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Comparison of propofol infusion rate required to abolish swallowing or pedal withdrawal reflexes in dogs

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Abstract

In a prospective, randomized, experimental non-blinded study, the continuous infusions rates of propofol required to prevent swallowing (P-SR) or pedal withdrawal reflex (P-WR) were evaluated in healthy premedicated dogs. Dogs were randomly assigned to one of two treatments at weekly intervals. Following premedication with a combination of acepromazine and methadone, anesthesia was induced with propofol (4.00 mg kg^{-1} per min) and was maintained for 90 min. The propofol infusion rate was increased or decreased by 0.05 mg kg^{-1} per min based on positive or negative swallowing (P-SR) or pedal withdrawal reflexes (P-WR). Propofol induction doses were 2.12 ± 0.43 mg kg^{-1} (P-SR) and 2.14 ± 0.31 mg kg^{-1} (P-WR), which were not significantly different. The mean (±SD) propofol infusion rate was significantly higher for P-WR (0.26 ± 0.10 mg kg^{-1} per min) when compared to P-SR (0.22 ± 0.12 mg kg^{-1} per min). During the last 30 min, the mean propofol infusion rates were 0.09 ± 0.02 and 0.18 ± 0.03 mg kg^{-1} per min for P-SR and P-WR, respectively. There were no significant differences between treatments with respect to heart rate (HR), respiratory rate, arterial blood pressure, end-tidal CO_2 partial pressure, hemoglobin oxygen saturation, partial pressures of oxygen or pH. Transient apnea lasting up to three minutes was observed in three dogs with each treatment. Propofol infusion rate of 0.22 ± 0.12 mg kg^{-1} per min can be used in premedicated dogs requiring tracheal intubation and undergoing mechanical ventilation, non-painful procedures or painful procedures with local anesthetic techniques.

Introduction

Inhalation anesthesia is commonly used for anesthetic maintenance in small animal practice. The disadvantages of inhalational anesthesia include costly anesthetic machines, environmental pollution from anesthetic gas and potential health hazard from chronic exposure to trace levels of inhalant anesthetics. Total intravenous anesthesia (TIVA) is a clinically acceptable alternative to inhalant anesthesia in both human and veterinary anesthesia, especially when there is no access to inhalational anesthesia. Propofol, a phenol derivative intravenous hypnotic agent, has become a popular injectable anesthetic in small animal practice because of its ease of use, reliability for induction and maintenance of anesthesia, and a high rate of clearance and lack of active metabolites.[1-3] Due to its fast onset and short duration of action attributable to its rapid redistribution and metabolism, propofol is widely used in a total intravenous anesthesia (TIVA) technique for the maintenance of sedation and anesthesia.

Acepromazine, in combination with methadone (a full μ-opioid agonist), has been used for premedication in dogs undergoing general anesthesia.[4,5] This combination provides sedation, reduces the minimum alveolar concentration of isoflurane by 68.30% and causes less vomiting than acepromazine combined with morphine.[4,6,7]

Propofol infusion may be used for non-painful procedures (to prevent movement during procedures like MRI or radiation therapy) or in patients that may require endotracheal intubation (to provide a patent airway and protect the lungs from aspiration of fluids) or mechanical ventilation (to maintain eucapnia and normoxemia in critically ill patients). To our knowledge, the infusion rate of propofol required to abolish swallowing reflex has not been investigated in dogs.

The present study aimed to compare the infusion rate of propofol required to prevent swallowing or withdrawal reflexes and to evaluate the effects of propofol infusion on cardiopulmonary variables in dogs. The hypothesis was that higher infusion rate of propofol would be required to

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prevent withdrawal reflex than that required to prevent swallowing reflex in healthy dogs premedicated with acepromazine-methadone combination.

Materials and Methods

A total of eight healthy mixed-breed intact male dogs were included in this study. Dogs ranged from one to four years of age (1.75 ±1.00 years), and body weight ranged from 17.40 to 23.70 kg (20.50 ± 2.00 kg). Dogs were considered healthy based on a physical examination and complete blood count (CBC) analysis. Food was withheld for 12 hr but water was available up until the time of premedication. Each dog was used in two treatments in a random order, with an interval of at least seven days between treatments.

This study was carried out after obtaining approval of the University Animal Care and Use Committee (Protocol number 9330102/2017). On the day of each experiment, the dogs were premedicated with a combination of 0.05 mg kg^{-1} acepromazine (Alfasan, Woerden, Holland) and 0.25 mg kg^{-1} methadone (Darrou Pakhsh, Tehran, Iran), mixed in a single syringe and injected into a lumbar epaxial muscle 30 min prior to induction of anesthesia. Before induction, both cephalic veins were catheterized using 20-G catheters which were used for infusions of propofol and fluid administration. Anesthesia was induced with slow intravenous (IV) injection of propofol (B. Braun, Melsungen, Germany) at a rate of approximately 4.00 mg kg^{-1} per min until a plane of anesthesia suitable for endotracheal intubation (loss of jaw tone, absence of resistance to protraction of the tongue and absence of swallowing and gag reflexes) was achieved.[8] Tracheal intubation was performed by the same person under direct laryngoscopic visualization with an appropriately sized cuffed endotracheal tube and the tube cuff was inflated until a leak was no longer audible at airway pressure of 15.00 cmH_2O. The total propofol dose required for induction was recorded. After endotracheal intubation, the endotracheal tube was connected to a small animal anesthesia machine (Fabius; Drager Medical, AG & Co. KGaA, Darmstadt, Germany) with a rebreathing circle system and an oxygen inflow of 2.00 L min^{-1}. All animals were placed in the left lateral recumbency and allowed to breathe spontaneously. Lactated Ringer's solution (IPPC, Tehran, Iran) was infused at 10.00 mL kg^{-1} per hr through-out the experiment. If post-induction apnea (defined as an absence of spontaneous breathing for longer than 30 sec) occurred, the lungs were inflated manually at a rate of two breaths per min, until spontaneous breathing resumed.

Dogs were randomly assigned (http://www.randomization.com, Accessed March 19, 2019) to one of two anesthetic maintenance techniques (n = 8) to determine minimum requirement of propofol to abolish swallowing reflex (P-SR) which indicates response to manipulation of endotracheal tube or pedal withdrawal reflex (P-WR).

Immediately following intubation of the trachea, an IV infusion of propofol (0.40 mg kg^{-1} per min) was started as initial dose using a syringe pump (JMS, Hiroshima, Japan). Intravenous infusion of propofol continued for 15 min before the first stimulus was applied. Then swallowing or pedal withdrawal reflexes were evaluated by the same observer at 10-min intervals for 90 min after induction. Swallowing reflexes were evaluated by a slow movement of endotracheal tube and anesthesia was maintained at the lightest anesthetic depth possible that allowed the animal to tolerate the endotracheal tube without any swallowing reflex (swallowing movement observed in the throat region) or coughing. Slow back and forth movement of endotracheal tube without deflation of the cuff was performed twice. If voluntary movement or spontaneous swallowing was observed, an IV bolus of 0.50 mg kg^{-1} propofol was administered. Pedal withdrawal reflex was evaluated by a toe pinch in the pelvic limb with a hemostat clamped to the third ratchet. The stimulus was applied for 10 sec or until a positive response was observed (withdrawal of the stimulated limb). If no response to stimulation occurred, propofol infusion rate was decreased by 0.05 mg kg^{-1} per min, and if there was a positive response, infusion rate was increased by 0.05 mg kg^{-1} per min.[9] Propofol infusion rate was held constant for 10 min before the next stimulation. Blinding was not possible due to the different stimulus used.

A 20-gauge catheter was inserted in the dorsal pedal artery for measuring blood pressures and collecting blood samples for blood gas analysis. The arterial catheter was connected to a disposable pressure transducer and a multi-channel monitor (PM-9000; Mindray, Shenzhen, China) for determination of arterial pressures (four dogs in each treatment). The level of the sternum was taken as the zero reference for all pressure determinations. The pressure transducer used for invasive blood pressure measurement was calibrated before use. Heart rate (HR), respiratory rate (f_R), oxygen saturation of hemoglobin (SpO_2) using pulse oximetry (placing the probe on the tongue), end-tidal carbon dioxide tension ($PE'CO_2$), non-invasive blood pressure and esophageal temperature (T) were recorded at 5 min intervals throughout anesthesia. Noninvasive arterial blood pressure was monitored with an oscillometric technique and a cuff with a width approximately 40.00% of the circumference of the limb placed on the pelvic limb. Arterial blood samples were collected at 60 and 90 min after induction (four dogs in each treatment) and analyzed immediately for determining packed cell volume, hemoglobin concentration, partial pressures of oxygen (PaO_2) and carbon dioxide ($PaCO_2$), pH, bicarbonate and base excess (OPTI Medical System Inc., Roswell, USA). If $PE'CO_2$ increased above 55.00 mmHg, assisted ventilation (by intermittent manual squeezing of the reservoir bag) was provided in an attempt to lower PE'CO2.

All variables were recorded before evaluation of swallowing or pedal withdrawal reflexes. Ninety min after the induction of anesthesia, propofol infusion was terminated and the dogs were allowed to recover from anesthesia. The tracheal tube was removed when swallowing was first noted and recovery was observed continuously by the study investigator. The time intervals between cessation of the propofol infusion and extubation (recovery of voluntary swallowing and extubation), head lift and sternal recumbency were recorded.

Statistical analysis. Normality of the data was tested using Shapiro-Wilk and Kolmogorov-Smirnov tests. Physiologic data including HR, systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), f_R, $PE'CO_2$, T, SpO_2, PCV, PaO_2, $PaCO_2$, base excess (BE), bicarbonate concentration (HCO_3^-), pH and hemoglobin (Hb) were analyzed with an ANOVA for repeated-measures, with time and treatment as factors. Paired *t* tests were used to compare propofol dose (induction and maintenance), recovery times and body weight between treatments. Statistical analysis was performed with SPSS Software (version 24.00; IBM Corp., Armonk, USA). A value of $p \leq 0.05$ was considered significant. Data are reported as mean ± SD.

Results

Acepromazine-methadone combination produced signs of moderate sedation allowing easy handling of the dogs. No dogs vomited following the administration of premedication. Mean induction dose (±SD) of propofol was 2.12 ± 0.43 mg kg^{-1} for P-SR and 2.14 ± 0.31 mg kg^{-1} for P-WR, which were not significantly different. The quality of induction of anesthesia following intravenous administration of propofol was satisfactory and excitement-free in all dogs, and there were no difficulties in endotracheal intubation. During the first 15 min of anesthesia, two dogs in each treatment required one or two bolus doses of propofol in order to prevent spontaneous limb or head movements.

The mean (±SD) propofol infusion rate for maintenance was significantly higher for P-WR (0.26 ± 0.10 mg kg^{-1} per min) when compared to P-SR (0.22 ± 0.12 mg kg^{-1} per min), (p = 0.001). Propofol infusion rate decreased over time in both treatments (Fig. 1). During the last 30 min, the mean propofol infusion rates were 0.09 ± 0.02 and 0.18 ± 0.03 mg kg^{-1} per min for P-SR and P-WR, respectively (p = 0.01). All the cardiopulmonary variables measured were within normal limits, and there were no significant differences between treatments with respect to HR, f_R, arterial blood pressure, $PE'CO_2$, SpO_2, PaO_2 or pH (Table 1). Esophageal temperature slightly decreased over time in both treatments. Transient apnea lasting up to three minutes was observed in three dogs with each treatment that required manual ventilation. In both treatments, some animals required manual ventilation at some points during the first 20 min in order to reduce $PE'CO_2$, when $PE'CO_2$ was higher than 55.00 mmHg.

After discontinuation of propofol infusion, intervals to extubation, head lift, and sternal recumbency, were not significantly different between treatments (Table 2). Recovery from anesthesia was considered smooth, quiet and uneventful.

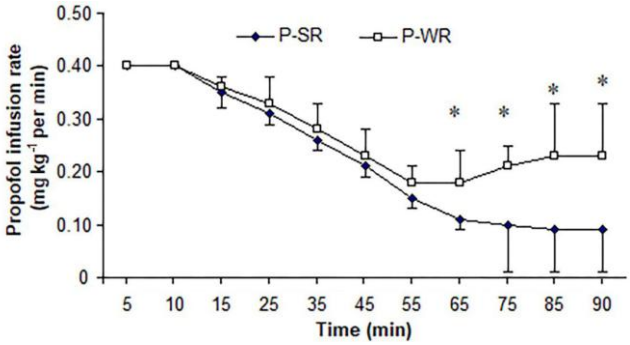

Fig. 1. Mean ± SD values of propofol infusion rate required to prevent swallowing reflex (P-SR) or pedal withdrawal reflex (P-WR) in eight dogs premedicated with acepromazine-methadone. * indicates significant differences between the treatments at $p < 0.05$).

Discussion

The results of the present study suggest that the dose required to obtain loss of the pedal reflex was significantly higher (by 18.00%) when compared to the dose required for loss of the swallowing reflex. These data confirm the original hypothesis of the study that the pedal withdrawal reflex (PWR) is abolished at higher levels of anesthesia than that required to tolerate an endotracheal tube.

In preliminary trials, we used the infusion rate of 0.30 mg kg^{-1} per min and then dogs invariably required several boluses of propofol in order to prevent movement or chewing the tracheal tube. This was likely due to relatively low dose of propofol (2.12 mg kg^{-1}) used for induction of anesthesia used in this study as compared to reported dose of 4.50 mg kg^{-1} in premedicated dogs.[1] Therefore, propofol infusion at a rate of 0.40 mg kg^{-1} per min was used as initial infusion rate.[10-14]

In this study, mean induction doses for propofol were similar to those reported in premedicated dogs.[15,16] The degree of dose-sparing effects for induction agents is related to the depth of sedation and analgesia induced by each preanesthetic medications. Premedication with acepromazine-methadone produce a state of neurolept-analgesia characterized by sedation and analgesia. In a previous study, the median dose of propofol required for induction of anesthesia in acepromazine-methadone premedicated dogs was 2.34 mg kg^{-1}.[5] The doses of acepromazine and methadone and initial infusion rate of propofol were chosen according to previous studies.[6,10,17]

Table 1. Mean ± SD heart rate (beats min^{-1}) and respiratory rate (breaths min^{-1}), mean arterial pressure (MAP), $PaCO_2$, PaO_2, base excess (BE) and esophageal temperature in eight premedicated, healthy crossbred dogs anesthetized with propofol infusion to abolish swallowing (P-SR) or pedal withdrawal reflexes (P-WR).

Parameters	10 min	20 min	30 min	40 min	50 min	60 min	70 min	80 min	90 min
HR (beats min^{-1})									
P-SR	85.00 ± 24.00	88.00 ± 22.00	82.00 ± 18.00.	78.00 ± 13.00	76.00 ± 13.00	72.00 ± 15.00	74.00 ± 15.00	77.00 ± 22.00	85.00 ± 22.00
P-WR	88.00 ± 19.00	88.00 ± 19.00	91.00 ± 29.00	79.00 ± 15.00	80.00 ± 13.00	77.00 ± 12.00	74.00 ± 15.00	75.00 ± 15.00	79.00 ± 7.00
f_R (breaths min^{-1})									
P-SR	8.00 ± 2.00	9.00 ± 6.00	9.00 ± 4.00	10.00 ± 8.00	11.00 ± 8.00	12.00 ± 9.00	16.00 ± 8.00	22.00 ± 12.00	23.00 ± 9.00
P-WR	10.00 ± 5.00	10.00 ± 5.00	9.00 ± 5.00	11.00 ± 4.00	12.00 ± 5.00	11.00 ± 5.00	15.00 ± 9.00	22.00 ± 9.00	21.00 ± 6.00
MAP (mmHg)									
P-SR	-	86.00 ± 10.00	84.00 ± 14.00	93.00 ± 12.00	90.00 ± 21.00	97.00 ± 24.00	86.00 ± 23.00	93.00 ± 22.00	94.00 ± 17.00
P-WR	-	82.00 ± 10.00	85.00 ± 8.00	80.00 ± 12.00	76.00 ± 13.00	75.00 ± 11.00	80.00 ± 15.00	94.00 ± 24.00	87.00 ± 21.00
SaO_2									
P-SR	96.80 ± 2.60	96.40 ± 2.60	96.30 ± 3.10	96.60 ± 3.50	96.80 ± 2.30	95.90 ± 1.20	96.00 ± 1.50	96.30 ± 1.40	96.40 ± 1.00
P-WR	96.10 ± 2.10	94.90 ± 2.00	94.40 ± 2.90	94.40 ± 2.70	94.80 ± 2.00	94.10 ± 5.20	95.60 ± 1.50	95.60 ± 2.70	96.00 ± 1.90
pH									
P-SR	-	-	-	-	-	7.31 ± 0.05	-	-	7.38 ± 0.04
P-WR	-	-	-	-	-	7.27 ± 0.03	-	-	7.36 ± 0.05
PaO_2 (mmHg)									
P-SR	-	-	-	-	-	390.00 ± 39.00	-	-	377.00 ± 15.00
P-WR	-	-	-	-	-	407.00 ± 29.00	-	-	385.00 ± 30.00
$PaCO_2$ (mmHg)									
P-SR	-	-	-	-	-	45.70 ± 7.60	-	-	36.00 ± 4.35
P-WR	-	-	-	-	-	48.00 ± 3.50	-	-	39.00 ± 5.24
HCO_3 (mmol L^{-1})									
P-SR	-	-	-	-	-	22.30 ± 1.40	-	-	21.00 ± 0.60
P-WR	-	-	-	-	-	22.00 ± 0.50	-	-	21.50 ± 0.90
BE(mmol L^{-1})									
P-SR	-	-	-	-	-	–3.90 ± 0.90	-	-	–3.50 ± 0.40
P-WR	-	-	-	-	-	–4.80 ± 0.90	-	-	–3.50 ± 1.30
$PE'CO_2$ (mmHg)									
P-SR		46.80 ± 5.50	47.60 ± 4.60	44.50 ± 7.80	46.60 ± 5.80	42.50 ± 6.50	45.80 ± 9.00	42.90 ± 7.80	44.50 ± 8.80
P-WR		47.30 ± 4.50	45.30 ± 6.50	46.30 ± 6.50	44.40 ± 4.50	41.30 ± 7.70	47.30 ± 5.70	44.80 ± 10.20	47.80 ± 11.00
Temperature (˚C)									
P-SR	37.50 ± 0.80	37.60 ± 0.60	37.40 ± 0.70	37.30 ± 0.80	37.40 ± 0.80	37.40 ± 0.60	37.30 ± 0.70	37.10 ± 0.70	37.20 ± 0.80
P-WR	37.80 ± 0.50	37.90 ± 0.30	37.60 ± 0.60	37.60 ± 0.60	37.50 ± 0.60	37.40 ± 0.70	37.40 ± 0.60	37.20 ± 0.70	37.20 ± 0.70

Table 2. Mean ± SD values for recovery time (min) in eight premedicated, healthy mixed-breed dogs after 90 min of propofol infusion in a crossover study design.

Variables	P-SR	P-WR
Extubation	10.40 ± 4.30	17.60 ± 10.10
Head lift	15.00 ± 7.00	20.40 ± 12.40
Sternal recumbency	20.30 ± 8.80	23.60 ± 14.30

P-SR: propofol-swallowing reflex, and P-WR: propofol-withdrawal reflex

Acepromazine, a phenothiazine derivative, is generally devoid of clinically significant analgesic properties and is often administered with an opioid analgesic agent in dogs to facilitate handling and preparation of dogs for surgical procedures.[18] Sedative and analgesic properties appear to be improved with the combination, compared with use of either drug alone. It has been reported that premedication with methadone alone (0.50 mg kg^{-1}, IV) or acepromazine (0.02 mg kg^{-1})-methadone (0.50 mg kg^{-1}) combinations reduced the minimum alveolar concentration of isoflurane in dogs by 35.00% and 68.30%, respectively.[4,19]

Propofol is rapidly metabolized with no active metabolites and eliminated from the body and its infusion results in a rapid recovery and good muscle relaxation.[20] Propofol, when used as a continuous infusion, has been reported to cause adverse events such as hypotension, apnea and respiratory depression in dogs.[21] Aguiar *et al.* observed dose-dependent respiratory depression, represented by a decrease in respiratory rate and increase in $PaCO_2$, following a continuous infusion of propofol in dogs, which was significant only with a high infusion rate of propofol (0.40 mg kg^{-1} per min).[10] In this study, some animals required temporary ventilatory support with manual intermittent positive pressure ventilation for apnea or hypoventilation. It was intended to evaluate the pulmonary effect of propofol infusion; therefore, dogs were not ventilated mechanically in the present study. Other adverse effects of propofol such as excitation, pain on injection, muscle fasciculation and opisthotonos were not observed in this study. All animals had uneventful anesthesia and all cardiopulmonary variables monitored were similar to that observed in a previous studies using

0.20 - 0.40 mg kg^{-1} per min of propofol.[10,14]

Total intravenous anesthesia with propofol has been compared to isoflurane in healthy dogs subjected to hindlimb orthopedic surgery under epidural anesthesia.[22] In that study, propofol anesthesia provided higher MAP, although a higher incidence of respiratory depression compared to isoflurane, may require mechanical ventilation during propofol infusion. In a clinical study, anesthetic maintenance with isoflurane in dogs undergoing diagnostic MRI were 14.70 times more likely to require dopamine infusion to treat hypotension than dogs maintained with propofol infusion.[9]

The slight progressive hypothermia observed in both treatments may be a result of low temperature of IV fluids and inhaled oxygen, and reduced muscle and metabolic activity.[23] The results of the present study suggest that a lower continuous infusion rate of propofol depresses the swallowing reflex in acepromazine-methadone pre-medicated dogs, as compared to that required to prevent pedal withdrawal reflex. In premedicated healthy dogs, higher induction dose of propofol was required for endotracheal intubation than that required for insertion of laryngeal mask airway.[24] Likewise, a deeper plane of isoflurane anesthesia was required for tolerance of endotracheal tube compared to laryngeal mask airway in human.[25] In the present study, stimulated (evoked) swallowing reflex was evaluated and, therefore, a lower propofol infusion rate may be required to prevent spontaneous swallowing reflex in dogs.

Swallowing reflex is a highly complex process elicited by the stimulation of pharyngolaryngeal receptors and afferent fibers of cranial nerves V, IX and X carry this information to the coordinating center within the medulla.[26] This reflex is probably very sensitive to depressant agents of the central nervous system, such as injectable and inhalation anesthetics. Propofol produces central nervous system (CNS) depression by activating the ionotropic subtype of the γ - aminobutyric acid (GABA) receptor known as GABAA. It has been reported that centrally acting GABAB receptor agonists inhibit spontaneous and stimulated (evoked) swallowing reflex in conscious dogs.[27] Subhypnotic blood concentrations of propofol is known to inhibit pharyngolaryngeal function in healthy human volunteers and in patients undergoing elective gastrointestinal endoscopy under propofol target-controlled infusion (TCI) sedation.[28,29] Methadone, an opioid μ-receptor agonist, which was used for premedication in the present study, has antitussive effects, and may have also contributed to the suppression of swallowing reflex.[30] In this study, a mean propofol infusion rate of 0.22 ± 0.12 mg kg^{-1} per min was required to prevent swallowing reflex and spontaneous movement in premedicated dogs. A similar infusion rate of propofol (0.27-0.29 mg kg^{-1} per min) has been reported in dogs undergoing epidural anesthesia using bupivacaine alone or in combination with either fentanyl or sufentanil for ovariohysterectomy.[31] However, that study is different in several aspects; a higher dose of acepromazine (0.10 mg kg^{-1}) was used for premedication; tracheal intubation was not performed; dogs received two IV boluses of 4.00 mg kg^{-1} of propofol before starting a propofol infusion; continuous infusion of propofol was used in a dose sufficient only to maintain sedation or a light plane of anesthesia; the mean duration of propofol was approximately 40 min; intraoperative analgesia was provided by epidural administration of bupivacaine; and finally, it is not clear how the depth of anesthesia has been monitored and propofol infusion rate has been adjusted.

One limitation of this study is that the plasma concentration of propofol was not measured. Another potential limitation is that propofol infusion was maintained for only 90 min. Although propofol infusion rate required to prevent P-WR seemed to plateau towards the end of anesthesia, infusion rate required to prevent swallowing reflex might have been lower if anesthesia was continued for a longer period. On the other hand, the temporal factor may influence the magnitude of reduction in propofol infusion rate induced by preanesthetic drugs administered as a single dose due to decreasing plasma concentrations over time. Evaluation of pedal and swallowing reflexes were made by a single observer, but blinding was not possible due to the nature of the study. This is unlikely to cause bias, because the clinical signs used (swallowing or coughing in P-SR and withdrawal movement in P-WR) were distinct and easy to observe.

In conclusion, our observations suggest that low continuous infusion rate of propofol (0.09 ± 0.02 mg kg^{-1} per min) can be useful in healthy dogs requiring endotracheal intubation and respiratory support. Higher doses are necessary to obtain loss of the pedal reflex. Although most cardiopulmonary variables were within normal ranges during the anesthetic procedure, respiratory depression caused by continuous infusion of propofol may require supplemental oxygen administration and ventilator support.

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Conflict of interest

The authors declare no conflict of interest.

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