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Anesthetic Properties of a Propofol Microemulsion in Dogs

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Abstract

Microemulsions of propofol with nanometer droplet diameter are alternative agents to soybean macroemulsions to induce anesthesia and may have important advantages. We used a propofol (10 mg/ml) microemulsion (particle diameter 24.5 ± 0.5 nm) and a commercial macroemulsion to induce anesthesia in dogs ($n=10$) using a randomized, crossover design separated by a 7 day rest interval. Endpoints were loss of leg withdrawal following a toe pinch and changes in vital signs. Venous blood samples were acquired at multiple times to measure plasma propofol concentrations and indices of erythrocytes, leukocytes and coagulation. All dogs were rendered insensitive to pain followed by successful recovery without noticeable complications. Comparing indices between microemulsion and macroemulsion formulations, no differences were noted with respect to dose (10.3 ± 1.2 and 9.7 ± 1.6 mg/kg, respectively, $P=0.39$), time to induction (1.0 ± 0.1 and 1.0 ± 0.2 min, $P=0.39$), time to recovery (17.4 ± 4.6 and 18.2 ± 3.8 min, $P=0.70$), heart rate ($P=0.62$), blood pressure ($P=0.81$), respiratory rate ($P=0.60$), hemogram parameters, prothrombin time ($P=0.89$),

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activated partial thromboplastin time ($P=0.76$), fibrinogen concentration ($P=0.52$), platelet concentration ($P=0.55$), or plasma propofol concentrations ($P=0.20$). Induction with a propofol microemulsion or macroemulsion did not significantly vary with respect to vital signs, the hemogram, clotting parameters, and plasma propofol concentrations.

Keywords

propofol; macroemulsion; microemulsion; intravenous anesthesia

Introduction

Propofol remains a popular intravenous agent to induce anesthesia and is conventionally formulated in a soybean oil macroemulsion. However, propofol can also be combined with biocompatible surfactants to form transparent, colorless, and thermodynamically stable, oil-in-water microemulsions of nanometer diameter without the need for excipient oils such as soybean oil (1). In these microemulsions, propofol serves the physical role as the core of the particles since this drug exists as an oil at room temperature and as the active pharmaceutical agent to induce anesthesia. Microemulsion technology offers theoretical advantages over macroemulsions if the release of free propofol is delayed with this technology (2-4). Some of these potential advantages include less pain with injection, longer shelf life due to the thermodynamic stability of microemulsions, and a decreased propensity to support bacterial growth due to the absence of soybean oil as a nutrient.

Previously, we have shown that these microemulsions can be used in vivo to induce anesthesia in rats (1). In that report, however, the limited blood volume (e.g., ~25-30 ml) of the rat compared to that volume (e.g., ~30 ml) necessary to repeatedly sample blood precluded determining possible interactions between the propofol particles and blood, the first biological tissue encountered with intravenous injection, and measurement of propofol concentrations in blood. Therefore, the present study was conducted in a larger animal model (i.e., dog) using a randomized, crossover design in order to determine possible alteration of erythrocytes, leukocyte, and platelet cell populations, and potential changes in coagulation parameters caused by microemulsions and macroemulsions of propofol. In addition, the concentrations of propofol in blood and some clinical effects of anesthesia were measured.

Methods and Materials

Propofol Formulations

Propofol (molecular weight 178.27) used in this study was a generous gift from the Albemarle Corporation (Baton Rouge, LA, U.S.A.). Purified poloxamer 188, a nonionic coblock polymer consisting of polyethylene and polypropylene monomers, was acquired from the BASF Corporation (Florham Park, NJ, U.S.A.). The sodium salts of C₈ fatty acid were supplied by Sigma Chemical Co. (St. Louis, MO, U.S.A.). The propofol microemulsion was prepared by combining propofol (10 mg/ml) with purified poloxamer 188 (50 mg/ml), and a fatty acid salt (2.1 mg/ml) in a normal saline (9 mg/ml NaCl) bulk media. Water was ultra-purified using a water purification system (Nanopure, Barnstead/Thermolyne, Dubuque, IA, U.S.A.) to provide a minimal electrical resistance of 18.2 MΩ. Following agitation with a magnetic stirrer, these components combined to form microemulsions. We then adjusted the pH to 7.40 using either HCl or NaOH as necessary. The microemulsion was kept under a nitrogen head to delay oxidation of propofol as occurs with commercial formulations of propofol. Before administration, the propofol microemulsion was filtered through a 0.45 μm sterile filter, but the macroemulsion

((Diprivan®, AstraZeneca Pharmaceuticals, Wilmington, DE, U.S.A.) was not filtered as it was assumed to be sterile as packaged by the manufacturer. Synthesis of microemulsions resulted in clear, colorless formulations of propofol. The mean diameter of the particles was 24.5 ± 0.5 nm as measured using a submicron particle size analyzer (90Plus, Brookhaven Instruments Corporation, Holtsville, NY, U.S.A.) as described previously with other physical parameters (5).

Animal Preparation

The Institutional Animal Care and Use Committee of Calvert Laboratories (Olyphant, PA, U.S.A.) approved the study protocol prior to investigation. Treatment of animals was in accordance with the conditions specified in the Guide for the Care and Use of Laboratory Animals.(6) Ten purpose-bred and experimentally naive beagles (Marshall Bioresources, North Rose, NY, U.S.A.) aged 7-8 months and weighing 7.0-8.9 kg were identified by ear tattoo. All animals had access to certified canine diet (Teklad, Harlan, Indianapolis, IN, U.S.A.) up to 400 g/day. Tap water was available *ad libitum* to each animal *via* an automatic watering device. Study animals were acclimated to their housing for a minimum of five days prior to entering the experimental protocol. After being fasted for 16-20 hours, dogs were weighed and prepared for the experiment. Peripheral intravenous catheters were inserted in the right and left leg veins for intravenous administration of propofol formulations and the collection of whole blood samples, respectively.

Experimental Protocol

On the day of experimentations, dogs (n=10) were randomized to receive either the propofol microemulsion (n=5) or macroemulsion (n=5) intravenously at a rate of 10 mg/kg/min *via* a microprocessor-controlled syringe pump in order to obviate potential confounding influences caused by variable administration rates from manual injection. During the infusion, the endpoint of anesthetic induction was the time necessary to cause the loss of reflexive withdrawal of the leg following a toe pinch every 15 sec with a rubber-shod clamp. After loss of withdrawal of the leg, the infusion was discontinued. The total drug dose to cause induction was the mass of propofol required to cause loss of leg withdrawal. Thereafter, the subject was observed for recovery of the withdrawal to a toe pinch. Also, we measured the heart rate by electrocardiography (Pagewriter, Hewlett Packard Company, Palo Alto, CA, U.S.A.), indirect peripheral blood pressure (9301V, Cardell Veterinary, MINRAD Inc., Buffalo, NY, U.S.A.), and respiratory rate for each subject at the following time points: pre-dose, immediately post-induction at one minute, and every five minutes thereafter until dogs emerged from anesthesia. The electrocardiogram was examined for arrhythmias. In addition to these parameters, animals were observed for apnea or other signs of respiratory distress. The dogs were allowed to recover and then returned to the kennel. After the first set of experiments, dogs were recovered for at least 7 days before being crossed over to receive the formulation in the opposite limb of the study. Thus, dogs who received microemulsion (or macroemulsion) first were switched to then receive the opposite formulation. Following anesthetic induction in the second limb of the investigation, dogs were recovered for at least 7 days before the investigation was terminated.

Blood Sample Acquisition and Processing

During these experiments, blood samples were taken for two purposes. *First*, samples were secured one minute before induction and at times 1, 5, 10, 15, and 20 min after induction (or until the dog emerged from anesthesia) to measure the propofol concentration in plasma. The blood samples were acquired from a second intravenous cannula placed in a vein on a leg contralateral to that used for propofol injection. These blood samples (1-2 ml each) for assessment of propofol concentration were stored in non-additive blood tubes and centrifuged at 3,000 revolutions/min. The resultant supernatant was aspirated and stored at

-80 °C until thawed for measurement of propofol concentrations using a liquid chromatography/mass spectrometry/mass spectrometry technique (API 4000, Applied Biosystems, Foster City, CA, U.S.A) employing a method previously described by this laboratory (7,8). *Second*, blood samples (4 ml each) were drawn to determine the effects of the propofol formulations on the hemogram (Advia-120 Analyzer, Bayer Diagnostics, Tarrytown, New York), prothrombin time, activated partial thromboplastin time, and fibrinogen concentrations (MLA-900 Coagulation Timer, Becton Dickinson, Sparks, MD, U.S.A.). These blood samples were collected pre-induction, immediately post-induction when concentration of propofol and excipients would be expected to peak in the plasma, and during recovery from anesthesia. In all cases, the maximum amount of blood collected during this investigation was limited to less than 1% of the body weight of each animal.

Statistical Analysis

The sample size calculation was centered around the dose to cause pain insensitivity in order to estimate a probable sample size. We considered a 25% reduction in dose of 10 mg/kg to be clinically relevant. Assuming a SD in all groups of 2.0 mg/kg for this variable, a two-sided type I error protection of 0.05, and a power of 0.80, approximately 8-9 dogs in each group were required to reveal a statistically significant difference among study groups using an analysis of variance design that allows sample size calculation for results with paired data (StatMate 2 for Windows, GraphPad Software Inc., San Diego, CA).

Measurements are reported as mean±standard deviation. Statistical analysis was performed with SigmaStat 3.1 (Systat Software, Inc., Point Richmond, CA, U.S.A.). Prior to parametric testing, the assumption of normality was validated using the Kolmogorov-Smirnov test with Lilliefors' correction. For normally distributed data with two groups, the paired t-test was used with two-tailed protection. For normally distributed data with more than two groups, two-way (factor 1: propofol formulation; factor 2: time) repeated measures analysis of variance was used to test for overall statistical significance followed by Tukey post-hoc pairwise testing, when appropriate, to analyze multiple comparisons between different formulations of propofol. Missing data points in the dog pharmacokinetic analysis were accounted for using Type IV sums of squares averaging to compensate for empty cells (9). For nonparametric data, Friedman repeated measures analysis of variance on ranks was used followed by Tukey testing when appropriate. $P<0.05$ was considered to be statistically significant.

Results

Anesthetic Induction Properties in the Dog

All dogs had anesthesia induced with subsequent recovery when injected with either formulation of propofol. The mean dose of microemulsion ($n=10$) or macroemulsion ($n=10$) to cause loss of leg withdrawal was 10.3 ± 1.2 and 9.7 ± 1.6 mg/kg, respectively, ($P=0.39$) at times 1.0 ± 0.1 and 1.0 ± 0.2 min, respectively. Although anesthetic induction caused marked changes in the heart rate ($P<0.001$), blood pressure ($P<0.001$) and respiratory rate ($P<0.001$) over time, these changes occurred in both groups of animals that received either the microemulsion or macroemulsion (fig. 1). There were no significant differences with respect to group assignment in the heart rate ($P=0.62$), blood pressure ($P=0.81$), or respiratory rate ($P=0.60$) for dogs administered the microemulsion or macroemulsion. There was no electrocardiographic evidence of arrhythmias. Neither apnea nor respiratory distress was observed. The durations of loss of pain insensitivity caused by these doses of propofol were 17.4 ± 4.6 and 18.2 ± 3.8 min for the microemulsion and macroemulsion, respectively ($P=0.70$).

Effects on Blood

Data stratified by group assignment (microemulsion, macroemulsion) and time (pre-induction, post-induction, recovery period) for parameters of the erythrocyte population are presented in table 1. No differences were observed between formulations with respect to indices of erythrocyte populations as noted by the statistical values in table 1. However, significant reductions in some indices were observed with respect to time. There were decrements in the red blood cell count ($P<0.001$), hemoglobin concentration ($P<0.001$), hematocrit ($P<0.001$), absolute reticulocyte count ($P=0.002$), and relative reticulocyte count ($P=0.030$) over time for both groups. A decrease in the total concentration of white blood cells also occurred ($P=0.004$). Neither the microemulsion nor macroemulsion of propofol affected platelet concentration, fibrinogen concentration, prothrombin time, or activated partial thromboplastin time (table 1). In one dog that received the propofol macroemulsion, the platelet concentration was measured to be 8,000 platelets/ μ l in the recovery period although the concentrations in the same dog determined at pre-induction and post-induction were 240,000 and 233,000 platelets/ μ l, respectively. Light microscopic examination of the specimen showed no clumping of platelets. Therefore, this outlying data point was retained and accounts for the large standard deviation for this group (111,000 platelets/ μ l) compared to the standard deviations for other groups (39,000-50,000 platelets/ μ l).

Propofol Concentrations

The plasma concentrations of propofol were measured at various times following administration of propofol as noted in table 2. Following a bolus of propofol at time 0 min, a large peak propofol concentration was measured followed by rapid decrements in the concentrations at times 1, 5, and 10 min. At times 15 and 20 min, increases in the propofol concentrations were observed for both the macroemulsion and microemulsions groups. Notwithstanding these time-related changes, no significant differences in plasma propofol concentrations were noted at times 1, 5, 10, 15, or 20 min between the dogs receiving the microemulsion or macroemulsion formulations.

Discussion

In this investigation, we observed the dose of propofol, micro- or macro-emulsions, administered to dogs to induce anesthesia along with possible effects on blood, the first tissue encountered by the formulations. The measured parameters of anesthesia, vital signs, indices of blood cell populations or thrombosis, and plasma concentrations of propofol did not significantly differ between the groups of animals given either the propofol microemulsion or macroemulsion.

Anesthetic Properties

In these studies, all animals experienced rapid induction of anesthesia as assessed by loss of leg withdrawal to a noxious stimulus with mean propofol doses of approximately 10 mg/kg for both the microemulsion and macroemulsion. This dose of propofol is greater than that previously reported in other studies investigating anesthetic induction in unpremedicated dogs using propofol formulated in a macroemulsion although direct comparison is problematic because drug administration in the studies differed with respect to dose and type (bolus vs. infusion). In those reports (10-15), the mean dose of propofol noted ranged from 3.8-6.9 mg/kg with a mean $\pm$ standard error of the mean calculated from those six studies of 5.8 $\pm$ 0.5 mg/kg. Because the mean dose observed by the present investigators was greater for both the macroemulsion and microemulsion, this increase may be due to differences in the study protocol including a faster rate of propofol infusion (10 mg/kg/min) and possibly the use of younger animals (i.e., 8 month old dogs vis-à-vis adult dogs) in the present report. Although we can not identify any studies detailing age-related effects on propofol dose in

dogs, previous investigations conducted in rats and humans demonstrate that greater doses are required in younger, compared to older, subjects (16). For example, Schnider and colleagues elegantly demonstrated that younger (25 years) adult patients need higher infusion rates of propofol than older (50 and 75 years) subjects (17). Others have shown that the dose of propofol required for anesthetic induction in children is inversely related to age (18-20). Likewise, we observed a proportional increase in propofol macroemulsion dose (9.7 mg/kg / 5.8 mg/kg or 1.67-fold greater) for younger dogs compared to the mixed age dog populations calculated from the previously reported dog studies (10-15). In addition, the duration of anesthesia (from induction to recovery) was similar to that previously reported for dogs (i.e., we observed a mean duration of pain insensitivity to be 18.2 min whereas Watkins and colleagues reported a value of 18 min) (10). Therefore, the effects of propofol administered in either formulation are consistent with previously reported values in dogs. One limitation of this type of investigation remains that any conclusions are limited to the dose studied. Extrapolation to other doses and sustained infusion of propofol require additional work and evidence. Furthermore, any extension of this data to potential human use should be interpreted cautiously because of possible species differences and the need for additional safety investigations (e.g., dose escalation studies).

Propofol Concentrations

The plasma propofol concentrations reported in the present study demonstrated a high peak concentration (25-32 μ M) followed by rapid decline. Similar findings for the propofol macroemulsion were noted by Zoran and colleagues who observed peak concentrations of 2.3 μ g/ml (12.9 μ M) and 3.29 μ g/ml (18.5 μ M) in mixed breed dogs and Greyhounds, respectively (21). Similarly, Cockshott and colleagues noted peak concentrations of approximately 4 μ g/ml (22.4 μ M) in specimens obtained from dogs following injection of a 7 mg/kg propofol bolus (22). The lesser concentrations reported for previous investigations may be due to the fact that the dogs enrolled in their previous studies received less propofol (5 mg/kg) over a longer time period than did dogs in our investigation. The observation of secondary peaks in plasma propofol concentrations at times 15-20 min in our study was unexpected by the investigators. We had previously hypothesized the existence of a single, large peak concentration of propofol immediately after bolus injection followed by steady decrements. Two possible reasons may account for these secondary peaks in propofol concentrations. First, this finding may be an artifact of the protocol. We stopped sampling blood for propofol concentrations when dogs emerged from anesthesia. Therefore, dogs with the least plasma propofol concentrations were excluded from the summary data at times 15 and 20 min. This event would tend to cause the mean propofol concentrations to increase. Second, this phenomenon has been observed by others studying the pharmacokinetics of propofol in both dogs (21) and humans (23,24). For example, Zoran and colleagues described a secondary peak concentration of propofol in 5 of 8 mixed breed dogs and 8 of 10 Greyhounds (21). Similar to the present investigation, they noted that this peak occurred at the time that the dogs emerged sufficiently to achieve a sternal position (i.e., righting reflex). The exact cause of this secondary peak is unknown, but previously suggested reasons include changes in cardiac output associated with movement following anesthesia, influx of propofol from peripheral tissues with loss of venodilation caused by propofol, use of venous (vis-à-vis arterial) sampling, and changes in blood components due to splenic contraction in dogs associated with phlebotomy necessary for acquiring multiple blood specimens (21).

In summary, we have shown that propofol formulated as a microemulsion can be used successfully to induce anesthesia in dogs in a manner that does not significantly vary from induction caused by a commercially available propofol macroemulsion.

Implications Statement

A clear, colorless microemulsion or an opaque macroemulsion of propofol was used to induce anesthesia in dogs and did not significantly vary with respect to dose, time to induction and recovery, vital signs, hemogram, coagulation time, or plasma propofol concentrations from one preparation to the other.

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References

1. Morey TE, Modell JH, Shekhawat D, et al. Preparation and Anesthetic Properties of Propofol Microemulsions in Rat. *Anesthesiology*. In Press.
2. Centers for Disease Control and Prevention. Postsurgical Infections Associated with an Extrinsically Contaminated Intravenous Anesthetic Agent -- California, Illinois, Maine, and Michigan, 1990. *MMWR* 1990;39:426–7. [PubMed: 2113169]
3. Doenicke AW, Roizen MF, Rau J, et al. Reducing pain during propofol injection: the role of the solvent. *Anesth Analg* 1996;82:472–4. [PubMed: 8623945]
4. Ho CM, Tsou MY, Sun MS, et al. The optimal effective concentration of lidocaine to reduce pain on injection of propofol. *J Clin Anesth* 1999;11:296–300. [PubMed: 10470630]
5. Morey TE, Varshney M, Flint JA, et al. Treatment of local anesthetic-induced cardiotoxicity using drug scavenging nanoparticles. *Nano Letters* 2004;4:757–9.
6. Committee to Revise the Guide for the Care and Use of Laboratory Animals. *Guide for the Care and Use of Laboratory Animals*. Washington, D.C: National Academy Press; 1996.
7. Bajpai L, Varshney M, Seubert CN, Dennis DM. A new method for the quantitation of propofol in human plasma: efficient solid-phase extraction and liquid chromatography/APCI-triple quadrupole mass spectrometry detection. *J Chromatogr B Analyt Technol Biomed Life Sci* 2004;810:291–6.
8. Bajpai L, Varshney M, Seubert CN, et al. Mass spectral fragmentation of the intravenous anesthetic propofol and structurally related phenols. *J Am Soc Mass Spectrom* 2005;16:814–24. [PubMed: 15907697]
9. Milliken, GA.; Johnson, DE. *Analysis of Messy Data, Volume I: Designed Experiments*. Boca Raton, FL: CRC Press LLC; 1996.
10. Watkins SB, Hall LW, Clarke KW. Propofol as an intravenous anaesthetic agent in dogs. *Vet Rec* 1987;120:326–9. [PubMed: 3495923]
11. Watney GC, Pablo LS. Median effective dosage of propofol for induction of anesthesia in dogs. *Am J Vet Res* 1992;53:2320–2. [PubMed: 1476315]
12. Geel JK. The effect of premedication on the induction dose of propofol in dogs and cats. *J S Afr Vet Assoc* 1991;62:118–23. [PubMed: 1770481]
13. Weaver BM, Raptopoulos D. Induction of anaesthesia in dogs and cats with propofol. *Vet Rec* 1990;126:617–20. [PubMed: 2378046]
14. Sano T, Nishimura R, Mochizuki M, et al. Clinical usefulness of propofol as an anesthetic induction agent in dogs and cats. *J Vet Med Sci* 2003;65:641–3. [PubMed: 12808220]
15. Morgan DW, Legge K. Clinical evaluation of propofol as an intravenous anaesthetic agent in cats and dogs. *Vet Rec* 1989;124:31–3. [PubMed: 2783794]

16. Schnider TW, Minto CF, Gambus PL, et al. The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. *Anesthesiology* 1998;88:1170–82. [PubMed: 9605675]
17. Schnider TW, Minto CF, Shafer SL, et al. The influence of age on propofol pharmacodynamics. *Anesthesiology* 1999;90:1502–16. [PubMed: 10360845]
18. Manschot HJ, Meursing AE, Axt P, et al. Propofol requirements for induction of anesthesia in children of different age groups. *Anesth Analg* 1992;75:876–9. [PubMed: 1443704]
19. Westrin P. The induction dose of propofol in infants 1–6 months of age and in children 10–16 years of age. *Anesthesiology* 1991;74:455–8. [PubMed: 2001024]
20. Aun CS, Short SM, Leung DH, Oh TE. Induction dose-response of propofol in unmedicated children. *Br J Anaesth* 1992;68:64–7. [PubMed: 1739570]
21. Zoran DL, Riedesel DH, Dyer DC. Pharmacokinetics of propofol in mixed-breed dogs and greyhounds. *Am J Vet Res* 1993;54:755–60. [PubMed: 8317769]
22. Cockshott ID, Douglas EJ, Plummer GF, Simons PJ. The pharmacokinetics of propofol in laboratory animals. *Xenobiotica* 1992;22:369–75. [PubMed: 1496826]
23. Cockshott ID, Briggs LP, Douglas EJ, White M. Pharmacokinetics of propofol in female patients. Studies using single bolus injections. *Br J Anaesth* 1987;59:1103–10. [PubMed: 3499160]
24. Kay NH, Uppington J, Sear JW, Allen MC. Use of an emulsion of ICI 35868 (propofol) for the induction and maintenance of anaesthesia. *Br J Anaesth* 1985;57:736–42. [PubMed: 3874642]

Figure 1. Time-dependent effects of a propofol microemulsion or macroemulsion on heart rate (panel A), mean arterial blood pressure (panel B), and respiratory rate (panel C) in dogs. Data is expressed as mean $\pm$ standard deviation. The dogs were subjected to a randomized, crossover design with dogs receiving both the microemulsion (closed squares) and macroemulsion (open circles) propofol formulations.

Table 1
Effects of Propofol *Microemulsions* (Micro) and *Macroemulsions* (Macro) on Parameters of the Blood Indices in Dog.

Parameter	Pre-Induction		Post-Induction		Recovery		ANOVA	
	Micro	Macro	Micro	Macro	Micro	Macro	Micro vs. Macro	
RBC ($10^6/\mu\text{l}$)	6.04 $\pm$ 0.45	6.13 $\pm$ 0.43	5.99 $\pm$ 0.41	6.07 $\pm$ 0.34	5.47 $\pm$ 0.71	5.40 $\pm$ 0.50		0.41
Hemoglobin (g/dl)	14.1 $\pm$ 0.8	14.3 $\pm$ 0.8	14.0 $\pm$ 0.7	14.4 $\pm$ 0.5	12.7 $\pm$ 1.4	12.6 $\pm$ 1.0		0.66
Hematocrit (%)	42.0 $\pm$ 2.3	42.7 $\pm$ 2.7	41.9 $\pm$ 2.0	42.4 $\pm$ 1.5	37.9 $\pm$ 4.0	37.5 $\pm$ 2.8		0.78
MCV (fl)	69.6 $\pm$ 2.4	69.7 $\pm$ 2.3	70.0 $\pm$ 2.5	69.9 $\pm$ 2.2	69.6 $\pm$ 2.3	69.5 $\pm$ 2.2		0.84
MCH (pg)	23.4 $\pm$ 0.7	23.3 $\pm$ 0.7	23.4 $\pm$ 0.8	23.7 $\pm$ 0.7	23.3 $\pm$ 0.7	23.3 $\pm$ 0.8		0.45
MCHC (g/dl)	33.7 $\pm$ 0.5	33.5 $\pm$ 0.6	33.5 $\pm$ 0.4	33.9 $\pm$ 0.4	33.5 $\pm$ 0.5	33.6 $\pm$ 0.4		0.48
Reticulocytes ($10^3/\mu\text{l}$)	67.3 $\pm$ 18.7	73.9 $\pm$ 33.8	67.4 $\pm$ 17.5	64.3 $\pm$ 20.3	53.7 $\pm$ 11.5	50.8 $\pm$ 12.4		0.97
Reticulocytes (%)	1.12 $\pm$ 0.30	1.21 $\pm$ 0.50	1.15 $\pm$ 0.28	1.06 $\pm$ 0.36	1.01 $\pm$ 0.22	0.96 $\pm$ 0.30		0.88
WBC ($10^3/\mu\text{l}$)	8.55 $\pm$ 1.04	9.48 $\pm$ 2.20	7.24 $\pm$ 1.50	8.81 $\pm$ 2.23	7.72 $\pm$ 1.30	8.15 $\pm$ 2.79		0.14
Platelets ($10^3/\mu\text{l}$)	338 $\pm$ 43	330 $\pm$ 48	319 $\pm$ 39	322 $\pm$ 50	331 $\pm$ 42	299 $\pm$ 111		0.55
Fibrinogen (mg/dl)	202 $\pm$ 30	219 $\pm$ 80	202 $\pm$ 23	227 $\pm$ 87	204 $\pm$ 30	206 $\pm$ 81		0.52
PT (s)	8.7 $\pm$ 0.4	8.7 $\pm$ 0.3	9.0 $\pm$ 0.4	9.0 $\pm$ 0.4	8.9 $\pm$ 0.4	8.9 $\pm$ 0.5		0.89
aPTT (s)	10.1 $\pm$ 0.6	10.2 $\pm$ 0.4	10.3 $\pm$ 0.5	10.3 $\pm$ 0.4	10.2 $\pm$ 0.6	10.1 $\pm$ 0.6		0.76

Table 1 Notes: Data are reported as mean $\pm$ standard deviation for 10 dogs per formulation. P values denote differences between formulations.

Abbreviations: RBC, red blood cell concentration; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; WBC, white blood cell concentration; PT, prothrombin time; aPTT, activated partial thromboplastin time. The uncorrected reticulocytes count was used since no dog was anemic.

Table 2

Plasma Propofol Concentration after Induction of Anesthesia in Dogs.

Time (min)	Plasma Propofol Concentration (μM)	
	Microemulsion (n)	Macroemulsion (n)
-1	<0.05 (10)	<0.05 (10)
1	25.2 ± 8.7 (10)	31.7 ± 14.1 (10)
5	2.9 ± 1.2 (10)	3.7 ± 1.9 (10)
10	1.9 ± 0.6 (10)	2.1 ± 0.7 (10)
15	2.3 ± 1.3 (9)	1.6 ± 0.5 (9)
20	1.9 ± 1.4 (4)	2.4 ± 1.1 (6)

Notes: The number in parentheses indicates the number of observations at a given time. The limit of quantitation was 0.05 μM. Data are reported as mean±standard deviation. Overall P value for formulation differences was 0.20.