dose was recorded. Arterial blood gas samples were collected and analyzed (i-STAT 1; Abbott) immediately after catheter placement, at the time of isoflurane MAC determination, immediately after extubation, and within 2 minutes of attaining a standing position.

Isoflurane MAC determination was performed using the bracketing design[16] and initiated after 60 minutes of the induction of anesthesia to allow propofol washout. The ET_{iso} was set at 1.3% for a minimum of 20 minutes and a supramaximal noxious electrical stimulus (50 V, 50 Hz, 10 ms) was applied (DG2A Train Delay Generator; Digitimer) to the maxillary gingival mucosa for 60 seconds or until movement. The tips of the electrodes were positioned 2 centimeters apart, and the site of electrical stimulation on the gingival mucosa was different for each application. A response was considered positive if a donkey moved its lips, head, neck, or legs. Swallowing, muscle tremors, or an immediate tonic lip muscle response after the stimulus were not considered a positive response. If a positive response occurred, ET_{iso} was increased by approximately 10% and if a negative response occurred, the ET_{iso} was decreased by 10%. A minimum of 20 minutes was observed before additional stimulation once the targeted ET_{iso} had been achieved. MAC was considered determined when a crossover was obtained, defined as the average of the highest ET_{iso} that allowed and the lowest ET_{iso} that prevented movement during noxious stimulation. The individual isoflurane MAC was determined in duplicate and considered as the average between the 2 values. The reported isoflurane MAC is the average of the individual isoflurane MAC of all animals. The average of the cardiorespiratory data at the crossovers (4 data points for each donkey) is reported.

At the end of the study, animals were weaned off the ventilator and isoflurane was discontinued after donkeys were breathing spontaneously. Donkeys were allowed to breathe room air and extubated after swallowing or limb movement. Unassisted recovery was evaluated by the same observer (BTD) using a recovery scoring system **(Appendix 1)**.[17]

Anesthetic times were recorded as follows: intubation time (from the initial administration of propofol to intubation), instrumentation time (from the initial administration of propofol to completion of placement of the monitoring equipment), time to MAC determination (from the end of the 60-minute

Table 1—Median (range) of pH, arterial partial pressure of oxygen (Pa_{O_2}) and carbon dioxide (Pa_{CO_2}), bicarbonate (HCO_3^-), base excess (BE), lactate, and arterial saturation of oxygen (Sa_{O_2}) collected immediately after arterial catheter placement, isoflurane minimum alveolar concentration (MAC) determination, extubation, and standing position in 6 donkeys anesthetized with isoflurane.

Variable	Arterial catheter placement	Isoflurane MAC determination	Extubation	Standing
pH	7.36 (7.31 to 7.38)	7.38 (7.30 to 7.42)	7.39 (7.33 to 7.48)	7.35 (7.28 to 7.46)
Pa_{O_2} (mm Hg)	395 (319 to 507)[a]	483 (232 to 515)[a]	63 (46 to 72)[b]	110 (75 to 130)[a,b]
Pa_{CO_2} (mm Hg)	46 (44 to 56)	48 (42 to 53)	40 (32 to 49)	39 (38 to 41)
HCO_3^- (mmol/L)	27 (25 to 29)[a,b]	29 (26 to 29)[a]	25 (22 to 28)[a,b]	22 (19 to 27)[b]
BE (mmol/L)	1 (0 to 2)[a,b]	3 (–1 to 4)[a]	1 (–4 to 3)[a,b]	–3.5 (–8 to 3)[b]
Lactate (mmol/L)	2.5 (1.4 to 3.1)	2.8 (1.8 to 3.1)	2.6 (1.7 to 3.4)	6.4 (1.1 to 8.1)
Sa_{O_2} (%)	100 (100 to 100)[a]	100 (100 to 100)[a]	93 (84 to 93)[b]	98 (94 to 99)[a,b]

[a,b]Different superscripted letters indicate statistical significance ($P \leq 0.05$).

washout period to the end of determination of the individual's MAC), time to extubation (from cessation of isoflurane administration to extubation), and time to recover (from cessation of isoflurane administration to standing position).

Statistical analysis

Normality of data was assessed using the Shapiro-Wilk test. Normally distributed data are reported as mean ± SD, and asymmetric data are reported as median (range). Arterial blood gas parameters were compared by the Friedman test, followed by the Dunn's test. Body temperatures before the study and at MAC determination time points were compared using a paired *t* test. Significance of analyzed data was set at 5%.

Results

The mean ± SD propofol dose required to induce anesthesia in the nonpremedicated donkeys was 3.0 ± 0.6 mg/kg; 1 donkey required a propofol dose of 4 mg/kg for induction of anesthesia.

The mean ± SD isoflurane MAC was 1.44 ± 0.13%. Individual MAC was determined for 6 donkeys, with 1 donkey excluded from the study due to failure to obtain a crossover during the electrical stimulation within safe margins of isoflurane dose. The excluded donkey continued to respond positively to the supramaximal electrical stimulation even at ET_{iso} 2.8%. To avoid excessive vasodilation or dobutamine-induced arrhythmias, this donkey was recovered from anesthesia and excluded from analysis.

Median values for HR, RR, SAP, MAP, DAP, Sp_{O_2}, and P_{ETCO_2} at isoflurane MAC were 36 (31 to 48) beats/minute, 8 (8 to 8) breaths/minute, 104 (86 to 130) mm Hg, 75 (59 to 103) mm Hg, 57 (43 to 86) mm Hg, 98% (97% to 100%), and 36 (33 to 36) mm Hg, respectively. The mean dose of dobutamine during the anesthetic period was 4.5 ± 2.1 µg/kg/min. Body temperatures before induction and at MAC determination were 35.7 (34.6 to 37.1) °C and 35.6 (35.2 to 36.1) °C, respectively, and were not significantly different. Arterial blood gas parameters are reported **(Table 1)**. The partial pressure of arterial oxygen (Pa_{O_2}) of the donkeys immediately after extubation was significantly lower than perianesthetic time points, and 3 donkeys had Pa_{O_2} values lower than 60 mm Hg. After recovery from anesthesia, the base excess and bicarbonate concentrations were significantly lower compared with values at the MAC determination time point. Times to intubation, instrumentation, MAC determination, extubation, and recovery were 1.7 ± 0.8 minutes, 15.3 ± 5 minutes, 56 (42 to 233) minutes, 4.5 ± 1.8 minutes, and 13 (7 to 38) minutes, respectively. The median induction and recovery scores were 3.5 (1 to 5) and 3 (2 to 5), respectively.

Discussion

The present study reports the MAC of isoflurane and its recovery characteristics in donkeys. The MAC of isoflurane reported in the present study is similar to that reported in adult horses (1.44 ± 0.07% and 1.31 ± 0.07%)[4,5] and higher than that reported in ponies (0.97 ± 0.17% and 1.0 ± 0.2%).[6,7] Anesthesia with isoflurane in donkeys has been reported by various authors[18–22] but with no reference to the ET_{iso} required to maintain general anesthesia. The knowledge of species-specific anesthetic requirement is important to predict cardiopulmonary changes associated with fluctuations in the anesthetic depth and to compare the pharmacokinetics and pharmacodynamics of different anesthetic agents. Furthermore, accurate information on anesthetic requirement allows the recognition of sparing effects of metabolic abnormalities and drugs used as part of balanced anesthesia techniques. Although the isoflurane MAC in donkeys observed in the present study is similar to values reported in horses,[4,5] 1 donkey had to be excluded because it was still moving with an ET_{iso} of 2.8%, which is almost 2 times the isoflurane MAC observed in the present study. A variation as much as 44% in isoflurane MAC has been previously reported among mouse strains, and this was attributed to genetic variations.[23] In clinical practice, the ET_{iso} should be adjusted for individual patients based on anesthetic goals and clinical signs.

Altered physiological parameters, such as hypothermia, hypercapnia, hypoxemia, metabolic acidosis, and severe hypotension can decrease MAC.[16,24] In the present study, most of the physiologic variables that can affect MAC were within normal limits and maintenance of body temperature was attempted using a thermal blanket. Although the

mean donkey's body temperature at the time of MAC determination was approximately 1 °C lower than the reference value for donkeys (36.5 to 37.8 °C),[8] its baseline body temperature was similar to that recorded at MAC determination. It is known that isoflurane MAC decreases by approximately 5% for each 1 °C of reduction in body temperature,[25] so it is unlikely that hypothermia significantly affected the isoflurane MAC value observed in the present study. The type of supramaximal stimulation used does not affect MAC;[24] however, it has been shown to alter the sevoflurane MAC in one study in thick-billed parrots, when MAC was significantly higher when determined by electrical versus mechanical stimulation.[26] In Shetland ponies, isoflurane MAC was the same when 3 different types of electrical stimulation were used.[6] Studies determining isoflurane MAC in horses[4,5] used an electrical stimulus (50 V, 50 Hz, 10 ms) similar to that used in the present study.

A limitation of the present study was the use of propofol for induction of anesthesia. Ideally, MAC studies should avoid the use of drugs other than the inhalant anesthetic of interest. Propofol was used in the interest of safety and to achieve a rapid and smooth induction to anesthesia. The pharmacokinetics of propofol in donkeys has not been reported, but in horses propofol has a high clearance (45.8 mL/kg/min) and short mean residence time (13.7 min).[27] In addition, it has been demonstrated that after a single dose of propofol (2.2 ± 0.3 mg/kg, IV) for induction of anesthesia in horses, the plasma concentrations after 30 minutes of administration were below the limit of quantification.[28] In the present study, isoflurane MAC determination began at 60 minutes after administration of propofol to allow for adequate washout and minimize its interference in the isoflurane MAC determination.

In the present study, 3 donkeys had a good or excellent induction characterized by them slowly and gently attaining recumbency with no rigidity or paddling; however, 1 donkey had a very poor induction with potential of injury to itself and personnel. Most donkeys were successfully induced with a propofol dose of 3 mg/kg, but additional propofol should be available to supplement induction of anesthesia in nonpremedicated donkeys in the case of signs of excitement and muscle rigidity. The mean dose of dobutamine required to maintain normotension in the present study was on the higher end of the dose range recommended in horses (1 to 5 µg/kg/min).[29] It is likely that cardiovascular depression induced by propofol in the first 30 minutes could have increased the dobutamine requirement. In unpremedicated horses anesthetized with isoflurane, induction with guaifenesin and propofol increased the dobutamine requirement in the first hour of anesthesia.[28] It is also possible that the dobutamine requirement for donkeys is higher than for horses.

All donkeys in this study had low Pa_{O_2} (< 75 mm Hg) or were hypoxemic (Pa_{O_2} < 60 mm Hg) immediately after extubation while breathing room air. Low Pa_{O_2} values are commonly observed in donkeys and horses under general anesthesia and during recovery.[30] It has been reported that both fasted and unfasted laterally recumbent donkeys anesthetized with isoflurane in oxygen can have a severe degree of venous admixture most likely induced by ventilation-perfusion mismatch.[20] Most donkeys breathing room air and anesthetized with guaifenesin-ketamine-xylazine or propofol-ketamine were hypoxemic, but the Pa_{O_2} increased once they attained standing position.[11,12] A decrease in Pa_{O_2} has also been reported in miniature donkeys anesthetized with xylazine-propofol or xylazine-butorphanol-tiletamine-zolazepam.[10] The observations of the present study suggest a need for administration of supplemental oxygen during recovery of isoflurane anesthesia in donkeys to avoid hypoxemia.

Recovery from isoflurane anesthesia in most donkeys was fast and without any adverse incidents. To fully assess recovery quality, donkeys were allowed to stand unassisted, which increased the number of premature attempts to stand and knuckling. Hand-assisted or head-tail-rope-assisted recovery should be considered to minimize the risk of injury to domesticated donkeys during recovery from anesthesia in clinical settings.

An increase in muscular activity and therefore oxygen demand likely induced a clinically relevant increase in lactate concentration after donkeys were standing. In addition, muscular lactate levels may increase during isoflurane anesthesia in horses[31] and tissue reperfusion of hypoxic tissues during recovery may have contributed to the increased plasma lactate. Blood lactate has been shown to increase after recovery of isoflurane-anesthetized horses.[32]

The MAC of isoflurane in donkeys observed in the present study is similar to that reported in horses and various other mammalian species. Oxygen supplementation during recovery from isoflurane anesthesia is recommended.

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Appendix 1

Induction and recovery scores for 6 donkeys anesthetized with propofol and maintained with isoflurane.

Score	Induction	Recovery
1	Very poor, donkey fell heavily and unpredictably with rigidity and paddling and with potential to cause injury	Very poor, donkey attempted to stand and fell repeatedly with excitement and potential cause of injury
2	Poor, donkey fell heavily and unpredictably with rigidity ± paddling	Poor, repeated attempts to stand with some falls and excitement
3	Average, donkey attained recumbency heavily with some rigidity ± paddling	Average, donkey stood after more than one attempt with knuckling and ataxia
4	Good, donkey slowly and moderately gently attained recumbency with minimal or no rigidity or paddling	Good, donkey stood on first attempt with some knuckling and ataxia
5	Excellent, donkey slowly and gently attained recumbency with no rigidity or paddling	Excellent, donkey stood on first attempt with no knuckling and minimum ataxia