Effect of remifentanil on requirements for propofol administered by use of a target-controlled infusion system for maintaining anesthesia in dogs

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Objective—To evaluate the effect of remifentanil administered by use of a constant rate infusion on the predicted plasma concentration (Cp

predicted
) of propofol required to prevent awareness in 50% of anesthetized dogs (Cp50

predicted
).

Animals—6 healthy dogs.

Procedures—Each dog received 2 treatments (1-week interval): induction and maintenance of anesthesia with propofol alone and induction of anesthesia with propofol and maintenance of anesthesia by use of propofol and a constant rate infusion of remifentanil (0.3 µg/kg/min). To induce anesthesia, propofol was administered by use of a target-controlled infusion system to achieve Cp

predicted
 of 6.0 µg/mL. Propofol Cp

predicted
 was adjusted in 0.5 µg/mL increments or decrements; the motor response to a supramaximal electrical nociceptive stimulus was assessed after each change to determine Cp50

predicted
 (mean of the highest Cp

predicted
 at which gross purposeful movement was detected in response to stimulation and the lowest Cp

predicted
 at which such movement was not detected).

Results—Mean ± SD duration of anesthesia for dogs receiving propofol (148 ± 35 minutes) and dogs receiving propofol-remifentanil treatment (141 ± 28 minutes) did not differ. Overall mean propofol Cp

predicted
 for induction of anesthesia was 6.0 ± 0.5 µg/mL. For maintenance of anesthesia, propofol Cp50

predicted
 was significantly reduced following addition of remifentanil to the protocol (2.0 ± 0.5 µg/mL vs 0.9 ± 0.4 µg/mL; 55% decrease).

Conclusions and Clinical Relevance—In nonpremedicated dogs, propofol Cp50

predicted
 of 6.0 µg/mL may be recommended for induction of anesthesia. Propofol requirements for maintaining target-controlled infusion system–based anesthesia were reduced via infusion of remifentanil at a rate of 0.3 µg/kg/min. (Am J Vet Res 2009;70:703–709)

The use of TIVA in humans has many advantages over inhalational anesthesia, such as more precise anesthetic depth control, improved quality of anesthesia, and faster recovery from anesthesia. Total IV anesthesia with propofol is reported to be superior to anesthesia achieved by use of inhalation agents in humans, although there are authors who describe a prolonged recovery period with this technique. In a recent study in dogs, dogs that underwent propofol TIVA had a slower and smoother recovery from anesthesia, compared with dogs that were anesthetized with isoflurane.

Abbreviations

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<th>Cp50</th>
<th>Plasma concentration required to prevent awareness during anesthesia in 50% of dogs</th>
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| Cp50

predicted
 | Predicted plasma concentration required to prevent awareness during anesthesia in 50% of dogs |
| Cp95          | Plasma concentration required to prevent awareness during anesthesia in 95% of dogs |
| Cp

predicted
 | Predicted plasma concentration |
| CRI           | Constant rate infusion |
| DAP           | Diastolic arterial blood pressure |
| ETCO

2
 | End-tidal tension of CO

2
 |
| HR            | Heart rate |
| MAC           | Minimum alveolar concentration |
| MAP           | Mean arterial blood pressure |
| SAP           | Systolic arterial blood pressure |
| TCI           | Target-controlled infusion |
| TIVA          | Total IV anesthesia |
Maintenance of a steady plasma concentration of an agent that is administered IV requires continuous adjustments in infusion rate according to the drug’s pharmacokinetic properties. Intravenous administrations of single bolus doses result in fluctuations in the plasma concentration of the drug, whereas administration via CRI achieves steady-state plasma concentration after a period of 5 to 7 half-lives has elapsed. New TIVA methods that are based on TCI have been used in human medicine for the last 10 years and are now being incorporated into veterinary medicine. Use of TCI allows an anesthetist to predict an estimate of real plasma drug concentrations in the central compartment and to titrate target drug concentrations according to patient requirements in the same way that expired concentrations of inhaled anesthetic drugs are adjusted according to response. The Cp50predicted is defined as the calculated plasma concentration after steady-state plasma concentration is achieved at which 50% of patients anesthetized by use of a drug that was administered IV do not respond to a standard surgical stimulus. This concept mimics alveolar concentration (ie, MAC) of inhalant anesthetics, which is the alveolar concentration at which 50% of anesthetized individuals fail to respond to a standard noxious stimulus.

Propofol TCI is commonly used to achieve anesthesia in humans, but its use in dogs has only recently been reported. In humans, the TCI technique is frequently used to administer propofol in combination with opioids, which may affect the pharmacokinetics of propofol. The use of TCI of propofol in combination with remifentanil in dogs was reported recently. Remifentanil is considered an ideal analgesic component for continuous infusion when combined with propofol because its pharmacokinetic properties allow for rapid equilibration in plasma and provide a fast elimination half-life that is independent from duration of the infusion. The purpose of the study reported here was to evaluate the effect of remifentanil administered by use of a CRI on the Cp50predicted of propofol in dogs. The Cp50predicted was calculated as the mean of the highest CPMpredicted that allowed gross purposeful movement in response to a supramaximal electrical nociceptive stimulation and the lowest CPMpredicted that prevented such a response.

Materials and Methods

Animals—Six healthy crossbred dogs that were 2 to 5 years old were used; there were 3 males and 3 females. Mean ± SD weight of the dogs was 26.5 ± 3.6 kg. Health status of each dog was assessed on the basis of results of a physical examination, CBC, and serum biochemical analyses. Findings were within reference ranges for all dogs. Dogs were housed in individual cages, fed dry laboratory dog food, and provided with water ad libitum. Before each experimental procedure, food and water were withheld for 12 and 2 hours, respectively. The study was performed following Brazilian College of Animal Experimentation guidelines and was approved by the Ethics and Animal Experimentation Committee (protocol No. 382/2004 CEEA).

Study design and procedures—Each dog underwent 2 treatments in a randomized order with a 1-week interval between experiments. One treatment involved administration of propofol, and the other involved administration of propofol and remifentanil. No premedication was administered before either treatment. For each dog, a 20-gauge, 3-cm-long catheter was placed in a cephalic vein for propofol administration and in a femoral vein for remifentanil administration.

Weight, height, age, sex, and desired target concentration data were entered into a computer program. Propofol was administered by use of a TCI system that incorporated propofol pharmacokinetic variables for dogs as determined by Beths et al. Remifentanil was administered by use of a continuous infusion pump at a rate of 0.3 µg/kg/min.

During the induction of anesthesia, the propofol CPMpredicted was initially set at 5.0 µg/mL and additional propofol was administered in increments of 0.5 µg/mL until the laryngeal reflexes were abolished. The initial propofol CPMpredicted had been used in a preliminary study and adjusted according to the clinical assessment of each dog for the induction of anesthesia. This infusion was interrupted when conditions favorable for endotracheal intubation were achieved; typically, each dog became laterally recumbent, and endotracheal intubation was achieved without resistance (associated with a light plane of anesthesia) or development of apnea (associated with a deep plane of anesthesia). Immediately thereafter, the propofol CPMpredicted was reduced to 3.0 µg/mL in the dogs receiving propofol and to 2.1 µg/mL in the dogs receiving the propofol and remifentanil. These concentrations were based on data from pilot studies performed in our laboratory; at these propofol CPMpredicted values, a moderate depth of anesthesia was established (determined on the basis of clinical signs that included absence of palpebral reflex, relaxed jaw tone, and absence of spontaneous respiratory efforts during mechanical ventilation).

In the dogs receiving the propofol-remifentanil treatment, the propofol CPMpredicted was reduced to 2.1 µg/mL because this represented a 30% reduction, compared with the value set for treatment with propofol alone (the minimum reduction in propofol CPMpredicted attributable to administration of remifentanil determined during our previous preliminary studies was 30%). The propofol CPMpredicted was maintained constant for 15 minutes before application of the supramaximal nociceptive stimulation used for Cp50predicted determination.

After intubation and positioning in left lateral recumbency of each dog (regardless of treatment), intermittent positive-pressure ventilation was applied during anesthesia by use of a volume-cycled ventilator and oxygen was provided at a flow rate of 2 L/min by use of a circle system to maintain ETCO2 at 30 to 35 mm Hg. Peak inspiratory pressure in each dog was adjusted to 7 to 15 cm H2O, and the respiratory rate was adjusted to maintain ETCO2 within the expected range. Ventilation settings included a low inspiratory flow sensor that allowed spontaneous respiratory efforts from the dog to trigger assisted ventilation cycles during application of the noxious stimulus and the determination of propofol Cp50predicted. Body temperature was measured.
by use of an esophageal probe placed at the level of the thoracic inlet; the temperature was maintained at 37.5°C to 38.5°C with the aid of a forced warm-air blanket throughout the study.

**Nociceptive stimulus**—The supramaximal nociceptive stimuli used for propofol 

*Propofol Cp50* determination consisted of an electrical current (50 V and 50 Hz for 10 milliseconds) administered to a forelimb of each dog by means of an electrical stimulator which was connected to 2 hypodermic needles (0.7 × 30 mm) placed 5 cm apart in the ulnar nerve region of the distal third of the radius. The stimulation protocol consisted of 2 single stimuli and 2 continuous stimuli of 3 seconds’ duration each, with 5-second intervals between stimuli. If a purposeful response was detected before cycle completion, the electrical stimulus was immediately discontinued.

The motor response to nociceptive stimulation was classified as positive (presence of gross purposeful movement) or negative (absence of gross purposeful movement). Motor response classification criteria were based on those used in a previous study.

**Propofol Cp50 determination in dogs receiving propofol alone**—If a negative motor response to the nociceptive stimulus was initially detected, the propofol 

*Propofol Cp50* predicted was reduced in increments of 0.5 µg/mL until it was 1.0 µg/mL and was then reduced in increments of 0.2 µg/mL. After each adjustment, an equilibration period (15 minutes) elapsed before the nociceptive stimulation was repeated; this was the interval considered necessary for propofol concentration in the tissues to achieve a steady state. This procedure was repeated until a positive motor response was detected. After detection of the positive motor response, propofol 

*Propofol Cp50* predicted was increased in increments of 0.2 µg/mL until the motor response to the nociceptive stimulus was inhibited.

If a positive motor response to the nociceptive stimulus was initially detected, the propofol 

*Propofol Cp50* predicted was increased in increments of 0.5 µg/mL until a negative motor response was detected. After each adjustment, an equilibration period (15 minutes) elapsed before the nociceptive stimulation was repeated. Propofol 

*Propofol Cp50* predicted was calculated as the mean value of the highest concentration at which purposeful movement was detected and the lowest concentration at which purposeful movement was not detected.

**Propofol Cp50 predicted determination in dogs receiving propofol and remifentanil**—The experimental procedure for dogs receiving the propofol-remifentanil treatment was similar to the procedure described for dogs receiving propofol alone, except that each dog also received 0.3 µg of remifentanil/kg/min via CRI starting immediately after induction of anesthesia and continuing throughout the experiment.

**Cardiopulmonary measurements**—Each dog was maintained in left lateral recumbency, and adhesive electrodes were placed for continuous lead II ECG monitoring. Heart rate and rhythm were obtained from the ECG traces. Catheterization of the right dorsal pedal artery was performed to allow monitoring of arterial blood pressures; the catheter was connected to a fluid-filled pressure transducer system for measurements of SAP, MAP, and DAP. Before each stimulus application, a blood sample (1 mL) was collected from the arterial catheter in a heparinized syringe and immediately analyzed by use of an automated blood gas analyzer. Cardiovascular variables (HR, SAP, DAP, and MAP), esophageal temperature, and blood pH, PaO2, PaCO2, and bicarbonate concentration were monitored continuously during each experiment. The cardiopulmonary measurements were recorded immediately before and after application of each nociceptive stimulus, but only measurements obtained immediately before stimulation in the highest concentration at which purposeful movement was detected and the lowest concentration at which purposeful movement was not detected were used to calculate the mean value (time of 

*Propofol Cp50* predicted determination). The mean values were used for comparisons between treatment groups.

**Data analysis**—Data are reported as mean ± SD. Values of propofol 

*Propofol Cp50* predicted for induction and maintenance of anesthesia, total infused dose of propofol, and time to completion of 

*Propofol Cp50* predicted determination (in minutes) were analyzed by use of an ANOVA for a random-block design followed by a Tukey test. For physiologic variables, data were analyzed by use of a t test after normal distribution of the data had been verified. All statistical analyses were performed by use of computer software; a value of P < 0.05 was considered significant.

**Results**

**Propofol Cp50 predicted determination**—The time required to complete the propofol 

*Propofol Cp50* predicted determination did not differ between treatments (Table 1). There was no difference in 

*Propofol Cp50* predicted for induction of anesthesia between treatments. Propofol 

*Propofol Cp50* predicted for the maintenance of anesthesia was decreased by 55% in the dogs receiving the propofol-remifentanil treatment, compared with the value in the dogs receiving propofol alone; thus, the addition of remifentanil to the anesthetic protocol reduced the total infusion dose of propofol used.

**Physiologic variables**—Although physiologic variables were monitored continuously during each experiment, only the values recorded at the time of 

*Propofol Cp50* predicted determination during each treatment were analyzed for comparison (Table 2). The main hemodynamic effect associated with inclusion of remifentanil in the anesthetic protocol was alteration in HR. Heart rate was decreased in dogs receiving the propofol-remifentanil treatment (61.3 ± 19.0 beats/min), compared with findings in dogs receiving the propofol treatment (78.2 ± 17.2 beats/min), and remained lower during the determination of propofol 

*Propofol Cp50* predicted; however, no cardiac dysrhythmia was detected in dogs receiving either treatment. Compared with dogs receiving propofol treatment, SAP was significantly decreased and SAP was slightly increased (albeit not significantly) in dogs receiving the propofol-remifentanil treatment. Values of arterial blood gas variables, ETCO2, and esophageal temperature were not significantly changed by inclusion of remifentanil CRI in the anesthetic protocol.
of propofol with another agent is widely used for anesthesia in human\textsuperscript{13} and veterinary medicine\textsuperscript{24}, by use of such a technique, the requirement for the hypnotic agent can be reduced and the adverse effects of each individual drug are minimized. In a study\textsuperscript{22} in dogs, the induction of anesthesia with a propofol-alfentanil combination administered via a TCI system was achieved with a lower propofol $C_{p\text{predict}}$ (1.5 $\mu$g/mL) than that needed for propofol alone (2.5 $\mu$g/mL).

The propofol pharmacokinetic model of Beths et al\textsuperscript{9} was developed from data collected from dogs of various ages and weights. With regard to propofol administration in humans, pharmacokinetic and pharmacodynamic differences among children, adults, and elderly patients have been identified.\textsuperscript{20,25} The variability of pharmacokinetics within a study population was described principally to variability in clearance from the central compartment.\textsuperscript{20} Pharmacokinetic simulation predicted optimized performance of the TCI system when gender and age covariates were applied, especially in elderly female patients.\textsuperscript{20}

A parallel can be inferred for dogs in that there are important differences in the pharmacokinetics of propofol use among breeds, ages, and weights.\textsuperscript{24} All of these factors could result in pharmacokinetic variability among animals and may explain differences in values of propofol $C_{p\text{predict}}$ among studies. Nevertheless, studies\textsuperscript{9,10} have revealed that use of TCI and this pharmacokinetic model\textsuperscript{9} in dogs allowed better propofol titration with improved control of anesthetic depth and fewer adverse effects, compared with results of manual infusion.

Following administration, the time required for transfer of propofol to the effect site depends on the concentration gradient, and an increase in the gradient reduces the time required to achieve induction of anesthesia.\textsuperscript{19} In our study, induction of anesthesia was achieved in 3 minutes.

Excitatory phenomena following the administration of propofol in dogs have been detected.\textsuperscript{30,27} Signs include muscle twitching, paddling, and limb rigidity with opisthotonus; some signs persist into the recovery period.\textsuperscript{30} In the present study, we observed muscle twitching with limb hyperextension during the induction phase in one of the dogs. Respiratory depression is an important complication of propofol anesthesia in people, cats, and dogs.\textsuperscript{27} It has been the most common-
ly reported adverse effect of propofol in dogs. Respiratory depression and hypotension are less pronounced when the drug is administered IV via slow injection and when a low total dose of the drug is used, both of which are characteristics of administration by use of a TCI device. Results of a study in humans indicated that there is less cardiorespiratory depression when anesthesia is induced with propofol administered by use of a TCI system, compared with a manual technique. This is most probably because the drug is administered via a TCI system at a relatively slower rate and induction dose is smaller.

Remifentanil, like other opioid drugs with a high affinity for OP3 (µ) receptors, induces considerable respiratory depression in a dose-dependent manner. Many authors recommend provision of supplemental oxygen when propofol is used during anesthesia because of the degree of respiratory depression it causes. Thus, in the present study, controlled ventilation was used to maintain adequate ventilation by providing 100% oxygen and maintaining ETCO 

\[ \text{\( \text{PaCO}_2 \) between 35 and 45 mm Hg. Because of this artificial ventilation, no significant differences in arterial blood pH, \( \text{PaO}_2 \), or \( \text{PaCO}_2 \) were detected between treatments. During the induction of anesthesia, apnea was not detected in any dog; the induction process was characterized as slow and smooth.

For volatile anesthetic agents, determination of MAC is a well-known standard experimental technique with which to define potency of inhalant anesthetics. Researchers use a lack of movement in response to painful stimulation as a measure of potency because it is an all-or-none response, which is easily measured in humans and in other animals. Supramaximal noceptive stimulation is the most potent stimuli used to assess the level of unconsciousness during anesthesia. Nociceptive stimulation is considered supramaximal if increases in the stimulus intensity do not result in changes in the observed response among the studied population. In the present study, electrical stimulation was used, which is comparable to other nociceptive methods such as mechanical stimulation. One of the requirements for determination of MAC for inhalant anesthetic agents is that sufficient time should be allowed to elapse to establish anesthetic equilibrium between blood and tissues; this state must also be attained prior to determination of Cp50 for agents that are administered IV. In our study, the interval allowed to elapse after propofol \( \text{CP}_{\text{predicted}} \) was adjusted before a stimulus was applied was 15 minutes; this interval was expected to allow equilibration of propofol concentrations between blood and brain and was based on findings of previous studies.

Although the Cp50 is traditionally used in studies as a measure of anesthetic potency, the Cp95 (the concentration at which only 5% of patients respond to stimulation) is more relevant in clinical practice because clinicians must adequately anesthetize all of their patients, not just half. The Cp95 is determined in population studies via logistic regression of data (ie, positive and negative responses from individuals). The method used in our study was not adequate to determine propofol Cp95 because the number of dogs evaluated was small and the responses were detected in the same 6 animals. However, the results of our study could be a reference for future population studies to determine propofol Cp99. With regard to inhalant anesthetics in humans, the concentration that yields a desired effect in 95% of the test population (ED95) of the agent is 20% to 40% higher than its MAC. Further studies will be necessary to determine whether a similar pattern is derived for propofol administered by use of a TCI system in dogs.

In the present study, the propofol-remifentanil treatment was commenced at a lower propofol \( \text{CP}_{\text{predicted}} \) (2.1 \( \mu \)g/mL) than that used for the propofol treatment (3.0 \( \mu \)g/mL); this adjustment was made so that the time required for determination of propofol \( \text{CP}_{\text{predicted}} \) was comparable between groups and to reduce the number of supramaximal stimuli that would be required during the maintenance infusion period for determination of \( \text{CP}_{\text{predicted}} \) for the propofol-remifentanil treatment if the \( \text{CP}_{\text{predicted}} \) was the same in both groups. Thus, desensitization at the site of electrical stimulation in the dogs receiving the propofol-remifentanil treatment and the possibility of decreased response to the electrical stimulus were avoided.

To maintain a satisfactory anesthetic condition for purposes of surgery, the propofol infusion rate should be varied according to a patient’s responsiveness to stimulation. Administration of propofol alone has proved unsatisfactory for major surgical procedures because it has minimal, if any, analgesic properties and because the dose required to suppress responses to surgery induces marked respiratory and cardiovascular depression. The somatic responses to noxious (electrical) stimuli among dogs anesthetized with propofol (administered IV by use of a TCI system) alone and in combination with CRI of remifentanil have not been investigated to our knowledge. The propofol \( \text{CP}_{\text{predicted}} \) among dogs receiving the propofol treatment was higher than that among dogs receiving the propofol-remifentanil treatment (2.0 vs 0.9 \( \mu \)g/mL). With regard to anesthesia in humans, the combination of propofol with remifentanil (as the analgesic component of the protocol) is becoming increasingly popular. Remifentanil is a potent synthetic opioid, and its use has been clinically investigated in dogs.

Infusion of propofol and remifentanil in dogs has been described, and it was concluded that remifentanil may have advantages over other short-acting opioids that are currently used in combination with propofol for TIVA because of its rapid action and because dogs anesthetized with a propofol-remifentanil combination recover completely without complications. Remifentanil has a terminal half-life in dogs of 6 minutes; its biotransformation is rapid with rapid establishment of equilibrium between concentrations in blood and the effect site. Therefore, the CRI of remifentanil was started immediately after the induction of anesthesia. In a previous study, a propofol CRI (0.2 \( \mu \)g/kg/min) administered with infusion of remifentanil at a variable rate (range, 0.25 to 0.31 \( \mu \)g/kg/min) attenuated autonomic responses (HR and SAP) during ovariohysterectomy in dogs that had been premedicated with acepromazine. A target of 3 to 3.5 \( \mu \)g of propofol/mL of
blood in combination with remifentanil administered at an infusion rate of 0.2 to 0.6 µg/kg/min provides adequate reflex suppression in dogs.  

Administration of remifentanil has been reported to reduce the MAC of enflurane by as much as 63% in dogs and to reduce the MAC of sevoflurane by 60% in humans. Remifentanil causes an exponential dose-dependent reduction in the MAC of isoflurane in humans; in 1 study, 77% and 91% reductions in isoflurane MAC were achieved via administration of 1.37 and 3.2 ng of remifentanil/mL, respectively.

In the present study, a 0.3 µg/kg/min CRI of remifentanil in conjunction with propofol administration was associated with a 55% reduction in propofol Cp50pred and resulted in substantial reduction in propofol requirements for maintenance of satisfactory depth of anesthesia. This reduction in the quantity of hypnotic agent required to maintain adequate anesthesia could reduce the dose-dependent hypotensive effects associated with propofol and improve cardiovascular stability.

A lack of motor response is not an accurate predictor of the ability of an agent to depress hemodynamic reactions during anesthesia. When propofol was administered alone in a study in humans, blood pressure and HR after stimulation increased considerably even at propofol concentrations greater than those needed to obtund motor reaction in patients exposed to noxious stimuli. In the present study, HR decreased considerably in dogs receiving the propofol-remifentanil treatment and remained lower than values in dogs receiving the propofol treatment throughout the observational period (i.e., the interval required for determination of Cp50pred)-. Opioids have a high affinity for OP3 receptors and exert major effects on the cardiovascular system. Most opioids reduce HR via a central mechanism that is mediated by the parasympathetic nerve; the negative chronotropic effects are influenced by dose and speed of administration. However, in our study, the changes in arterial blood pressure measurements were not clinically relevant; despite bradycardia in the dogs receiving the propofol-remifentanil treatment, there was a significant difference in DAP only between treatments. The mean MAP for the 2 treatments was approximately 80 mm Hg and could be attributed to a compensatory mechanism that increased systemic vascular resistance. Blood pressure changes during propofol anesthesia are concentration dependent. Blood concentration of propofol that is required to prevent movement after painful incision is decreased significantly by administration of fentanyl, alfentanil, and nitrous oxide. These adjuvants may have less deleterious effects on arterial blood pressure than the effects for propofol alone.

Target-controlled infusion of propofol in association with CRI of remifentanil has been proposed as a useful anesthetic technique for cardiac surgery in humans. This technique optimizes hemodynamic stability intraoperatively, establishes a stable anesthesia depth, and has a predictable and rapid recovery phase. In the present study, the TCI system was easy to use; a change in target concentration results in a change in anesthesia depth as would changing the position of a vaporizer dial. On the basis of the findings of our study, a propofol Cp50pred of 6.0 µg/mL may be recommended for slow, smooth, and controlled induction of anesthesia in nonpremedicated dogs. For maintenance of anesthesia in dogs, a remifentanil CRI at a rate of 0.3 µg/kg/min reduced requirements for propofol administered by use of a TCI system.

References


