Pharmacokinetic profile in relation to anaesthesia characteristics after a 5% micellar microemulsion of propofol in the horse

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Background. To define the pharmacokinetic profile of propofol 5% microemulsion formulation in horses.

Methods. First, propofol was administered as bolus injection (2 mg kg⁻¹) to six xylazine-sedated horses. Secondly, after sedation and bolus injection, propofol was maintained with continuous infusion for 3 h [8.1 (SD 3.2) mg kg⁻¹ h⁻¹] to the same six horses. Thirdly, in two horses, a commercial propofol was used for comparison. Response to noxious stimulation was used to evaluate analgesia. Venous blood samples were obtained to measure propofol plasma concentration using liquid chromatography-mass spectrometry analysis. The plasma concentrations were related to the anaesthesia characteristics to determine the ED₅₀.

Results. The pharmacokinetic profile of propofol is best characterized by a non-compartmental model. The mean (confidence interval) for area under plasma concentration–time curve, elimination half-life, mean residence time, and clearance was 41 min (±7.7), 44.8 min (±21.3), 13.7 min (±3.2), and 45.8 ml min⁻¹ kg⁻¹ (±6.5), respectively. Linear regression analysis showed a correlation between plasma concentration and infusion rate (r²=0.47). Most propofol infusion rates did not inhibit the response to noxious stimulation and rates above 11.9 mg kg⁻¹ h⁻¹ caused involuntary muscle contractions. Better recoveries were associated with lower propofol plasma concentrations. Propofol plasma concentration frequently increased when horses woke from anaesthesia.

Conclusions. Caution is warranted when propofol is used for continuous infusion due to variable kinetics, myoclonal activity, poor analgesia, and less desirable recovery quality.

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The characteristics of propofol (2,6-diisopropylphenol) makes it frequently a desirable agent to induce and maintain anaesthesia in both human and some veterinary patients.1–3 These characteristics are: rapid onset of action, short duration, rapid and extra-hepatic metabolism, and no biologically active metabolites.4,5 Studies have shown an additional benefit for propofol use in horses. Propofol improves the quality of recovery from anaesthesia by preventing violent movements and facilitating the transition from lateral recumbency to the standing position in a coordinated manner.5–7

Historically, propofol has been available only as a 1% oil emulsion preparation with droplet sizes of 100–200 nm. Newer formula, including micellar microemulsions of propofol, has been developed to further improve the characteristics of the drug. Microemulsion formulations are characterized by micellar droplet sizes below 20 nm, stable oil in water emulsions, optically clear, and exhibit a broad antimicrobial spectrum.4,8–10 In this study, we tested a propofol micellar microemulsion formulation with specific advantages for equine anaesthesia that include: higher drug concentration (5%), optically clear, 12 nm
diameter micelles, reduced production cost, and increased resistance to microbial growth.

The purpose of the study was to define the pharmacokinetic profile in relation to the anaesthetic and recovery characteristics of this newer propofol formulation in the horse. We tested the propofol as a single dose and with a constant rate of infusion to estimate the ED_{50} in the horse. In addition, we compared the effect of an i.v. infusion from this novel propofol with an i.v. infusion of a commercially available formula. Previous reports from our laboratory described the cardiovascular, respiratory, blood chemistry, and recovery characteristics of this propofol formulation in horses.\textsuperscript{7,11}

**Methods**

Six healthy horses were studied (five thoroughbreds and one standardbred). There were four geldings and two mares with [mean (SD)] age of 9 (2) yr old (range 6–12 yr) and weight of 557 (22) kg. The horses were obtained from the university’s equine research facility (Center for Equine Health), and the study protocol was approved by the Animal Use and Care Committee at the University of California, Davis.

Each horse was anaesthetized twice, with at least a 2 month interval between phases using a new 5% micellar microemulsion propofol formulation. This new formulation is optically clear and has 12 nm diameter micelles and low microbial growth. The propofol is dissolved in normal sterile saline and stabilized with the non-ionic parenteral pharmaceutical emulsifier PEG-600 15-hydroxystearate [MEDDS, Inc. (Micro Emulsion Drug Delivery Systems), Rancho Cucamonga, CA, USA]. Details from the new propofol microemulsion formulation were previously published.\textsuperscript{7} At random, two of the horses were selected and anaesthetized a third time with a commercially available propofol formulation to compare the results (propofol, Abbott, Abbott Park, IL, USA). Horses were fasted for 12 h before anaesthetic induction but water was available at all times.

After aseptic preparation, a 14 G 13 cm catheter was inserted percutaneously in the right and left external jugular veins before anaesthesia. The catheter placed in the left jugular vein was used for drug administration and the one placed in the right jugular vein for blood sampling. Anaesthesia was induced in a padded stall with the horse’s head supported using a long rope that was attached to a ring embedded in the wall.\textsuperscript{12,13} If the horse moved in response to the noiceptive stimulus, the propofol infusion rate was increased by 0.04 mg kg\(^{-1}\) min\(^{-1}\). If the horse did not move, the propofol infusion rate was decreased by 0.04 mg kg\(^{-1}\) min\(^{-1}\). The propofol infusion rate changes represent \~30% of the average calculated initial infusion rate. When the propofol infusion rate was changed, at least 30 min were allowed in an attempt to reach steady plasma concentration before the electrical stimulus was applied. Blood samples to determine the actual propofol plasma concentrations were obtained before stimulation.

The propofol plasma concentrations were measured from blood samples obtained during both infusion and recovery periods. For the anaesthesia recovery period, the plasma propofol concentrations were correlated to the times for first movement, first attempt to achieve sternal recumbency, first attempt to standing, and when the horses stood.

The recovery for all horses at the end of the propofol infusion period (3 h) was without assistance by placing them in a padded recovery stall as described for phase I.

Heart rate and rhythm, arterial partial pressure of O\(_2\) and CO\(_2\), pH, packed cell volume, plasma protein concentration, inspired and expired O\(_2\) and CO\(_2\) concentrations, ventilatory frequency, pharyngeal temperature, and serum concentrations were recorded. The recovery characteristics are correlated to the propofol plasma concentrations.

**Phase II (second anaesthesia: continuous infusion)**

The horses received the same sedation and induction drugs as described for phase I. After anaesthesia induction, orotracheal intubation (cuffed tracheal tube; 30 mm internal diameter) was performed and the horses were hoisted and positioned in left lateral recumbency on a thick foam pad. The tracheal tube was connected to a standard large animal semiclosed anaesthetic circle system providing a measured inspired oxygen fraction >0.95. The horses were allowed to breathe spontaneously. Five minutes after the induction of bolus injection, a syringe pump was started with the constant infusion of 5% micellar microemulsion propofol at a specific rate for each horse guided by previously determined individualized pharmacokinetic parameters from phase I (see Results). The infusion was adjusted according to the response from a nociceptive electrical stimulus of the oral mucous membrane. The electrical stimulation was chosen as the most common method to determine the response to noxious stimulation in anaesthetized horses. The stimulus consisted of 50 V, 5 Hz, 10 ms until purposeful movement was observed or for 1 min of duration as previously described for the horse.\textsuperscript{12,13}
biochemical analyses during the study were monitored and reported elsewhere.11

**Commercial propofol (third anaesthesia: continuous infusion)**

Following the same phase II methods, two randomly chosen horses were anaesthetized a third time with a commercial propofol formulation. The infusion rates used were the same as in phase II for these two horses. The propofol plasma concentrations were measured during the infusion rate and the recovery period as in phase II. The goal was to compare the anaesthetic characteristics from the 5% micellar microemulsion propofol with the commercial formula.

**Venous blood samples**

After proper scavenging of blood from the right jugular catheter, 20 ml of blood was obtained for propofol measurement. For phase I, the first sample (control) was obtained before any drug administration, then at 1, 2, 4, 6, 8, 10, 12, 15, 20, 25, 30, 40, 50, 60, 75, 90, 120, 150, 180, and 240 min after propofol administration. The samples were placed in heparinized glass tubes and centrifuged; the plasma was harvested and stored at −70°C until analysed.

For phase II, the first sample was obtained after propofol was continuously infused for 45 min. Then, a sample was obtained at the end of each infusion rate (dose rate), which was ~30 min after each infusion adjustment. For anaesthesia recovery, samples were obtained at 1, 2, 4, 6, 8, 10, 12, 15, 20, 25, 30, 40, 50, 60, 75, 90, 120, 150, 180, 240, 300, and 360 min after the propofol infusion was stopped. Similar to phase I, the samples were centrifuged and plasma was stored at −70°C until analysis.

**Analytical procedures for propofol assay**

The propofol in plasma was quantitated using liquid chromatography-mass spectrometry (LC-MS) analysis of protein-precipitated samples. The calibration standards were prepared as follows: stock solutions were made by dissolving 10.0 mg of propofol standard in 10.0 ml of MeOH. Three separate propofol working standard solutions were prepared in methanol (MeOH) at 100, 10, and 1.0 μg ml−1. Serial dilutions were prepared from the propofol standard solution by diluting 10 μl of the 100, 10, or 1.0 mg ml−1 with MeOH in a volumetric flask.

Plasma calibrators were prepared by dilution of the working propofol solutions with drug-free plasma to concentrations of 10, 20, 50, 100, 300, 800, 1000, 2000, 3000, 4000, and 5000 ng ml−1. Calibration curves and negative control samples were prepared fresh for each quantitative assay. Two separate preparations of the propofol reference material were used for the preparation of the calibrators and the quality control samples. The quality control samples (plasma fortified with propofol at two concentrations, 10 and 500 ng ml−1) were routinely included as an additional check of accuracy.

Quantitative analyses were performed on a TSQ Quantum Ultra triple quadrupole mass spectrometer (Thermo Scientific, San Jose, CA, USA) coupled with an 1100 Series Liquid Chromatography System (Agilent Technologies, Palo Alto, CA, USA). Chromatography used an ACE C18, 100×2.1 mm, 3 μm, column (Mac-Mod Analytical, Chadds Ford, PA, USA) and a linear gradient of MeOH in water with a constant ammonium hydroxide 0.05% at a flow rate of 0.3 ml min−1. The MeOH concentration was held at 10% for 0.5 min, ramped up to 90% over 4.5 min. Before analysis, the plasma proteins, controls, and calibrators were extracted by precipitation with 0.5 ml 9:1 acetonitrile (ACN):1 M acetic acid containing 300 mg ml−1 thymol (internal standard, IS), vortex mixed for 2.0 min, refrigerated for 30.0 min, followed by centrifugation (1800g for 15 min). The injection volumes were 25.0 μl.

Detection and quantification used full-scan LC-MS/MS transitions of initial product ions for propofol [mass to charge ratio (m/z) 177.2]. The response for the major product ion for propofol was plotted and peaks at the proper retention time integrated using LCQuan software (Thermo Scientific). LCQuan software was used to generate calibration curves and quantitate these analytes in all samples. The concentration of propofol in each sample (e.g. calibrators, quality control, and unknowns) was determined by an IS method using the peak area ratio and linear regression analysis. The response for propofol was linear and gave correlation coefficients (r2) of 0.99 or better. The technique was optimized to provide a limit of detection at 1.0 ng ml−1 and limit of quantitation at 10 ng ml−1. Intra-day accuracy (% of nominal concentration) was 90% and 94% for 10 and 500 ng ml−1, respectively. Inter-day accuracy (% of nominal concentration) was 91% and 96% for 10 and 500 ng ml−1, respectively. Intra-day precision (% relative s.d) was 5.6% and 4.8% for 10 and 500 ng ml−1, respectively. Inter-day precision (% of nominal concentration) was 9.4% and 5.5% for 10 and 500 ng ml−1, respectively.

The chemicals used were acetic acid, ACN, MeOH, all HPLC grade, and were obtained from Fisher Scientific (Pittsburgh, PA, USA), water, HPLC grade, was from Burdick and Jackson (Muskegon, MI, USA), and ammonium hydroxide was spectrophotometric grade from Sigma-Aldrich (St Louis, MO, USA). The analytical reference standards for propofol were obtained from Radian International (Austin, TX, USA) and US Pharmacopeia (Rockville, MD, USA) and IS was thymol obtained from Sigma-Aldrich.

**Pharmacokinetic calculations and statistical analysis**

The clinical data are shown as mean (±SD). The pharmacokinetic data are shown as mean with (95% confidence intervals). The recovery data were analysed and compared using paired t-test using GraphPad Prism®. Significance level was defined at P<0.05.
The pharmacokinetic profile was calculated with compartmental non-linear regression analysis based on the Gauss–Newton (Levenberg and Hartly) method and non-compartmental analysis using the linear trapezoidal (linear interpolation) method (WinNonlin Version 5.2). The following parameters were estimated: maximum concentration ($C_{\text{max}}$), time when maximum concentration occurred ($T_{\text{max}}$), area under the plasma concentration–time curve calculated from the time of dosing to the last measurable concentration (AUC), terminal elimination half-life ($t_{1/2\text{el}}$) calculated as $t_{1/2\text{el}}=\ln(2)/\lambda_z$, volume of distribution calculated as $V_d=\text{dose}/(\lambda_z \times \text{AUC})$, total body clearance calculated as $CL=\text{dose}/\text{AUC}$, and mean residence time calculated as $\text{MRT}=\text{AUMC}/\text{AUC}$ in which AUMC is the area under the first moment curve calculated using the linear trapezoidal rule.

**Results**

**Phase I**

Xylazine administration provided adequate pre-anaesthetic sedation in all horses. Horses stood with a wider foot base, the head was held low, and they were less or non-responsive to their surroundings.

Anaesthesia induction with propofol occurred without complication. The anaesthesia induction and recovery characteristics have been reported.\(^1\) However, to correlate the specific recovery times with the kinetic profile, we summarized the data as follows. The time for first movement, usually a gentle ear, head, or limb movement, was 16.1 (2.5) min. The time for the first attempt to reach sternal recumbency was 29.6 (7.7) min and the horses averaged 2.6 (1.9) attempts to reach sternal recumbency. The standing time was 44.7 (13.7) min and all horses stood very smoothly on the first attempt.

Pharmacokinetic calculations during phase I are described using a non-compartmental analysis due to the poor fit of the data for compartmental models resulting in high residual values (Fig. 1 and Table 1). The plasma $t_{1/2\text{el}}$ for propofol was 44.8 min ($\pm$ 21.3). During recovery, the plasma concentrations ranged between 0.16 and 0.65 $\mu$g ml\(^{-1}\) at first movement, 0.17 and 0.33 $\mu$g ml\(^{-1}\) at first attempt to sternal position, and 0.03 and 0.20 $\mu$g ml\(^{-1}\) when the horses stood (Fig. 1). Although not significant, in two of the horses, the propofol plasma concentration increased when the horses were trying to achieve sternal position. Further, in five of the six horses, the propofol concentration increased when the horses tried to stand. In these five horses, the propofol concentration before standing was 0.11 $\mu$g ml\(^{-1}\) and increased to 0.17 $\mu$g ml\(^{-1}\) within 8 min after standing. In the remaining horse, the propofol concentration was already elevated when trying to reach the sternal position. The unexpected change decreased the drug elimination slope, which is evident between 20 and 60 min during recovery (Fig. 1).

**Phase II**

Data from one of the horses in phase II were excluded. The horse developed severe bradycardia and was woken up before the end of the study. For the remaining horses, xylazine administration provided adequate sedation similar to that observed in phase I.

After anaesthesia induction, two of the five horses required a second propofol bolus injection dose (0.8 and 2.7 mg kg\(^{-1}\)) to allow movement on to the padded cart.

**Fig 1** Logarithmic propofol plasma concentrations after 2 mg kg\(^{-1}\) single injection (phase I). Data for each horse are shown and the mean for all horses ($n=6$) is depicted with a solid line. Left arrow indicates mean time for first movement, middle arrow indicates mean time for first attempt to reach sternal position, and right arrow indicates mean time when horses stood.
The mean propofol infusion rate for all horses was 8.1 (3.2) mg kg$^{-1}$ h$^{-1}$ (Table 2). The infusion rate was calculated using the propofol plasma clearance for each individual horse according to results from phase I. The chosen targeted plasma concentration was 0.2 µg ml$^{-1}$, which was the average plasma concentration observed between 20 and 30 min during phase I. The targeted plasma concentration was aimed to obtain a light plane of anaesthesia. We expected to see a small amount of movement without the horses waking up.

The propofol plasma concentrations during the different infusion rates are depicted in Figure 2. A moderate-to-poor correlation between plasma concentration and infusion rate was observed when analysing the raw data using linear regression analysis $r^2=0.47$.

The initial infusion rate of 8.1 (3.2) mg kg$^{-1}$ h$^{-1}$ was adequate to maintain anaesthesia, but the electrical noxious stimulation elicited purposeful movements in all horses. Infusion rates above 11.9 (1.6) mg kg$^{-1}$ h$^{-1}$ triggered continuous involuntary myoclonal contractions in four of the five horses. In three of the five horses, infusion rates above 14.9 (1) mg kg$^{-1}$ h$^{-1}$ were able to prevent purposeful movement in response to noxious stimulation. Using the linear regression formula, the predicted plasma concentration when involuntary muscle movement occurred was 4.29 µg ml$^{-1}$ ($\pm$ 0.26). Using the same method, the predicted plasma concentration that prevented purposeful movement during electrical noxious stimulation was 5.64 µg ml$^{-1}$ ($\pm$ 0.47).

In the recovery period, the time to first movement after discontinuation of the prolonged propofol infusion was 12.2 (6.0) min. The time to first attempt to stand was 35.5 (12.2) min, horses averaged 8.4 (6.5) attempts to reach sternal position. The horses attempted to stand for the first time at 55.5 (27.6) min and stood at 70 (29.4) min. The horses averaged 2 (1.7) attempts to reach and sustain the standing position.

Pharmacokinetic calculations for phase II were not possible due to the variable plasma concentrations and inadequate data to characterize the terminal elimination phase at the end of the infusion period. However, horses with higher propofol plasma concentrations had longer and worse recoveries. These recoveries consisted of poor coordination, ataxia, falling down, trashing against the walls, and several attempts to reach sterna and standing position. The plasma concentrations during recovery ranged between 1.30 and 3.57 µg ml$^{-1}$ at first movement, 0.77 and 3.54 µg ml$^{-1}$ at first attempt to the sternal position, and 0.55 and 2.31 µg ml$^{-1}$ for both first attempt to stand and when the horses stood (Fig. 3). All propofol concentrations were higher when compared with phase I recovery ($P<0.05$).

The propofol plasma concentration seems to correlate with the recovery quality. For example, one horse had a poor recovery and had a propofol plasma concentration of 2.31 µg ml$^{-1}$ when standing. A second horse had only a moderate–good recovery and the propofol plasma concentration was 1.56 µg ml$^{-1}$ when standing. A third horse had an excellent recovery but staggered when standing and his plasma concentration was 1.26 µg ml$^{-1}$ when standing. The remaining two horses had excellent recoveries and standing with propofol concentrations of 1.17 and 0.55 µg ml$^{-1}$, respectively.
Similar to the results from phase I but not statistically significant, the propofol plasma concentration increased in two horses when they started moving. The concentration increased as well in three horses when they were trying to stand and in two horses when they stood. In total, two horses increased their plasma concentration twice and three horses once during the recovery period.

Commercial propofol
Two horses were anaesthetized a third time with a commercial propofol formulation to confirm the myoclonal contractions observed with the micellar microemulsion. The method used was identical to phase II for these horses. The commercial propofol induction dose was 2 mg kg\(^{-1}\) and the infusion rate started at 5.8 and 7.9 mg kg\(^{-1}\) h\(^{-1}\) for horses 1 and 3, respectively.

After anaesthesia induction, one of the horses required a second propofol dose (0.7 mg kg\(^{-1}\)) to allow movement onto the padded cart.

The infusion rates were adjusted according to the rates used during phase II (Fig. 4). One of the horses developed involuntary myoclonal contractions when the commercial propofol infusion rate was increased to 17 mg kg\(^{-1}\) h\(^{-1}\). The propofol plasma concentrations during the infusion were similar to those obtained with the micellar microemulsion (Fig. 4). A linear regression analysis to correlate the infusion rates and the plasma concentrations revealed almost identical results for both commercial and micellar propofol with a similar 95% confidence interval. The \(r^2\) and slope values for commercial and micellar propofol were 0.64 vs 0.64 and 427 (105) vs 411 (116), respectively. The horses had similar recovery characteristics with both propofol formulations.

**Discussion**
The new 5% micellar microemulsion of propofol is capable of inducing and maintaining anaesthesia in horses. The pharmacokinetic profile in the horse is best described with a non-compartmental model, which is different when compared with other species such as humans and dogs in which propofol follows two or three compartment models.\(^{14-16}\) The propofol ED\(_{50}\) to prevent a response during noxious stimulation is \(\sim\)14 mg kg\(^{-1}\) h\(^{-1}\). However, myoclonic contractions were observed at infusion rates below the ED\(_{50}\).

The propofol plasma concentration appears to be associated with the quality of recovery. However, the plasma
concentration did not indicate when the horses will wake up or stand up. For example, the mean propofol plasma concentration when the horses first moved and stood during phase II are at least three- and 10-fold higher to the concentrations observed during phase I. These results indicate that the propofol plasma concentration and the desired effect do not fully correlate. The sampling site (jugular vein) may have played a role on this poor correlation. Arterial sampling may elicit different results.

An additional influence in the recovery time and quality not addressed in the study is the use of xylazine for sedation. Xylazine is an α2-agonist drug commonly used in horses for sedation and analgesia. On the other hand, xylazine causes ataxia and bradycardia and decreases cardiac output in horses. Xylazine has been shown to delay and improve the recovery quality in horses. It has also been shown to prolong the recovery time in horses anaesthetized with propofol. Thus, horses waking up during phase I still had large xylazine influence whereas the same horses waking up during phase II may have negligible xylazine effect. This could explain why the horses woke up with higher propofol plasma concentrations during phase II. We used xylazine in the study because it is common practice for equine anaesthesia and surgery.

The effect of xylazine may have been the reason why one of the horses was excluded from phase II due to severe bradycardia.

In the present study, propofol did not elicit adequate analgesia before causing involuntary myoclonal activity. Modest analgesia from propofol has been previously reported in veterinary and human medicine. However, propofol showed a sedative effect, which improved the quality of recovery mostly during phase I. One of the challenges of equine anaesthesia is that morbidity and mortality during recovery is much higher than desired. Propofol appears to improve the recovery quality by making the horses have a more coordinated transition from the lateral to standing position and thus, preventing trauma. We observed similar results only when propofol was administered for a short period of time or phase I.

Involuntary myoclonal muscle contractions with propofol have been reported in other species. Similar muscle activity has been reported in horses with enflurane anaesthesia. We advise caution when using propofol in horses because muscle movement is often correlated with a light plane of anaesthesia. Then, increasing the propofol dose may further increase the involuntary muscle movement.

An interesting finding is the changes of drug plasma concentrations when the horses were recovering from anaesthesia. In all horses, the propofol clearance decreased and the plasma concentration even increased during recovery. We hypothesize that cardiac output and blood distribution increased during recovery retrieving a larger pool of drug from peripheral tissues. The later effect may re-anaesthetize the horses prolonging and worsening the recovery quality.

In the study, we did not find any difference between the micellar microemulsion of propofol and the commercial form. In addition, the micellar propofol infusion rates used are comparable with rates published using commercial propofol formulations in horses. Similar results have been reported in other species such as rat and dog in which no differences were observed between micro- and macroemulsions of propofol formulations.

One of the goals for this study was to estimate the micellar propofol ED50 in the horse. Consequently, we did not maintain an equal propofol infusion dose in all horses. For this reason, we could not calculate a meaningful pharmacokinetic profile for the infusion phase.

In conclusion, the new 5% micellar microemulsion of propofol is a suitable anaesthetic drug to improve horse recovery quality only when used for short periods of time. However, caution is warranted when propofol is used for prolonged continuous infusions due to the variable kinetic profile, myoclonal activity, poor analgesia properties, and decreased recovery quality. An additional advantage from the new more concentrated propofol formulation is that instead of using 100 ml of propofol per horse for a 1% propofol formulation, we can now use 20 ml per horse when using the 5% formulation.

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Micellar propofol pharmacokinetic profile in horses


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