Balanced anesthesia is a technique whereby smaller amounts of multiple anesthetic and analgesic drugs are administered concurrently to maximize the advantages of each drug while minimizing the adverse effects. The use of balanced techniques is widespread in human and small animal anesthesia because it decreases the requirement for inhalation anesthetics and usually minimizes the dose-dependent depressant effects of these agents on the cardiovascular system.1–4

Horses are more sensitive to the cardiovascular and respiratory depressant effects of inhalation anesthetics than are dogs.3 Therefore, minimizing doses of inhalation anesthetics by augmenting analgesia and sedation with other drugs would appear to be a logical approach to improving anesthetic management in horses. Unfortunately, some of the MAC-sparing drugs commonly used in dogs and humans, particularly the opioids, do not have similar MAC-sparing effects in horses, probably because of central excitatory effects.6–8 For this reason, balanced anesthesia in horses has focused mainly on nonopioid drugs, such as α2-adrenoceptor agonists, ketamine, and lidocaine.9–11

Intravenous administration of lidocaine has been reported to reduce the risk of postoperative ileus after abdominal surgery in horses.12,13 It also can increase the thermal threshold in conscious horses14 and augment analgesia during halothane-induced anesthesia for castration.15 A continuous IV infusion of lidocaine decreases the halothane MAC in ponies16 and isoflurane requirement in horses.17 Several studies of IV infusion of lidocaine in horses as well as the clinical use of IV administration of lidocaine in anesthetized horses by our

Effects of intravenous administration of lidocaine on the minimum alveolar concentration of sevoflurane in horses

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Objective—To determine effects of a continuous rate infusion of lidocaine on the minimum alveolar concentration (MAC) of sevoflurane in horses.

Animals—8 healthy adult horses.

Procedures—Horses were anesthetized via IV administration of xylazine, ketamine, and diazepam; anesthesia was maintained with sevoflurane in oxygen. Approximately 1 hour after induction, sevoflurane MAC determination was initiated via standard techniques. Following sevoflurane MAC determination, lidocaine was administered as a bolus (1.3 mg/kg, IV, over 15 minutes), followed by constant rate infusion at 50 µg/kg/min. Determination of MAC for the lidocaine-sevoflurane combination was started 30 minutes after lidocaine infusion was initiated. Arterial blood samples were collected after the lidocaine bolus, at 30-minute intervals, and at the end of the infusion for measurement of plasma lidocaine concentrations.

Results—IV administration of lidocaine decreased mean ± SD sevoflurane MAC from 2.42 ± 0.24% to 1.78 ± 0.38% (mean MAC reduction, 26.7 ± 12%). Plasma lidocaine concentrations were 2,589 ± 811 ng/mL at the end of the bolus; 2,065 ± 441 ng/mL, 2,243 ± 699 ng/mL, 1,168 ± 359 ng/mL, and 2,254 ± 215 ng/mL at 30, 60, 90, and 120 minutes of infusion, respectively; and 2,206 ± 329 ng/mL at the end of the infusion. Plasma concentrations did not differ significantly among time points.

Conclusions and Clinical Relevance—Lidocaine could be useful for providing a more balanced anesthetic technique in horses. A detailed cardiovascular study on the effects of IV infusion of lidocaine during anesthesia with sevoflurane is required before this combination can be recommended. (Am J Vet Res 2011;72:446–451)
research group and others have revealed that lidocaine administration allows a lower anesthetic vaporizer setting to be used\(^{10,16,17}\) and that the lidocaine administration is not associated with adverse effects on heart rate or MAP.\(^{13,17-19}\) Because of the potential benefits of IV administration of lidocaine on gastrointestinal tract motility and inflammation, pain management, and the reported MAC reduction, the use of IV infusions of lidocaine during anesthesia in horses has increased over the past few years.

Sevoflurane has similar cardiovascular and respiratory effects, compared with those for isoflurane,\(^{20}\) but the use of sevoflurane is increasing in horses because its lower blood-gas partition coefficient may result in more rapid, and possibly smoother, recovery characteristics, compared with those for isoflurane.\(^{21,22}\) However, when higher doses (\(\geq 1.5 \text{ MAC}\)) are used, sevoflurane appears to cause greater depression of both respiratory and cardiovascular performance than is evident for equipotent doses of isoflurane,\(^{23}\) which makes the use of a balanced technique with sevoflurane potentially beneficial.

The objective of the study reported here was to determine the effects of a continuous rate infusion of lidocaine on the sevoflurane MAC in horses. We hypothesized that lidocaine would decrease the sevoflurane MAC in horses in a manner similar to the reduction of halothane MAC in ponies.

**Materials and Methods**

**Animals**—Eight healthy adult horses were used in the study. The horses comprised 4 geldings and 4 mares that ranged from 3 to 15 years of age (mean \(\pm SD, 9 \pm 5\) years) and that weighed between 334 and 482 kg (mean \(\pm SD, 417 \pm 59\) kg). The study protocol was approved by the Colorado State University Institutional Animal Care and Use Committee.

**Experimental procedures**—Horses had access to grass hay and water at all times, except for the morning of the experiment. Approximately 1 hour before induction of anesthesia, the body weight, rectal temperature, heart rate, and respiratory rate of each horse were recorded. A 14-gauge catheter was placed percutaneously in the right jugular vein of each horse to facilitate administration of anesthetic agents and maintenance fluids. Horses were sedated by administration of xylazine hydrochloride (0.7 mg/kg, IV) 5 minutes before administration of anesthetic agents and maintenance fluids. Horses were positioned in the right jugular vein of each horse to facilitate administration of anesthetic agents and maintenance fluids. Horses were sedated by administration of xylazine hydrochloride (0.7 mg/kg, IV) 5 minutes before administration of anesthetic agents and maintenance fluids.

**Determination of MAC**—Approximately 1 hour after anesthetic induction (which allowed for instrumentation, a washout period for induction drugs, and equilibration of sevoflurane), determination of baseline sevoflurane MAC was initiated via standard techniques.\(^{24}\) End-tidal sevoflurane concentration was maintained constant for at least 20 minutes before each stimulation time to minimize differences in alveolar-arterial anesthetic partial pressures. Sevoflurane concentration was increased (when a positive response was obtained) or decreased (when a negative response was obtained) by approximately 10% (but not more than 20%) of the previous concentration. A response was considered positive when purposeful movement was detected in response to electrical stimulation\(^1\) of the horse’s oral mucosa (noxious stimulus of 50 V, 5 Hz, and 10 milliseconds applied over a period of \(\leq 60\) seconds). The stimulus was discontinued when a positive response was observed before 60 seconds had elapsed. The MAC was determined as the mean of the lowest concentration that prevented a positive response and the highest concentration that allowed a positive response. A minimum of 3 determinations was performed for each horse, and the mean value was calculated on the basis of the gas analyzer calibration curves and adjusted to a sea level barometric pressure of 760 mm Hg. Following determination of the sevoflurane MAC in each horse, lidocaine \((0.7 \text{ mg/kg})\) was administered IV. A load-
ing dose (bolus) of 1.3 mg/kg administered over a 15-minute period was followed by a constant rate infusion at 50 µg/kg/min; this dose protocol was chosen because it has been found to improve gastrointestinal tract motility\textsuperscript{23} and hence is widely favored by equine clinicians. Because prior pharmacokinetic studies\textsuperscript{18,26} have revealed that steady-state lidocaine concentrations are reached within 30 minutes by use of this protocol, MAC determination for the combination of lidocaine and sevoflurane was started 30 minutes after lidocaine infusion was initiated; MAC determination was performed as previously described.

**Determination of plasma lidocaine concentrations**—Heparinized arterial blood samples (20 mL of blood/sample) were collected from the catheter placed in the transverse facial artery. Blood samples were collected after the lidocaine bolus, at 30-minute intervals during the lidocaine infusion, and at the conclusion of the infusion. Samples were centrifuged, and plasma was harvested and immediately frozen and stored at –70°C until analyzed. Plasma concentrations of lidocaine were measured by use of an HPLC system with mass spectral detection. The HPLC system consisted of a binary pump,\textsuperscript{6} vacuum degasser, thermostatted column compartment,\textsuperscript{6} and system autosampler.\textsuperscript{6} The HPLC column was a phenyl column (internal diameter, 4.6 X 50 mm; bead size, 5.0 µm)\textsuperscript{6} protected by a C18 cartridge (internal diameter, 4 X 2.0 mm),\textsuperscript{6} which was maintained at approximately 21°C. The mobile phase consisted of an aqueous component (solution A, 0.1% formic acid in water) and an organic component (solution B, acetonitrile). Each 4.0-minute assay consisted of the following linear gradient elution: 98% solution A and 2% solution B at 0 minutes, 2% solution A and 98% solution B at 2.5 minutes, 2% solution A and 98% solution B at 3.2 minutes, 98% solution A and 2% solution B at 3.5 minutes, and 98% solution A and 2% solution B at 4.0 minutes. The system operated at a flow rate of 1.5 mL/min.

Mass spectrometric detection was performed on a triple quadrupole instrument\textsuperscript{6} via multiple reaction monitoring. Ions were generated in positive ionization mode by use of an electrospray interface. Lidocaine compound-dependent settings were as follows: declustering potential, 33 V; entrance potential, 5 V; collision cell entrance potential, 11 V; collision energy, 28 V; and collision cell exit potential, 2.5 V. Trazodone (internal standard) compound-dependent settings were as follows: declustering potential, 56.86 V; entrance potential, 4.08 V; collision cell entrance potential, 20.56 V; collision energy, 32.75 V; and collision cell exit potential, 2.72 V. Source-dependent settings were as follows: nebulizer gas, 483 kPa; auxiliary (turbo) gas, 414 kPa; turbo gas temperature, 600°C; curtain gas, 345 kPa; collision-activated dissociation gas (nitrogen), 41 kPa; ionspray voltage, 5,500 V; and interface heater, 100°C. Peak areas ratios obtained from multiple reaction monitoring of lidocaine (mass-to-charge ratio, 235.3 → 86.2) and trazodone (mass-to-charge ratio, 372.2 → 176.1) were used for quantification.

Standard solutions of lidocaine and trazodone were prepared in acetonitrile. Lidocaine was extracted from plasma by adding 300 µL of 2% formic acid in acetonitrile to 100 µL of plasma, vortexing for 10 minutes, and centrifuging at 18,000 X g for 10 minutes. An aliquot of 50 µL of the resulting supernatant was injected into the liquid chromatography–mass spectrometry–mass spectrometry system for analysis.

**Measurement of physiologic variables**—Heart rate, MAP, body temperature, and end-tidal sevoflurane concentrations were monitored throughout the anesthetic period and recorded immediately before and after each electrical stimulation during MAC determination. The lowest and highest values obtained during each period of MAC determination (ie, sevoflurane MAC and lidocaine-sevoflurane MAC) were reported. Articul blood samples were collected and evaluated to determine pH, Pa\textsubscript{CO}\textsubscript{2} and Pa\textsubscript{O}\textsubscript{2} before sevoflurane and lidocaine-sevoflurane MAC determination.

**Evaluation of recovery from anesthesia**—At the end of the experimental period, lidocaine infusion was discontinued and sevoflurane concentration was increased to 1.2 times the MAC for that specific horse for 15 minutes; the horse was then moved to the recovery stall. All the monitoring equipment was removed, and the horse then was disconnected from the anesthesia machine and moved to a padded and darkened recovery stall. Horses were positioned in left lateral recumbency and received oxygen insufflation via the endotracheal tube until they moved. Horses were allowed to recover without assistance, but they were constantly observed. Time to first movement, time to first attempt at sternal recumbency, time to sternal recumbency, number of attempts to achieve sternal recumbency, time to first attempt to stand, time to standing, and the number of attempts to stand were recorded. Anesthetic recovery was also evaluated subjectively by 2 observers (THF and MLR) by use of a 5-point scale (5 = excellent [single coordinated effort to stand with minimal or no ataxia], 4 = very good [single attempt to stand, with some ataxia], 3 = good [quiet recovery with > 1 attempt to stand], 2 = fair [uncoordinated attempts to stand with or without minor injury, such as a superficial laceration], and 1 = poor [multiple, uncoordinated attempts to stand resulting in major or life-threatening injury, such as a fractured limb]). A similar scoring system has been described in greater detail elsewhere.\textsuperscript{37,38}

**Statistical analysis**—A paired t test was used to compare sevoflurane and lidocaine-sevoflurane MAC values and to compare the horses’ body temperatures at the times of MAC determination (sevoflurane vs lidocaine-sevoflurane). Plasma lidocaine concentrations were analyzed by use of a repeated-measures ANOVA. Values of P < 0.05 were considered significant. Data were reported as mean ± SD, except as indicated.

**Results**

Doses of injectable drugs used for induction of anesthesia were often insufficient to result in adequate anesthetic depth to allow the horses to be safely transported from the induction stall to the surgery room. Therefore, after endotracheal intubation was performed, most of the horses were connected to the an-
esthetically circle system and sevoflurane was administered until anesthetic depth was considered adequate for safe transport. One horse (an Arabian gelding) required additional doses of ketamine (1.4 mg/kg), diazepam (0.03 mg/kg), and xylazine (0.7 mg/kg) for induction and to allow endotracheal intubation. Time elapsed from induction of anesthesia to the first electrical stimulation for MAC determination ranged from 58 to 95 minutes (mean ± SD, 77 ± 13 minutes).

Sevoflurane MAC corrected to 1 atmosphere at sea level (barometric pressure of 760 mm Hg) in these 8 horses ranged from 2.21% to 2.95% (mean ± SD, 2.42 ± 0.24%). The IV administration of lidocaine caused a significant (P < 0.001) decrease in sevoflurane MAC (range, 1.55% to 2.40%; mean ± SD, 1.78 ± 0.38%), which represented a reduction for sevoflurane MAC that ranged from 6.3% to 44.6% (mean ± SD, 26.7 ± 12%).

Mean ± SD plasma lidocaine concentrations were 2.58 ± 0.811 ng/mL at the end of the lidocaine bolus; 2.065 ± 0.411 ng/mL, 2.243 ± 0.699 ng/mL, 2.168 ± 0.339 ng/mL, and 2.525 ± 0.215 ng/mL at 30, 60, 90, and 120 minutes respectively, and 2.206 ± 0.329 ng/mL at the end of the infusion. There were no significant differences in the plasma lidocaine concentrations at any time point.

Mean ± SD body temperature at the time of MAC determination for sevoflurane alone was 35.8 ± 0.4°C, whereas mean body temperature was 35.5 ± 0.8°C at the time of MAC determination for lidocaine-sevoflurane. However, these values did not differ significantly.

During the study period, mean ± SD PaCO₂ was maintained at 45.7 ± 3.2 mm Hg, mean pH was maintained at 7.4 ± 0.05, and mean PaO₂ was never < 300 mm Hg. Mean ± SD heart rate ranged from 37 ± 4 beats/min to 46 ± 2 beats/min during sevoflurane MAC determination and from 35 ± 6 beats/min to 40 ± 5 beats/min during lidocaine-sevoflurane MAC determination, whereas MAP ranged from 64 ± 5 mm Hg to 95 ± 12 mm Hg and from 78 ± 6 mm Hg to 96 ± 11 mm Hg for sevoflurane and lidocaine-sevoflurane, respectively.

Mean ± SD total anesthesia time (determined from the time of induction to the time a horse was disconnected from the anesthesia breathing circuit) was 376 ± 44 minutes. Horses were at 1.2X MAC for sevoflurane for each specific horse at the time of disconnection. All recoveries were considered acceptable. Mean ± SD values were calculated for time to first movement (10.5 ± 4.5 minutes), time to first attempt at sternal recumbency (16.8 ± 2.9 minutes), time to sternal recumbency (23.4 ± 8.7 minutes), number of attempts to achieve sternal recumbency (3.0 ± 3.0), time to first attempt to stand (28.4 ± 7.4 minutes), time to standing (46.1 ± 10.7 minutes), and number of attempts to stand (8.0 ± 11.0).

Recovery quality for all 8 horses was good (mean ± SD, 3.5 ± 1.0; median, 3.3). Only 1 horse (an Arabian gelding) had a fair recovery (score of 2); all other horses had a recovery quality of good or better (score of 3 or higher). The Arabian gelding also required a much higher number of attempts to stand (3+) compared with the number of attempts for the other horses in the study.

**Discussion**

Mean ± SD sevoflurane MAC for the horses in the study reported here was 2.42 ± 0.24%, which is similar to the values in other reports. Administration of a continuous rate infusion of lidocaine provided constant mean plasma lidocaine concentrations and decreased mean sevoflurane MAC to 1.78 ± 0.38% (a mean MAC reduction of 26.7 ± 12%). Similar results were reported in other studies in horses in which plasma lidocaine concentrations < 2 µg/mL promoted a maximum halothane MAC reduction of 20% and plasma lidocaine concentrations between 2.14 and 4.23 µg/mL significantly decreased the required isoflurane concentration by 25%. It is possible that higher plasma lidocaine concentrations would provide a greater reduction of sevoflurane MAC because a dose-dependent effect of lidocaine has been observed with use of halothane in horses and dogs and with use of isoflurane in cats. A reduction of halothane MAC up to 70% was described in ponies with plasma lidocaine concentrations ranging from 5 to 7 µg/mL, which are much higher than the plasma concentrations achieved in the present study. The lidocaine dose and rate used in the present study were chosen because the pharmacokinetics had been previously evaluated in sevoflurane-anesthetized horses and found to result in steady-state plasma concentrations after 30 minutes; in addition, this lidocaine dose is commonly used in equine practice.

When evaluating the MAC reduction values for each of the horses in the present study, it is important to mention the variability among horses. The MAC reduction varied from 6.3% to 44.6%. Although plasma lidocaine concentrations and body temperature variations in each horse could have contributed to differences in the MAC reduction, the degree of variation for those variables does not appear to be sufficient to justify the magnitude of the variability observed, which suggested individual variability was the most likely explanation.

Several factors, such as hypothermia (PaCO₂ > 90 mm Hg, PaO₂ < 40 mm Hg, MAP < 50 mm Hg, and drugs that cause CNS depression, can decrease MAC. Although the use of injectable drugs for sedation (xylocaine) and anesthetic induction (ketamine and diazepam) of the horses provided a more clinical perspective and a safer and presumably less stressful anesthetic induction for the horses, it added another factor that could have influenced MAC determination. To minimize any potential influence from the induction drugs, lower doses of these agents were used, which resulted (as expected) in an anesthetic depth adequate for immediate transport of the horses to the surgery room. As an alternative to administering additional induction drugs, most of the horses were intubated in the induction stall and connected to the anesthetic circuit and then sevoflurane was administered until it was considered safe to transport the horses. Additionally, MAC determination was not initiated until at least 1 hour after anesthetic induction, which allowed time for drug elimination and minimized the influence of the induction agents. Sevoflurane MAC was determined first; thus, by the time of the lidocaine-sevoflurane MAC determination, an even longer period had elapsed from the time of anesthetic induction, which would result...
in an even smaller influence of the induction drugs at the time of lidocaine-sevoflurane MAC determination, compared with the influence on sevoflurane MAC determination. Therefore, even though interference of the induction drugs on MAC cannot be fully negated, its effects (if any) would likely have decreased the amount of MAC reduction obtained with the use of lidocaine (ie, it is more likely that we underestimated the difference in sevoflurane MAC without and with lidocaine).

Adequate ventilation, oxygenation, and MAP were successfully maintained; however, body temperature of the horses decreased to approximately 35.5°C despite the use of blankets, forced-air heat, and heat lamps. This decrease in body temperature could have influenced the absolute sevoflurane MAC obtained in this study. Hypothermia can decrease anesthetic requirement in a linear manner such that for each 1°C decrease in body temperature, MAC decreases by approximately 5% to 10%.33–35 Considering the baseline temperature in the awake horses was approximately 37°C, there was a mean decrease in body temperature of 2°C, which would represent an MAC reduction of approximately 10% to 20%. However, the mean MAC value obtained for sevoflurane alone (2.42%) was extremely close to the values reported for horses in other studies1,12,19,130 (2.31% and 2.84%), which indicates that if there were any influence of temperature on the values obtained, it was of minimal importance. More importantly, body temperature of the horses did not differ significantly between sevoflurane MAC and lidocaine-sevoflurane MAC determinations, which indicated that any influence of body temperature on the degree of MAC reduction obtained with lidocaine in the present study was minimized.

Continuous infusion of lidocaine has been reported to have a negative effect on the recovery quality of horses anesthetized with sevoflurane or isoflurane, and discontinuation of the infusion 30 minutes before the end of anesthesia has been recommended to decrease ataxia during the recovery period.19 In the present study, lidocaine infusion was discontinued approximately 15 minutes before the end of anesthesia but anesthetic recoveries were still considered satisfactory, with a mean ± SD quality score of 3.5 ± 1.0.

Administration of a continuous infusion of lidocaine, at the dose and rates used in the study reported here, decreased mean ± SD sevoflurane MAC by 26.7 ± 12% and could be a useful adjunct to provide a more balanced anesthetic technique in horses because it may allow lower concentrations of sevoflurane to be used. Although the cardiovascular variables monitored during the study remained within reference limits, a detailed cardiovascular study on the effects of IV infusion of lidocaine during sevoflurane-induced anesthesia is required to determine whether the reduction in sevoflurane concentrations observed in the present study will translate into improved cardiovascular performance before this anesthetic combination can be recommended for clinical use.

References


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