Effect of ketamine on the minimum infusion rate of propofol needed to prevent motor movement in dogs

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OBJECTIVE
To determine the minimum infusion rate (MIR) of propofol required to prevent movement in response to a noxious stimulus in dogs anesthetized with propofol alone or propofol in combination with a constant rate infusion (CRI) of ketamine.

ANIMALS
6 male Beagles.

PROCEDURES
Dogs were anesthetized on 3 occasions, at weekly intervals, with propofol alone (loading dose, 6 mg/kg; initial CRI, 0.45 mg/kg/min), propofol (loading dose, 5 mg/kg; initial CRI, 0.35 mg/kg/min) and a low dose of ketamine (loading dose, 2 mg/kg; CRI, 0.025 mg/kg/min), or propofol (loading dose, 4 mg/kg; initial CRI, 0.3 mg/kg/min) and a high dose of ketamine (loading dose, 3 mg/kg; CRI, 0.05 mg/kg/min). After 60 minutes, the propofol MIR required to prevent movement in response to a noxious electrical stimulus was determined in duplicate.

RESULTS
Least squares mean ± SEM propofol MIRs required to prevent movement in response to the noxious stimulus were 0.76 ± 0.1 mg/kg/min, 0.60 ± 0.1 mg/kg/min, and 0.41 ± 0.1 mg/kg/min when dogs were anesthetized with propofol alone, propofol and low-dose ketamine, and propofol and high-dose ketamine, respectively. There were significant decreases in the propofol MIR required to prevent movement in response to the noxious stimulus when dogs were anesthetized with propofol and low-dose ketamine (27 ± 10%) or with propofol and high-dose ketamine (30 ± 10%).

CONCLUSIONS AND CLINICAL RELEVANCE
Ketamine, at the doses studied, significantly decreased the propofol MIR required to prevent movement in response to a noxious stimulus in dogs. (Am J Vet Res 2015;76:1022–1030)
context-sensitive pharmacokinetics can increase recovery times as a result of accumulation of propofol in the tissues, especially after prolonged infusion.\textsuperscript{7} Additionally, propofol lacks substantial antinociceptive properties.\textsuperscript{8} Total IV anesthesia is less commonly used in small animals, perhaps in part because controlled infusion devices are not commercially available for animals. Nevertheless, the propofol MIR in various domestic animals has been investigated.\textsuperscript{9-12}

In human patients undergoing anesthesia with propofol, adjunctive use of ketamine has been recommended because of its analgesic properties and to improve hemodynamic stability.\textsuperscript{13} When ketamine was administered to dogs in combination with propofol, there was an increase in heart rate and MAP in comparison to values recorded when propofol was administered alone.\textsuperscript{14} and a CRI of ketamine reportedly decreased the propofol MIR in cats\textsuperscript{15} and ponies.\textsuperscript{16} Therefore, we suspected that ketamine would decrease the propofol MIR in dogs as well.

The purpose of the study reported here was to determine the propofol MIRNM in unpremedicated dogs anesthetized with propofol alone or with propofol in combination with a CRI of ketamine. We hypothesized that ketamine would decrease the propofol MIRNM in a dose-dependent manner.

**Materials and Methods**

**Animals**

The study protocol was approved by the University of Tennessee’s Institutional Animal Care and Use Committee (protocol No. 2223). Six healthy adult male Beagles weighing 11 to 13 kg were used in the study. Food, but not water, was withheld for 12 hours prior to anesthesia. Each dog was studied on 3 occasions in a randomized crossover design.

**Experimental protocol**

Hair over the right cephalic vein was clipped 1 hour prior to each anesthetic episode, a lidocaine 2.5% and prilocaine 2.5% cream\textsuperscript{a} was applied to the skin over the area of anticipated catheter placement, and the limb was wrapped for a minimum of 40 minutes prior to catheter placement. A 20-gauge, 1-inch catheter\textsuperscript{b} was then placed in the right cephalic vein for administration of anesthetic drugs and balanced electrolyte solution.\textsuperscript{b}

Anesthesia was induced with a loading dose of propofol alone or with a loading dose of propofol and ketamine as a single bolus administered manually at a constant rate for 60 seconds. A CRI of propofol or propofol and ketamine was initiated immediately after induction of anesthesia with a syringe pump.\textsuperscript{c} The balanced electrolyte solution was administered at a rate of 3 mL/kg/h. Dogs were tracheally intubated and positioned in right lateral recumbency. Oxygen was delivered (2 L/min) with a small animal anesthesia machine\textsuperscript{e} with a circle breathing system. Dogs were allowed to breathe spontaneously; however, mechanical ventilation was instituted if the PET\textsubscript{CO2} reached 60 mm Hg. The PET\textsubscript{CO2} was monitored continuously with an infrared gas analyzer.\textsuperscript{f} Airway samples were collected at the proximal end of the endotracheal tube at a rate of 150 mL/min. The gas analyzer was calibrated according to the manufacturer’s instructions at the start of each anesthetic episode.

An 18-gauge, 1.5-inch catheter\textsuperscript{b} was placed in the left jugular vein to collect blood for measurement of ketamine and propofol concentrations. Body temperature was monitored with an esophageal probe,\textsuperscript{g} and a circulating warm water blanket\textsuperscript{h} was used to maintain body temperature between 37.5° and 38.5°C. Heart rate and an ECG were monitored continuously.\textsuperscript{i,j} Blood pressure was monitored indirectly\textsuperscript{j} with an oscillometric technique and an appropriately sized cuff (ie, a cuff with a width approx 40% of the circumference of the limb) placed over the right dorsal pedal artery. A dobutamine\textsuperscript{i} infusion was planned if MAP decreased to < 60 mm Hg. The urinary bladder was expressed intermittently as needed to prevent overdistension.

Dogs were anesthetized on 3 occasions with propofol\textsuperscript{i} alone (loading dose, 6 mg/kg; initial CRI, 0.45 mg/kg/min), propofol (loading dose, 5 mg/kg; initial CRI, 0.35 mg/kg/min) and a low dose of ketamine\textsuperscript{b} (loading dose, 2 mg/kg; CRI, 0.025 mg/kg/min), or propofol (loading dose, 4 mg/kg; initial CRI, 0.3 mg/kg/min) and a high dose of ketamine (loading dose, 3 mg/kg; CRI, 0.05 mg/kg/min). A bolus of propofol (2 mg/kg) was given if the loading dose and initial CRI were insufficient to prevent spontaneous movement in the first 60 minutes after anesthetic induction. Anesthetic treatments were performed in random order in individual dogs, with a minimum washout period of 7 days between anesthetic episodes.

Determination of MIRNM was initiated 60 minutes after the propofol and ketamine CRIs were started. A noxious electrical stimulus (50 V and 50 Hz for 10 milliseconds) was delivered via two 25-gauge needle electrodes that were placed SC and 5 cm apart on the lateral aspect of the left ulna. Two single stimuli of 1 second in duration were delivered initially, followed by 2 continuous stimuli of 5 seconds’ duration, with a 5-second interval between stimuli.\textsuperscript{17} Withdrawal or twitching of the nonstimulated limbs, movement of the head, chewing, licking, or swallowing was considered a positive response. Movement of the stimulated limb was not considered a positive response. If there was a response, the propofol infusion rate was increased by 0.025 mg/kg/min; conversely, if there was no response, the propofol infusion rate was decreased by 0.025 mg/kg/min. A 15-minute equilibration time was allowed after each change in infusion rate before the next stimulus was applied.

For the purpose of this study, the MIRNM was considered to be the MIR that abolished all motor movements (purposeful and nonpurposeful) in response to the noxious stimulus. The MIRNM was determined in duplicate and the mean calculated for each dog. Time from intubation to completion of MIRNM determina-
tion was recorded. At the end of each experiment, the propofol and ketamine infusions were stopped and the dogs were allowed to recover. Time from the end of drug infusion to extubation and time from the end of drug infusion to when dogs could walk unaided were recorded. Dogs were continuously observed throughout the recovery period.

Blood samples were collected for measurement of plasma propofol, ketamine, and norketamine concentrations immediately after the first and second MIRNM determinations, at the time of extubation, and when dogs could walk unaided. On each occasion, 6 mL of blood was collected from the left jugular vein and placed in a tube containing lithium heparin; tubes were stored on ice prior to centrifugation. Blood samples were centrifuged, and the plasma was removed. Samples taken at the time of the first and second MIRNM determinations were combined, in equal volumes, for analysis. Plasma samples were then stored at -80°C until determination of drug concentrations and analyzed within 4 weeks after collection.

Drug analysis

Plasma ketamine and norketamine concentrations were measured by means of high-performance liquid chromatography with UV detection, as described previously. In brief, the system consisted of a separation module, a fluorescence detector, and analysis software. The mobile phase was an isocratic mixture of 0.02M potassium dihydrogen phosphate (pH, 6) with concentrated phosphoric acid and acetonitrile (84:16). It was prepared fresh daily with double-distilled, deionized water that was filtered (0.22 µm) and degassed before use. The flow rate was 1.0 mL/min, and UV absorbance was measured at 205 nm.

Previously frozen plasma samples were thawed and vortexed. The sample (1 mL) was placed in a 15-mL screw cap tube, and 25 µL of trimethoprim (internal standard; 50 µg/mL) was added. Sodium hydroxide (200 µL, 1M) and methylene chloride (5 mL) were added. Tubes were placed on a rocker for 15 minutes and then centrifuged at 2,050 X g for 15 minutes. The bottom layer was removed and placed in a clean test tube and evaporated with nitrogen. The samples were reconstituted with 1 mL of mobile phase, and a 100-µL aliquot of sample was injected into the liquid chromatograph for analysis. Standard curves for plasma analysis were prepared by spiking canine plasma with ketamine, which produced a linear concentration range of 5 to 7,000 ng/mL. Calibration samples were prepared exactly as plasma samples. Mean recovery for propofol was 89%, and the intra- and interassay variability ranged from 2.0% to 8.2% and from 0.6% to 11%, respectively. The lower limit of quantification was 5 ng/mL.

Statistical analysis

The effect of anesthetic treatment on percentage change in MIRNM was estimated in a generalized linear mixed model, with dog as a random effect and treatment as the dependent variable. Treatment was included as an explanatory variable in the model; other variables controlled for in the model were week, time, and body weight. Similar models were used to investigate the effect of treatment on time to extubation and time to walking. In the model used to investigate the effect of treatment on time to extubation, the latter was specified as the dependent variable, whereas treatment, time, week, and body weight of the dog were specified as fixed effects (or explanatory variables). Similarly, in the model investigating the association between treatment and time to walking, the latter was specified as the dependent variable, whereas treatment, week, time, and body weight were again specified as fixed effects (or explanatory variables). Dog was included as a random effect in all models. Model assumptions of normality were assessed by means of the Shapiro-Wilk test for normality of residuals. Where necessary, data were log transformed to ensure that the residuals met this assumption. Least squares mean values and their SEMs were computed for all dependent variables and compared across treatments. A 2-tailed value of P < 0.05 was considered significant for all tests of significance.
When multiple comparisons were performed, $P$ values were adjusted by use of the Tukey method. All statistical analyses were performed with commercially available statistical software.\(^1\)

Values for heart rate, respiratory rate, and MAP were obtained at 15-minute intervals, and values obtained during the first 60 minutes of each anesthetic episode were compared with values obtained after the first 60 minutes to elucidate any changes in these parameters that might have been associated with high initial plasma propofol and ketamine concentrations resulting from the loading doses.

**Results**

Least squares mean ± SEM propofol MIRNMs for dogs anesthetized with propofol alone, propofol and low-dose ketamine, and propofol and high-dose ketamine were 0.76 ± 0.1 mg/kg/min, 0.60 ± 0.1 mg/kg/min, and 0.41 ± 0.1 mg/kg/min, respectively. The propofol MIRNM was significantly lower when dogs were anesthetized with propofol and low-dose ketamine ($P < 0.001$) or with propofol and high-dose ketamine ($P = 0.003$) than when dogs were anesthetized with propofol alone. The propofol MIRNM when dogs were anesthetized with propofol and high-dose ketamine was significantly ($P = 0.002$) lower than the MIRNM when dogs were anesthetized with propofol and low-dose ketamine. Anesthesia with propofol and low-dose ketamine and with propofol and high-dose ketamine was associated with decreases of 27 ± 10% and 30 ± 10% in the propofol MIRNM, respectively; however, percentage decreases did not differ significantly ($P = 0.864$) between the 2 treatments. Least squares mean ± SEM times from intubation to completion of MIRNM determination when dogs were anesthetized with propofol alone, propofol and low-dose ketamine, and propofol and high-dose ketamine were 185 ± 32 minutes, 230 ± 34 minutes, and 202 ± 34 minutes, respectively; there were no significant differences among groups.

One dog when anesthetized with propofol alone, 4 dogs when anesthetized with propofol and low-dose ketamine, and 3 dogs when anesthetized with propofol and high-dose ketamine required an additional propofol bolus within the first hour of anesthesia to prevent spontaneous movement. There was no significant ($P ≥ 0.05$) difference among treatments in regard to plasma propofol concentrations at the time of MIRNM determination, extubation, or walking (Table 1).

Plasma ketamine concentrations at the time of MIRNM determination were significantly ($P = 0.005$) greater when dogs were anesthetized with propofol and high-dose ketamine than when dogs were anesthetized with propofol and low-dose ketamine. Plasma norketamine concentrations at the time of MIRNM determination did not differ significantly ($P = 0.563$) between treatments, and plasma ketamine and norketamine concentrations did not differ significantly ($P ≥ 0.05$) between treatments at the time of extubation or walking (Table 2).

During the first 60 minutes, heart rate was higher when dogs were anesthetized with propofol and low-dose ketamine ($P = 0.002$) or propofol and high-dose ketamine ($P = 0.001$) than when dogs were anesthetized with propofol alone (Table 3). Heart rates when dogs were anesthetized with propofol and low-dose ketamine were significantly ($P ≥ 0.05$) different from rates when dogs were anesthetized with propofol and high-dose ketamine. After 60 minutes, heart rates when dogs were anesthetized with propofol and low-dose ketamine were significantly ($P = 0.008$) higher than rates when dogs were anesthetized with propofol alone, but heart rates when dogs were anesthetized with propofol alone did not differ significantly ($P ≥ 0.05$) from rates when dogs were anesthetized with propofol and high-dose ketamine. When dogs were anesthetized with propofol alone, heart rate was significantly ($P < 0.001$) higher after the first 60 minutes than during the first 60 minutes. When dogs were anesthetized with propofol and low-dose ketamine or with propofol and high-dose ketamine, there was no significant ($P ≥ 0.05$) difference in heart rates after the first 60 minutes versus during the first 60 minutes.

Respiratory rates when dogs were anesthetized with propofol and high-dose ketamine were significantly higher during the first 60 minutes than rates when dogs were anesthetized with propofol alone ($P = 0.001$) or propofol and low-dose ketamine ($P = 0.010$; Table 3); however, $P_{\mathrm{ETCO}_{2}}$ did not differ significantly.

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**Table 1** — Plasma propofol concentrations (µg/mL) at the time of MIRNM determination in dogs (n = 6) anesthetized with propofol alone (0.76 ± 0.1 mg/kg/min), propofol (0.60 ± 0.1 mg/kg/min) and a low dose of ketamine (0.025 mg/kg/min), or propofol (0.41 ± 0.1 mg/kg/min) and a high dose of ketamine (0.05 mg/kg/min); at the time of extubation; and at the time dogs were first able to walk unaided after recovering.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>MIRNM determination</th>
<th>Extubation</th>
<th>Walking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol alone</td>
<td>14.5 ± 1.0</td>
<td>5.8 ± 1.0</td>
<td>3.8 ± 1.0</td>
</tr>
<tr>
<td>Propofol and low-dose ketamine</td>
<td>13.3 ± 1.0</td>
<td>4.9 ± 1.0</td>
<td>3.3 ± 1.0</td>
</tr>
<tr>
<td>Propofol and high-dose ketamine</td>
<td>10.9 ± 1.0</td>
<td>2.9 ± 1.0</td>
<td>2.3 ± 1.0</td>
</tr>
</tbody>
</table>

Data are least squares mean ± SEM.

In each column, values are not significantly ($P ≥ 0.05$) different from each other.

In each dog, MIRNM was determined in duplicate for each anesthetic treatment; plasma samples obtained at the time of each MIRNM determination were combined for analysis.
Table 2—Plasma ketamine and norketamine concentrations (ng/mL) at the time of MIRNM determination in dogs (n = 6) anesthetized with propofol (0.60 ± 0.1 mg/kg/min) and a low dose of ketamine (0.025 mg/kg/min) or with propofol (0.41 ± 0.1 mg/kg/min) and a high dose of ketamine (0.05 mg/kg/min), at the time of extubation, and at the time dogs were first able to walk unaided after recovering.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>MIRNM determination</th>
<th>Extubation</th>
<th>Walking</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ketamine</td>
<td>Norketamine</td>
<td>Ketamine</td>
</tr>
<tr>
<td>Propofol and low-dose ketamine</td>
<td>446 ± 258a</td>
<td>140 ± 90a</td>
<td>95 ± 258a</td>
</tr>
<tr>
<td>Propofol and high-dose ketamine</td>
<td>1,399 ± 258b</td>
<td>346 ± 89b</td>
<td>400 ± 258b</td>
</tr>
</tbody>
</table>

<sup>a</sup>Within a column, values with different superscript letters were significantly (P < 0.05) different. See Table 1 for remainder of key.

Table 3—Heart rate, \( \text{PETCO}_2 \), respiratory rate, MAP, time to extubation, and time to walking in dogs (n = 6) anesthetized with propofol alone (0.76 ± 0.1 mg/kg/min), propofol (0.60 ± 0.1 mg/kg/min) and a low dose of ketamine (0.025 mg/kg/min), or propofol (0.41 ± 0.1 mg/kg/min) and a high dose of ketamine (0.05 mg/kg/min).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Heart rate (beats/min)</th>
<th>( \text{PETCO}_2 ) (mm Hg)</th>
<th>Respiratory rate (breaths/min)</th>
<th>MAP (mm Hg)</th>
<th>Time to extubation*</th>
<th>Time to walking†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol alone</td>
<td>91 ± 10&lt;sup&gt;A&lt;/sup&gt;</td>
<td>107 ± 10&lt;sup&gt;B&lt;/sup&gt;</td>
<td>45 ± 2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7 ± 2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>83 ± 4&lt;sup&gt;C&lt;/sup&gt;</td>
<td>92 ± 5&lt;sup&gt;D&lt;/sup&gt;</td>
</tr>
<tr>
<td>Propofol and low-dose ketamine</td>
<td>110 ± 10&lt;sup&gt;A&lt;/sup&gt;</td>
<td>116 ± 10&lt;sup&gt;A&lt;/sup&gt;</td>
<td>43 ± 2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10 ± 2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>91 ± 4&lt;sup&gt;C&lt;/sup&gt;</td>
<td>98 ± 5&lt;sup&gt;C&lt;/sup&gt;</td>
</tr>
<tr>
<td>Propofol and high-dose ketamine</td>
<td>114 ± 10&lt;sup&gt;a&lt;/sup&gt;A</td>
<td>113 ± 10&lt;sup&gt;a&lt;/sup&gt;A</td>
<td>42 ± 2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>14 ± 2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>92 ± 4&lt;sup&gt;C&lt;/sup&gt;</td>
<td>95 ± 5&lt;sup&gt;C&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Values for heart rate, \( \text{PETCO}_2 \), respiratory rate, and MAP were obtained at 15-minute intervals, and values obtained during the first 60 minutes of each anesthetic episode were compared with values obtained after the first 60 minutes. For \( \text{PETCO}_2 \) and respiratory rate, values were not recorded after the first 60 minutes because several dogs required mechanical ventilation.

<sup>a</sup>Time to extubation (minutes) was the time from the end of drug infusion to extubation. †Time to walking was the time (minutes) from the end of drug infusion to walking without assistance.

Significantly (P ≥ 0.05) among treatments during this time. Respiratory rates when dogs were anesthetized with propofol alone versus propofol and low-dose ketamine did not differ significantly (P ≥ 0.05) during the first 60 minutes. After 60 minutes, 4 dogs when anesthetized with propofol and low-dose ketamine, 3 dogs when anesthetized with propofol alone, and 3 dogs when anesthetized with propofol and high-dose ketamine required mechanical ventilation because \( \text{PETCO}_2 \) was > 60 mm Hg; thus, respiratory rates and \( \text{PETCO}_2 \) recorded after the first 60 minutes were not analyzed.

Hypotension, defined as MAP < 60 mm Hg, was not observed at any time; thus, dobutamine was not administered on any occasion. The MAP was not significantly (P ≥ 0.05) different among treatments during the first 60 minutes or after the first 60 minutes. When dogs were anesthetized with propofol alone, the MAP was significantly (P = 0.001) greater after the first 60 minutes than during the first 60 minutes. There were no significant (P ≥ 0.05) differences in MAP between time periods when dogs were anesthetized with propofol and low-dose ketamine or with propofol and high-dose ketamine.

There was no significant difference in time to extubation among treatments (Table 3). When anesthetized with propofol and high-dose ketamine, dogs had a shorter time to walking than they did when anesthetized with propofol alone (P < 0.001) or with propofol and low-dose ketamine (P = 0.012). Five of the 6 dogs experienced stertorous breathing during recovery with each treatment; this resolved within 15 to 45 minutes. Recovery was otherwise smooth and uneventful with all treatments.

**Discussion**

Results of the present study indicated that administration of ketamine at 25 or 50 mg/kg/min significantly decreased the propofol MIRNM in dogs in a dose-dependent, nonadditive fashion. Decreases in propofol MIRNM of 27% and 30%, respectively, were found when propofol was administered with ketamine at the lower or higher dose, compared with the MIRNM when propofol was administered alone. These percentage changes were not significantly different from each other, likely because of the variability in propofol infusion rates and plasma propofol concentrations and the small sample size. A post hoc power analysis indicated that a minimum of 10 dogs would have been needed to detect a significant difference in MIRNM between treatments with an α value of 0.05 and power of 80%. Regardless, the decrease in propofol MIRNM associated with ketamine was judged to be clinically important. Also, the study indicated a potential need for controlled ventilation during TIVA.
with propofol or with a combination of propofol and ketamine because hypoventilation was present with all 3 treatments.

The MIRNM was chosen as the end point for the present study because the authors believe that, in comparison to MIR, it is less subjective, in that observers do not have to differentiate between purposeful versus nonpurposeful movements, and more clinically relevant, given that typically no movement is tolerated during surgical procedures. The authors consider the MIRNM to be analogous to the MAC of a volatile anesthetic required to prevent all motor movement, purposeful and nonpurposeful, in response to a noxious stimulus, in all test subjects. In contrast, the traditional MAC and MIR end points are the values necessary to prevent purposeful movement only, in response to a noxious stimulus, in 50% of the study population.

Given the relationship between MAC and the MAC required to prevent all motor movement, the MIRNM could be expected to be approximately 20% greater than the MIR.

In the present study, mean propofol MIRNM when dogs were anesthetized with propofol alone was 0.76 mg/kg/min. Not surprisingly, considering that we measured MIRNM and not MIR, this was higher than published values for the propofol MIR in dogs. Studies of propofol anesthesia in unpremedicated, nonstimulated dogs have shown that infusion rates ranging from 0.44 to 0.6 mg/kg/min are necessary to maintain a light plane of anesthesia. A study involving unpremedicated dogs determined a propofol MIR of 0.51 mg/kg/min when an electrical stimulus was used. However, plasma propofol concentrations were not determined, and it is possible that the MIR was underestimated in that study because stimulation of the dogs began 10 minutes after administration of the loading dose. Thus, steady-state plasma propofol concentrations may not have been achieved at the time of MIR determination. A computer simulation study indicated that the initial loading dose of propofol has an effect on plasma concentrations, albeit a diminishing effect over time, but by 120 minutes, the plasma concentration is wholly dependent on the CRI. On the basis of these findings, a 60-minute equilibration time prior to beginning MIRNM determination was allowed in the present study, with the hope of approaching a steady-state plasma propofol concentration by the time of MIRNM determination. Time from intubation to the completion of MIRNM determination in this study was > 180 minutes for all treatments.

A potential weakness in the present study was that the time (15 minutes) allowed after a change in the propofol infusion rate may have been insufficient to achieve a new steady-state plasma propofol concentration. To overcome this limitation, longer equilibration times or the use of technologies that measure real-time propofol concentrations should be considered for future studies.

A propofol MIR of 0.9 mg/kg/min has been reported for unpremedicated rabbits subjected to tail clamping. This high MIR is consistent with the high propofol clearance of 340 mL/kg/min in rabbits, compared with a clearance of 50.1 mL/kg/min in dogs. A propofol MIR of 0.15 mg/kg/min was necessary to abolish the response to tail clamping in unpremedicated cats, but an MIR of 0.28 mg/kg/min was necessary to abolish the palpebral reflex at the time of MIRNM determination. This considerably lower MIR in cats can be attributed to the prolonged propofol elimination half-life in this species, which could possibly be due to impaired glucuronidation in cats. Few studies of propofol MIR have determined plasma or whole blood concentrations of propofol.

It has been reported that plasma concentrations between 2.5 and 4.7 µg/mL should be sufficient to maintain surgical anesthesia in dogs premedicated with acepromazine and methadone. A study performed at the authors’ laboratory (data currently in press) predicted that whole blood propofol concentrations of 7.4 µg/mL would decrease the MAC of sevoflurane that prevents all motor movement by 100% in unpremedicated dogs. In contrast to these findings, a study of human patients found that the whole blood concentration at which 50% of patients did not respond to a skin incision was 15.2 µg/mL, close to the plasma propofol concentration of 14.5 µg/mL in the present study when MIRNM was determined. Surprisingly, in the present study, there was no significant difference in plasma propofol concentrations among treatments despite the differences in MIRNM, but this could have been due to the small sample size and large interindividual variability among animals. According to a post hoc power analysis, 25 dogs would have been needed in each treatment group to detect a significant difference among treatments.

In unpremedicated subjects, there appear to be significant variations in propofol MIR and measured and predicted propofol concentrations. However, making comparisons among studies is difficult because of differences in experimental design (especially because some studies analyzed whole blood and others analyzed plasma) and differences in storage temperature and time. In the present study, plasma rather than whole blood was analyzed for propofol concentrations, and this was based on a recent study (unpublished data) performed at the authors’ laboratory, in which more propofol was recovered from canine plasma samples than canine whole blood samples and plasma propofol concentrations were not affected by storage at -80°C for up to 4 weeks.

A recent study investigating the effect of a mixture of propofol and ketamine (1:1 [wt/vol]) in unpremedicated dogs reported that the propofol MIR required to maintain a light plane of anesthesia decreased from 0.6 mg/kg/min with propofol alone to 0.3 mg/kg/min with the 1:1 mixture (300 µg of ket-
amine (kg/min). Although this represented a 50% decrease in the propofol MIR, the ketamine infusion rate in that study was much higher than the rate used in the present study. The ketamine infusion rates in the present study were chosen to achieve target plasma concentrations of 600 and 1,100 ng/mL, respectively, and were based on the effect of ketamine on sevoflurane MAC in dogs at these concentrations. In the present study, the ketamine concentrations were different between groups, but there was a high degree of interindividual variability and the calculated power was 0.54. To achieve a power of 0.8, 7 dogs/group would be needed. Mean plasma ketamine concentrations at 25 and 50 µg/kg/min were 446 and 1,399 ng/mL, respectively. The latter concentration was slightly higher than expected on the basis of findings reported by Wilson et al., in which a ketamine infusion of 50 µg/kg/min resulted in a plasma concentration of 1,057 ng/mL and was associated with a decrease of 40% in the MAC of sevoflurane. In unpremedicated cats anesthetized with propofol, ketamine infusions of 23 and 46 µg/kg/min resulted in plasma ketamine concentrations of 1,170 and 2,270 ng/mL, respectively. These values are considerably greater than those of the present study and were also greater than those authors predicted. Those authors attributed this either to inaccuracies of the pharmacokinetic models or to the effect of propofol infusion on ketamine metabolism in cats. On the basis of recent pharmacokinetic findings related to ketamine and propofol in cats, it is likely that the latter is the case. Nonetheless, that study found that the propofol MIR decreased from 0.15 to 0.11 mg/kg/min for the groups given ketamine at rates of 46 and 23 µg/kg/min, respectively. This represented a decrease of approximately 27% in the propofol MIR and is similar to the findings of the present study at an infusion rate of 50 µg/kg/min, albeit at a much higher plasma ketamine concentration.

An interesting finding of the present study was that there was no significant difference in MAP among treatments at any time, and hypotension (MAP < 60 mm Hg) did not occur with any treatment. It has been reported that propofol causes dose-dependent cardiovascular depression secondary to reductions in myocardial contractility and systemic vascular resistance. Previous studies comparing the effects of propofol alone and propofol in combination with ketamine on blood pressure have shown that TIVA with propofol and ketamine better supports MAP than does propofol alone. However, in the present study, blood pressure was not measured prior to induction of anesthesia, so it is unknown how much the blood pressure decreased from awake values.

Propofol has a dose-dependent negative chronotropic effect via direct depression of sinoatrial pacemaker activity. The heart rate during the first 60 minutes was significantly lower when dogs in the present study were anesthetized with propofol alone than when they were anesthetized with propofol and low-dose ketamine or propofol and high-dose ketamine, and this could have been due to the effect of a higher loading dose of propofol. Ketamine supports heart rate via direct stimulation of the sympathetic nervous system, and this could have also contributed to the higher heart rates when dogs were anesthetized with propofol and low-dose ketamine or propofol and high-dose ketamine. However, there was no difference in heart rate between propofol and low-dose ketamine and propofol and high-dose ketamine, although this may have been due to the small number of animals in this study and the ketamine infusion rates that were used.

Propofol causes respiratory depression and apnea by depressing the central respiratory center and inhibiting the response to hypercapnia. Additionally, ketamine is associated with dose-dependent respiratory depression. Therefore, it is not surprising that respiratory depression occurred during anesthesia. Dogs had significantly higher respiratory rates during the first 60 minutes when anesthetized with propofol and high-dose ketamine than when anesthetized with propofol alone or with propofol and low-dose ketamine; however, PETCO2 did not differ among treatments during the first 60 minutes. After the first 60 minutes, intermittent positive pressure ventilation was required for 3 dogs when anesthetized with propofol alone or with propofol and high-dose ketamine and 4 dogs when anesthetized with propofol and low-dose ketamine owing to PETCO2 > 60 mm Hg. This finding was consistent with the reported respiratory depressant effects of propofol in multiple species. The need for intermittent positive pressure ventilation across treatments limits the clinical utility of such TIVA protocols if assisted ventilation cannot be provided.

Recovery was smooth and uneventful across all treatments in the present study. It has been shown that recovery time from propofol infusion is dependent on the rate and duration of the infusion in dogs and humans. Therefore, it is not surprising that dogs had a significantly shorter time to walking when anesthetized with propofol and high-dose ketamine than when anesthetized with propofol alone or with propofol and low-dose ketamine. However, time to extubation did not differ among groups.

To the authors’ knowledge, there is no published information on plasma propofol concentrations at extubation or walking in unpremedicated dogs anesthetized with propofol. Studies of premedicated dogs have reported plasma propofol concentrations ranging from 1.6 to 2.3 µg/mL at extubation and 1.03 to 2.2 µg/mL at walking. Therefore, it was not surprising that the plasma concentrations when dogs in the present study were anesthetized with propofol alone were 5.8 µg/mL and 3.8 µg/mL at extubation and walking, respectively. Plasma propofol concentrations at each of these times were slightly lower when dogs were anesthetized with propofol and low-dose ketamine and propofol and high-dose ketamine; compared with concentrations when dogs were anesthetized with propofol alone. These differences were not signifi-
cant; owing to the high variability in plasma propofol and ketamine concentrations and the small sample size, there is a high possibility of a type II error in these results.

Five of the 6 dogs in the study had a moderate to severe stertorous breathing pattern during anesthetic recovery that lasted up to 60 minutes after extubation and occurred after all 3 treatments. These episodes were self-limiting, resolved spontaneously, and did not seem to threaten the well-being of the dogs. The authors were unable to find any report of this phenomenon in the literature and are unable to explain its origin or importance; oral examination did not reveal any abnormalities of the soft palate or larynx in these dogs. The fact that it occurred after all 3 anesthetic treatments would suggest that it was associated with propofol rather than ketamine administration.

Two of the 6 dogs in the present study (1 when anesthetized with propofol alone and the other when anesthetized with propofol and low-dose ketamine) developed myoclonus that persisted throughout anesthesia. At the time, both dogs were receiving their first treatment in the randomized order in which treatments had been assigned. Neither dog had myoclonus during any other treatment. At times, the myoclonus was so severe that it could have been clinically relevant if the patient had been anesthetized for surgery requiring a motionless subject. This phenomenon has been reported previously in dogs, and the incidence of myoclonus associated with a propofol infusion in clinical cases was 1.2% in a recent retrospective study. The cause of the myoclonus is uncertain, although it has been theorized that propofol may have an action similar to strychnine, via antagonism of glycine at the subcortical level.

Footnotes

a. EMLA Cream, APP Pharmaceuticals Inc. Schaumburg, Ill.
b. Surflo IV Catheter, Terumo Medical Corp, Somerset, NJ.
g. Gaymar-F Pump, Gaymar Industries, Orchard Park, NY.
h. Dobutamine, Hospira Inc, Lake Forest, Ill.
i. Propofol, Abbott Laboratories, North Chicago, Ill.
l. Compact II Centrifuge, Clay Adams Brand, Becton-Dickinson, Franklin Lakes, NJ.
m. 2095 Separations Module, Waters Corp, Milford, Mass.
n. Xterra RP18 column, Waters Corp, Milford, Mass.
o. Xterra guard column, Waters Corp, Milford, Mass.
p. 2487 absorbance detector, Waters Corp, Milford, Mass.
q. Empower 3, Waters Corp, Milford, Mass.
r. 2475 Fluorescence Detector, Waters Corp, Milford, Mass.
s. XBridge C18, Waters Corp, Milford, Mass.
t. XBridge C18 guard column, Waters Corp, Milford, Mass.
u. SAS, version 9.3 TS Level 1M2, SAS Institute Inc, Cary, NC.

References


