Effects of lidocaine administration via continuous rate infusion on the minimum alveolar concentration of isoflurane in New Zealand White rabbits (Oryctolagus cuniculus)

Rodney W. Schnellbacher, DVM; James W. Carpenter, MS, DVM; Diane E. Mason, DVM, PhD; Butch KuKanich, DVM, PhD; Hugues Beaufrère, DrMedVet, PhD; Courtney Boysen, DVM

Objective—To evaluate the effect of a continuous rate infusion (CRI) of lidocaine on the minimum alveolar concentration (MAC) of isoflurane in rabbits.

Animals—Five 12-month-old female New Zealand White rabbits (Oryctolagus cuniculus).

Procedures—Rabbits were anesthetized with isoflurane. Baseline isoflurane MAC was determined by use of the tail clamp technique. A loading dose of lidocaine (2.0 mg/kg, IV) was administered followed by a CRI of lidocaine at 50 µg/kg/min. After 30 minutes, isoflurane MAC was determined. Another loading dose was administered, and the lidocaine CRI then was increased to 100 µg/kg/min. After 30 minutes, isoflurane MAC was determined again. Plasma samples were obtained for lidocaine analysis after each MAC determination.

Results—Baseline isoflurane MAC was 2.09%, which was similar to previously reported values in this species. Lidocaine CRI at 50 and 100 µg/kg/min induced significant reductions in MAC. The 50 µg/kg/min CRI resulted in a mean plasma lidocaine concentration of 0.654 µg/mL and reduction of MAC by 10.5%. The 100 µg/kg/min CRI of lidocaine resulted in a mean plasma concentration of 1.578 µg/mL and reduction of MAC by 21.7%. Lidocaine also induced significant decreases in arterial blood pressure and heart rate. All cardiopulmonary variables were within reference ranges for rabbits anesthetized with inhalation anesthetics. No adverse effects were detected; all rabbits had an uncomplicated recovery from anesthesia.

Conclusions and Clinical Relevance—Lidocaine administered as a CRI at 50 and 100 µg/kg/min decreased isoflurane MAC in rabbits. The IV administration of lidocaine may be a useful adjunct in anesthesia of rabbits. (Am J Vet Res 2013;74:1377–1384)
in response to a noxious stimulus. This technique can also be used to measure the potency of a volatile inhalation anesthetic and to compare the analgesic or sedative effects of various drugs on anesthetic requirements.3,11 Few studies have been conducted to investigate the MAC-sparing effects of analgesics in rabbits. Investigators in 1 study12 found that discontinuation of diclofenac and ketoprofen leads to an increase in the MAC of halothane. In another study,13 investigators found that the administration of butorphanol (alone or in combination with meloxicam) significantly reduced the MAC of isoflurane by 7.6% and 12.4%, respectively. A study14 conducted to investigate the effects of IV administration of tramadol in rabbits revealed a reduction in the MAC of isoflurane by 9%.

Lidocaine contributes to multimodal analgesia, in part, by blocking sodium channels in sensory nerve fibers, thereby inhibiting the activity, amplitude, and conduction of electrical impulses.15 These effects are dose dependent and occur rapidly in the fibers responsible for transmitting pain sensations (ie, unmyelinated C nerve fibers and the small, thinly myelinated A-δ fibers).16,17 Lidocaine also causes suppression of spinal cord sensitization and inhibition of spinal visceromotor neurons.18,19 It also has substantial anti-inflammatory and free-radical scavenging properties that may reduce postoperative pain and have a direct excitatory effect on intestinal smooth muscles, which are thought to be the result of inhibition of the myenteric plexus.20 Systemic administration of lidocaine has been used in both human and veterinary medicine to reduce the requirements of volatile inhalation agents, reduce intraoperative and postoperative pain, promote gastrointestinal tract motility, and reduce the release of endotoxin and inflammatory mediators.20–22

Studies in equids,4 rodents,5 humans,6,7 dogs,8,9 cats,9 and small ruminants10 have revealed that IV administration of lidocaine significantly reduces the MAC of inhalation anesthetics. To the authors’ knowledge, the analgesic or MAC-sparing effects of lidocaine in rabbits have not been reported. The purpose of the study reported here was to evaluate the effects of a CRI of lidocaine on isoflurane MAC in rabbits. Specifically, we hypothesized that administration of lidocaine would decrease isoflurane MAC in rabbits.

Materials and Methods

Animals—Five female New Zealand White rabbits (Oryctolagus cuniculus) were included in the study. Rabbits were 12 months old and weighed between 4.0 and 4.7 kg. Rabbits were considered healthy on the basis of medical histories, results of physical examinations, evaluation of behavior, and assessment of serum total protein concentrations and Hct values. Rabbits were housed separately in pens in a temperature-controlled environment (20°C) with regulated lighting (12 hours of light and 12 hours of darkness). All were fed a diet consisting of timothy hay2 and pellets8 daily and were given water ad libitum. The protocol for the study was approved by the Kansas State University Institutional Animal Care and Use Committee.

Experimental procedures—Anesthesia was induced with 5% isoflurane in oxygen (2 L/min) adminis-
tion of sterile saline (0.9% NaCl) solution to a final concentration of 2 mg/mL and administered through one of the ports of the catheter. The lidocaine CRI was administered for a period of 30 minutes to achieve a steady-state plasma concentration. Once the steady state was reached, the previously described bracketing technique for MAC determination was performed. The CRI was continued throughout the MAC determination. The started at 0.67 MAC of lidocaine (40% was determined for each rabbit in duplicate. Once the MAC was determined, a blood sample (4 mL) was collected from the lateral saphenous vein. Plasma was harvested and stored at −70°C until used for analysis.

Each rabbit then received another lidocaine bolus (2 mg/kg, IV), which was administered over a 5-minute period, followed by a CRI of lidocaine (100 µg/kg/min). Thirty minutes after onset of the lidocaine CRI, the same bracketing procedure was performed in duplicate to determine the isoflurane MAC for a CRI of 100 µg of lidocaine/kg/min. The CRI was continued throughout the MAC determination. After the isoflurane MAC for a CRI of 100 µg of lidocaine/kg/min was established, a blood sample (4 mL) was collected from the lateral saphenous vein. Plasma was harvested and stored at −70°C until used for analysis.

Rabbits were allowed to recover from anesthesia. Interval from termination of isoflurane administration until extubation was recorded for each rabbit.

**Measurement of plasma concentrations of lidocaine**—Plasma lidocaine concentrations were determined by use of liquid chromatography with triple quadrupole mass spectrometry. Plasma samples and standards (0.1 mL) were treated with 0.4 mL of methanol that contained mepivacaine (250 ng/mL) as the internal standard. The qualifying ion for lidocaine had an m/z of 235, whereas the qualifying ion had an m/z of 86. The qualifying ion for the internal standard had an m/z of 247, whereas the qualifying ion had an m/z of 98. The mobile phase consisted of acetonitrile and 0.1% formic acid with a phenyl column (150 × 3 mm; 5µM) used to achieve separation. The mobile phase gradient started at 90% acetonitrile and with a linear gradient to the formic acid at 4 minutes, followed by a linear gradient to 90% formic acid at 5 minutes (total run time, 6.5 minutes). Mean ± SD accuracy of the assay was 95 ± 9%, which was determined on triplicate replicates for each of 3 concentrations (0.25, 1, and 2.5 µg/mL).

**Statistical analysis**—Longitudinal data analysis was performed with linear mixed modeling on the various outcome variables with time, treatment (baseline, lidocaine at 50 µg/kg/min, and lidocaine at 100 µg/kg/min), the time-by-treatment interaction, and ETiso (except when ETiso was the response) as fixed effects and subjects as a random effect. Residual plots were used to assess linearity, homogeneity of variances, normality, and outliers. Shapiro-Wilk tests and quantile plots were performed on the residuals of the treatment groups. Autocorrelation of the residuals over time was assessed with the autocorrelation function method. Regression models assumed that residuals were not correlated but that a significant and important autocorrelation of the residuals over time was evident (first-order autocorrelation, 0.86). This resulted from the procedure used, whereby modification of isoflurane concentration was based on isoflurane concentrations 5 minutes preceding a time point. Manipulation of the covariance matrix by use of a serial correlation structure was unsuccessful in addressing this autocorrelation. Adding the first-order lag for isoflurane concentration (isoflurane concentration 5 minutes preceding a time point) as a predictor in the model successfully removed autocorrelation, significantly improved fit, and allowed other model assumptions to be validated. Competing models were compared with standardized residuals plots and the Akaike information criterion. Differences between the 2 concentrations of lidocaine CRI were assessed with preplanned comparisons by contrast statements. A value of α = 0.05 was used to determine significance.

**Results**

Time did not significantly affect isoflurane concentrations, which depended mainly on the preceding concentrations in accordance with the experimental design. However, there was a significant treatment effect, with both treatments reducing the MAC. Doubling the concentration of the lidocaine CRI resulted in a doubling

### Table 1—Reduction in isoflurane MAC after administration of a bolus of lidocaine (2 mg/kg, IV) followed by a lidocaine CRI in 5 New Zealand White rabbits (Oryctolagus cuniculus).

<table>
<thead>
<tr>
<th>Variable</th>
<th>MAC</th>
<th>95% CI</th>
<th>MAC reduction (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline isoflurane MAC</td>
<td>2.0</td>
<td>1.9–2.1</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Isoflurane MAC with lidocaine</td>
<td>1.8</td>
<td>1.7–1.9</td>
<td>10.4</td>
<td>0.003</td>
</tr>
<tr>
<td>CRI at 50 µg/kg/min</td>
<td>1.6</td>
<td>1.5–1.6</td>
<td>21.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Isoflurane MAC with lidocaine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRI at 100 µg/kg/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI = Confidence interval. NA = Not applicable.

### Table 2—Estimates for a mixed linear model of isoflurane concentration used in 5 New Zealand White rabbits to determine the isoflurane MAC after bolus administration of lidocaine (2.0 mg/kg, IV) followed by CRI of lidocaine at 50 and 100 µg/kg/min.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>95% CI</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.27</td>
<td>0.17 to 0.37</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>First order lag of isoflurane</td>
<td>0.86</td>
<td>0.82 to 0.91</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Lidocaine CRI at 50 µg/kg/min</td>
<td>−0.03</td>
<td>−0.05 to 0.01</td>
<td>0.003</td>
</tr>
<tr>
<td>Lidocaine CRI at 100 µg/kg/min</td>
<td>−0.06</td>
<td>−0.09 to 0.03</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SD attributed to rabbits</td>
<td>0.016</td>
<td>0.006 to 0.042</td>
<td>0.015</td>
</tr>
<tr>
<td>Residual SD</td>
<td>0.000</td>
<td>0.006 to 0.064</td>
<td>NA</td>
</tr>
</tbody>
</table>

CRI = Conventional interval. NA = Not applicable.

*See Table 1 for key.*
of the effect on MAC reduction (Table 1). There was a significant \((P = 0.005)\) difference in the magnitude of MAC reduction between the 2 CRIs. Because isoflurane concentration was a function of preceding concentrations (it was changed on the basis of the response to the concentration 5 minutes preceding a time point), the MAC was obtained by the following equation: \[ \text{Isoflurane MAC} = \beta_0 + (\beta_1 \times \text{Iso5}) + (\beta_2 \times \text{lidocaine50}) + (\beta_3 \times \text{lidocaine100}), \] where \(\beta_0\) is the intercept, \(\beta_1–3\) are the parameter estimates \((\text{constant})\) for the model variables, Iso5 is the isoflurane concentration 5 minutes prior to the current time point, and lidocaine50 and lidocaine100 are dummy variables \((0,1)\) indicating the CRI treatment evaluated. This corresponded to a stabilization of the isoflurane concentration and meant that there was no increase or decrease in the isoflurane concentration because the MAC was reached. Parameter estimates were determined for the final model (Table 2).

Isoflurane significantly decreased arterial blood pressure (Table 3). There was a mild positive effect of time on the arterial blood pressure, except for the DAP. When controlling for the isoflurane concentration and time, lidocaine CRI induced a significant decrease in indirect arterial blood pressure (Figure 1). This decrease was not significantly different between the 50 and 100 \(\mu\)g/kg/min CRIs for the MAP \((P = 0.30)\) and SAP \((P = 0.89)\) but was for the DAP \((P = 0.007)\). Lidocaine CRI significantly \((P = 0.005)\) decreased the heart rate, with the 50 \(\mu\)g/kg/min CRI inducing the greatest effects (Figure 2). The heart rate also significantly decreased with time but significantly increased at higher isoflurane concentrations.

Lidocaine CRI significantly \((P < 0.001)\) increased \(\text{PETCO}_2\); this effect was greatest for the 100 \(\mu\)g/kg/min CRI. Finally, there was a significant \((P < 0.001)\) increase in \(\text{SpO}_2\) during lidocaine CRIs; this effect also was greatest for the 100 \(\mu\)g/kg/min CRI. Both \(\text{PETCO}_2\) and \(\text{SpO}_2\) increased significantly with time but not with increases in isoflurane concentration.

The random effect of rabbit was also significant for all models. This reflected interindividual variability.

### Table 3—Percentage decrease of each variable attributable to various factors in 5 New Zealand White rabbits used to determine the isoflurane MAC after bolus administration of lidocaine (2.0 mg/kg, IV) followed by CRI of lidocaine at 50 and 100 \(\mu\)g/kg/min.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time (h)</th>
<th>Isoflurane (%)</th>
<th>Lidocaine CRI at 50 (\mu)g/kg/min</th>
<th>Lidocaine CRI at 100 (\mu)g/kg/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>–1.4*</td>
<td>17.4†</td>
<td>6.8T</td>
<td>8.9T</td>
</tr>
<tr>
<td>SAP (mm Hg)</td>
<td>–2.1*</td>
<td>11.8†</td>
<td>5.8T</td>
<td>6.5T</td>
</tr>
<tr>
<td>DAP (mm Hg)</td>
<td>2.6†</td>
<td>25.5†</td>
<td>8.2T</td>
<td>12.6T</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>NA</td>
<td>–12.5†</td>
<td>9.0T</td>
<td>6.2†</td>
</tr>
<tr>
<td>PtnO2 (mm Hg)</td>
<td>–1.9*</td>
<td>NA</td>
<td>–3.8†</td>
<td>–8.3†</td>
</tr>
<tr>
<td>SpO2 (%)</td>
<td>–0.5†</td>
<td>NA</td>
<td>–1.5†</td>
<td>–2.2†</td>
</tr>
</tbody>
</table>

A negative value represents an increase in the value for a variable and a positive value represents a decrease in the value for a variable.

*†Effect is significant (*\(P < 0.05\); †\(P = 0.01\)).

![Figure 1](image-url) - Least squares mean ± SEM SAP (A), MAP (B), and DAP (C) in 5 New Zealand White rabbits (Oryctolagus cuniculus) after anesthesia with isoflurane (2%) for 30 minutes (baseline; circles) and during isoflurane-induced anesthesia 30 minutes after administration of a bolus of lidocaine (2 mg/kg, IV) followed by a lidocaine CRI at 50 \(\mu\)g/kg/min (squares) and 100 \(\mu\)g/kg/min (triangles).
The mean ± SD total anesthetic time was 7 hours and 14 minutes ± 2 hours and 13 minutes. Mean interval from end of isoflurane administration until extubation was 14 ± 3 minutes. All rabbits recovered from the procedures without complications. Most rabbits were observed eating 1 hour after extubation.

Discussion

The gas-sparing effects of IV administration of lidocaine have been established. Decreases in MAC differ depending on the study design, dose of lidocaine, and species of animal. Studies on the use of lidocaine in rabbits are lacking. In rodents, lidocaine reduces the MAC requirement of cyclopropane by approximately 40%. In cats, lidocaine at plasma concentrations of 3 µg/mL decreased isoflurane requirements by 7% to 28% and at 11 µg/mL reduced the MAC by as much as 59%. In a study, a loading dose of 2 mg/kg followed by CRI of 50 µg/kg/min resulted in a lidocaine plasma concentration of approximately 1.5 µg/mL and reduced the MAC of isoflurane by 18.7%. In that same study, administration of a loading dose of 2 mg/kg followed by CRI of 200 µg/kg/min resulted in a plasma concentration of approximately 4.5 µg/mL and decreased the MAC by 43.3%. In goats, a loading dose of 2.5 mg/kg and CRI of 100 µg/kg/min caused a reduction of 19% in the MAC of isoflurane. In human patients anesthetized with nitrous oxide and halothane, IV administration of lidocaine reduced MAC requirements by 10% to 28%.

The administration of lidocaine in the present study and the subsequent plasma concentrations correlated well with the reduction of isoflurane MAC. A loading dose of 2 mg/kg followed by CRI at 50 µg/kg/min resulted in a mean plasma lidocaine concentration of 0.654 µg/mL and reduction of MAC by 10.5%. A loading dose of 2 mg/kg followed by CRI at 100 µg/kg/min resulted in a mean plasma concentration of 1.578 µg/mL and reduction of isoflurane MAC by 21.7%. A comparison of the percentage reduction initially yielded the impression that rabbits were less responsive than other species to the effects of lidocaine; however, examination of plasma concentrations of lidocaine in relation to the MAC reduction revealed that rabbits responded in a similar manner. Analysis of lidocaine doses versus plasma concentrations suggested that rabbits might need to be administered a higher dose to achieve desired effects. The steady-state plasma concentrations achieved with a given dose are inversely proportional to the plasma clearance because as the clearance increases, the plasma concentration will decrease for a given dose. A lidocaine CRI at 50 µg/kg/min to isoflurane-anesthetized horses resulted in a median concentration of approximately 3.0 to 4.0 µg/mL. In another study in halothane-anesthetized horses, a lidocaine CRI at 100 µg/kg/min resulted in plasma concentrations between 3.0 and 7.0 mg/dL, which is a 2- to 4-fold increase in plasma concentrations. Therefore, analysis of these results suggested that rabbits in the present study had a faster plasma clearance than values reported for other species.

The analgesic properties of lidocaine must be considered when comparing results for the present study with results of other lidocaine studies. It has been suggested that lidocaine provides a multimodal analgesic response to acute pain. Lidocaine can suppress spinal cord sensitization and inhibit spinal visceral-motor neurons through blockage of sodium ion channels. Lidocaine also depresses activity, amplitude, and conduction in myelinated A-δ and unmyelinated C nerve fibers that are responsible for transmitting pain sensations.

It currently is unclear whether the dose-dependent reduction of the isoflurane MAC was associated with an analgesic or sedative effect of lidocaine. Regardless of the mechanism, there is considerable evidence of the efficacy of lidocaine infusion to provide analgesia in a number of species and situations. In rodents, IV administration of lidocaine selectively blocks polysynaptic activity of central C fibers associated with stimulation of the sural nerve. In humans, lidocaine decreases the sympathetic pain response to surgery. Analogic effects of lidocaine in humans with neuropathic pain have been established, with patients reporting a significant decrease in pain scores at plasma lidocaine concentrations ≥ 1.5 µg/mL. Preoperative or intraoperative administration of lidocaine also reduces postoperative analgesic requirements. Investigators in a study reported a decrease of 90% in postoperative pain in patients who received IV administration of lidocaine during surgery. A study involving horses undergoing castration revealed that IV administration of a lidocaine CRI at 100 µg/kg/min decreased arousal and pain response measured with electroencephalogram analysis.

The analgesic and sedative effects of lidocaine have also been described for conscious humans, rats, horses, dogs, and sheep. In a controlled study of men undergoing prostatectomy, lidocaine administered IV during and after surgery decreased the incidence of pain, hastened the return of intestinal motility, and shortened the duration of a hospital stay. In equids, lidocaine is commonly administered IV after colic surgery. Studies in horses suggest that lidocaine short-
ens the duration and severity of postoperative ileus and gastrointestinal pain and improves survival times. Lidocaine plasma concentrations of 1.0 µg/mL in conscious horses provide somatic analgesia; however, plasma concentrations between 1.85 and 4.50 µg/mL can cause adverse effects such as sedation, collapse, and seizures. These effects are postulated to be attributable to a combination of direct excitatory effects on intestinal smooth muscle, blockade of inhibitory spinal and peritoneal sympathetic reflexes, inhibition of central hyperalgesia, and anti-inflammatory and antieンドotoxic actions. It is possible that systemic administration of lidocaine provides species-specific effects that may differ in accordance with the nature of the pain. We are not aware of any studies performed to determine these effects in conscious rabbits.

The baseline isoflurane MAC of 2.09% in the present study is similar to other values of isoflurane MAC reported for New Zealand White rabbits in which the tail clamp technique was used as the noxious stimulus for MAC determination. Another study involving New Zealand White rabbits in which a digit-clamp technique was used revealed MAC values of 2.08% and 2.49%. The MAC of an inhalation anesthetic can differ substantially among animals of the same species and even among strains of the same species. Interindividual and intra-individual variations in MAC are typically reported to be <20% and 10%, respectively.

A study conducted to compare the relationship of various noxious stimuli on isoflurane MAC in rabbits and dogs found that there were no significant differences between an electrical stimulus and a clamping technique but that there was a significant underestimation of MAC when comparing these noxious stimuli to surgical stimuli to the skin. In another study, investigators found that mechanical and electrical stimuli result in similar effects on the reduction of halothane MAC. In the present study, use of the tail clamp technique as the noxious stimulus resulted in isoflurane MAC values at baseline and after lidocaine administration that are comparable to the values determined in other studies.

In the present study, there was no ceiling effect in the reduction of MAC over the range of plasma lidocaine concentrations. Isoflurane MAC decreased linearly as a function of the plasma lidocaine concentration. The plasma lidocaine concentration approximately doubled from 0.654 to 1.578 µg/mL; concurrently, there was a reduction of isoflurane MAC from 10.4% to 21.7%. It is unclear if further increases in lidocaine doses and subsequent plasma concentrations would have continued to induce a decrease in the MAC. In dogs, a ceiling effect on halothane MAC was observed at lidocaine concentrations >1.16 µg/mL. Additional studies must be performed to determine whether there is a similar plateau effect for lidocaine.

The pharmacodynamic characteristics of lidocaine administered IV have not been evaluated in rabbits, and the dose used in the present study was chosen on the basis of doses of lidocaine that appear to be safe for use in anesthetized dogs. We elected to start with the low-dose lidocaine CRI followed by the high-dose CRI, rather than to randomize the treatments. Lidocaine administered as a single bolus dose is rapidly redistrib-
results provide evidence that a multimodal approach, such as one that involves the IV administration of lidocaine, should be implemented during anesthesia to reduce the concentration of inhalation anesthetics to improve blood pressure.

Direct measurement of blood pressure is the criterion-referenced standard. Thus, one of the limitations of the study reported here is that blood pressure was measured via indirect techniques. Studies performed in rabbits to compare different methods of measuring blood pressure indicated positive agreement between both indirect and direct measurement of blood pressure, which supports the validity of the use of indirect blood pressure in the present study.

To obtain the most accurate and comparable $PETCO_2$ and $ETISO_2$, gas samples were collected from a catheter located 5 mm distal to the end of the endotracheal tube. This allowed collection of gas samples that were most consistent with alveolar gases. Comparison of results for the present study with comparable values for baseline MAC, MAC after a lidocaine CRI at 50 µg/kg/min, and MAC after a lidocaine CRI at 100 µg/kg/min in other studies performed in species revealed that the end-tidal gas values in the study reported here were as expected.

During the IV administration of lidocaine, there was a significant and dose-dependent increase in $SpO_2$ and $PETCO_2$. Both $SpO_2$ and $PETCO_2$ increased significantly with time but not with increases in isoflurane concentrations. Readers should be cautious not to overinterpret these effects of systemic administration of lidocaine on ventilatory variables. It is important not to confuse significant differences detected via statistical analysis with clinical relevance. A 2.2% change in $SpO_2$, a variable measured on a 100-point scale, is likely of little clinical importance because the values for $SpO_2$ remained within clinically acceptable limits throughout the anesthetic period. Changes in $PETCO_2$ during lidocaine administration represented an 8.3% increase during administration of the 100 µg/kg/min CRI. However, hyperventilation was not detected in any of the rabbits in the present study, and $PETCO_2$ values did not deviate from mammalian reference ranges. Small changes in pulmonary vascular resistance or cardiac output as a result of lidocaine administration or alterations in isoflurane concentrations over time may have induced increased delivery of $CO_2$ to the lungs or improved the dead space-to-tidal volume ratio during ventilation to cause subtle but significant changes in $SpO_2$ and $PETCO_2$ as a result of the infusions. Because cardiac output and vascular resistances were not measured or calculated, the effects that systemic administration of lidocaine may have had in this study are unknown.

Another limitation of the present study was the design. Because of logistics, time, and expense, this study consisted of a crossover experiment whereby both drugs were administered during the same anesthetic event. The order in which the drugs were administered was not randomized; instead, the 50 µg/kg/min CRI was administered first, which was then followed by the 100 µg/kg/min CRI. Despite the lack of a prolonged washout period between CRIs, we believe the results are reliable because lidocaine has a fairly short half-life. Furthermore, each CRI was preceded by administration of a bolus of lidocaine (2 mg/kg) and followed by a 30-minute period to ensure plasma drug concentrations reached a steady state. Additionally, plasma drug concentrations correlated well between infusion rate and MAC.

To our knowledge, the study reported here is the first in which investigators have determined the gas-sparing effects of IV administration of lidocaine on isoflurane MAC in rabbits. Whether this reduction was attributable to the analgesic or sedative effects of lidocaine is unclear. However, the analgesic effects must be considered when comparing the properties of lidocaine in other species. Systemic administration of lidocaine has been used in human and veterinary medicine to reduce the requirements of inhalation anesthetics, reduce preoperative and postoperative pain, promote gastrointestinal motility, and reduce the release of endotoxin and inflammatory mediators. Administration of a lidocaine CRI at the doses and rates described for the present study may be a useful adjunct to provide a balanced anesthetic technique (ie, multimodal analgesia) in rabbits. Further studies to assess the effects of lidocaine on anesthesia with isoflurane in clinical patients are needed.

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