

The Influence of Hemorrhagic Shock on Propofol

A Pharmacokinetic and Pharmacodynamic Analysis

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Background: Propofol is a common sedative hypnotic for the induction and maintenance of anesthesia. Clinicians typically moderate the dose of propofol or choose a different sedative hypnotic in the setting of severe intravascular volume depletion. Previous work has established that hemorrhagic shock influences both the pharmacokinetics and pharmacodynamics of propofol in the rat. To investigate this further, the authors studied the influence of hemorrhagic shock on the pharmacology of propofol in a swine isobaric hemorrhage model.

Methods: After approval from the Animal Care Committee, 16 swine were randomly assigned to control and shock groups. The shock group was bled to a mean arterial blood pressure of 50 mmHg over a 20-min period and held there by further blood removal until 30 ml/kg of blood was removed. Propofol $200 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ was infused for 10 min to both groups. Arterial samples (15 from each animal) were collected at frequent intervals until 180 min after the infusion began and analyzed to determine drug concentration. Pharmacokinetic parameters for each group were estimated using a three-compartment model. The electroencephalogram Bispectral Index Scale was used as a measure of drug effect. The pharmacodynamics were characterized using a sigmoid inhibitory maximal effect model.

Results: The raw data demonstrated higher plasma propofol levels in the shock group. The pharmacokinetic analysis revealed slower intercompartmental clearances in the shock group. Hemorrhagic shock shifted the concentration effect relationship to the left, demonstrating a 2.7-fold decrease in the effect site concentration required to achieve 50% of the maximal effect in the Bispectral Index Scale.

Conclusions: Hemorrhagic shock altered the pharmacokinetics and pharmacodynamics of propofol. Changes in intercompartmental clearances and an increase in the potency of propofol suggest that less propofol would be required to achieve a desired drug effect during hemorrhagic shock.

PREVIOUS researchers have investigated how blood loss influences the pharmacologic aspects of several intravenous anesthetics, including opioids,¹⁻³ sedative hypnotics,⁴⁻⁷ benzodiazepines,^{7,8} and local anesthetics.⁹ Their work has demonstrated that blood loss alters the pharmacology of common intravenous agents such that equivalent dosing leads to higher drug concentrations in the setting of severe blood loss when compared with

euvoletic, normotensive conditions. These findings are consistent with the clinical practice of reducing the dose of intravenous anesthetics for patients who have significant blood loss before or during surgery.

Many authors have quantified the pharmacokinetic changes associated with blood loss using compartmental models^{2-5,9} and have demonstrated that blood loss results in a decrease in central compartment volume, central compartment clearance, or both.²⁻⁵ These pharmacokinetic changes account for the often large differences observed in plasma or whole blood concentrations after equivalent dosing in studies of bled and unbled animals.^{2,3} A decrease in blood volume and cardiac output along with compensatory changes in regional blood flow are the likely physiologic mechanisms explaining these pharmacokinetic changes.

Previous work by DePaepe *et al.* studying the influence of blood loss on the pharmacokinetics and pharmacodynamics of propofol has demonstrated that moderate blood loss (17 ml/kg) results in a decrease in the central compartment clearance and volume and an increase in end-organ sensitivity in the rat isovolemic hemorrhage model.⁵ These pharmacokinetic and pharmacodynamic changes resulted in a 2.5-fold reduction in dose *via* continuous infusion to achieve the same drug effect. Previous work in our laboratory on the influence of blood loss on the pharmacokinetics of fentanyl and remifentanyl has revealed similar results: namely, a decrease in the central compartment clearance and volume resulting in a twofold increase in drug concentrations after equivalent dosing to unbled and moderately bled swine.^{2,3}

Similar to the work by DePaepe *et al.*,⁵ in our present study we explored how hemorrhagic shock influenced the pharmacokinetics and pharmacodynamics of propofol, but implemented a more severe hemorrhage model (30 ml/kg) in swine in the presence of isoflurane. Our hypotheses were that (1) hemorrhagic shock would alter the pharmacokinetics of propofol; and (2) for an equivalent effect site concentration, bled animals would have more pronounced end-organ sensitivity to propofol than unbled animals.

Methods and Materials

Experimental Design

Experiments were performed on commercial farmed swine of either sex. The study was approved by the Institutional Animal Care and Use Committee at the Uni-

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Received from the Department of Anesthesiology, University of Utah School of Medicine, Salt Lake City, Utah. Submitted for publication June 3, 2002. Accepted for publication April 28, 2003. Supported by a grant from the National Institute of Health, Bethesda, Maryland, No. K08GM00712, and by the Department of Anesthesiology, University of Utah, Salt Lake City, Utah. Presented in abstract form at the Annual Meeting of the Society of Intravenous Anesthesia in San Francisco, California, October 13, 2000.

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versity of Utah. Animals were randomly assigned to either an isobaric hemorrhage or a control group ($n = 8$ for each group). In the shock group, animals were first bled to a shock state and then administered the propofol infusion. In the control group, animals were instrumented in an identical fashion to the shock group and were maintained in an anesthetized, ventilated state for 30 min before receiving the propofol infusion. This was done to ensure that both groups would receive the propofol infusion after near-equivalent times under anesthesia.

Animal Preparation

Swine weighing between 20.6 and 35.0 kg (mean weight, 27.1 kg) were commercially obtained and quarantined for 6 days in an environment controlled for temperature and light. The animals had access to food and water *ad libitum*. Anesthesia was induced with an intramuscular injection of tiletamine HCl 1.3 mg/kg, zolazepam 1.3 mg/kg, ketamine 1.3 mg/kg, and xylazine 1.3 mg/kg. Intravascular access was obtained from an ear vein.

Each animal was then intubated and mechanically ventilated. Initial ventilator settings were a tidal volume of 8–10 ml/kg, a respiratory rate of 20 breaths/min, a F_{iO_2} of 100%, and no positive end-expiratory pressure. Tissue oxygenation was monitored using continuous pulse oximetry placed on the tongue or ear. Ventilation was monitored using an inspired/expired gas analyzer that measured oxygen, carbon dioxide, and potent inhalation agent concentrations. Ventilator settings were adjusted as needed to keep the pulse oximetry (Sp_{O_2}) above 95% and the end-tidal CO_2 at 38 ± 4 mmHg. Once satisfactory ventilator settings were established, a baseline arterial blood gas was obtained. Ventilator settings were adjusted further if needed to maintain the arterial pCO_2 at 40 ± 4 mmHg.

A continuous level of anesthesia was achieved with isoflurane and intermittent boluses of pancuronium (0.1 mg/kg). Expired isoflurane levels were monitored and kept at a 1.0 minimum alveolar concentration equivalent for swine.¹⁰ Subcutaneous electrocardiograph electrodes were placed and the electrocardiogram was monitored throughout the study.

The left femoral artery was cannulated with a 16-gauge arterial sheath to monitor arterial blood pressure and heart rate continuously. The right femoral artery was cannulated with a 16-gauge arterial sheath for blood removal and subsequent reinfusion. An internal jugular vein was cannulated with a pulmonary artery catheter for thermodilution estimates of cardiac output. Colonic temperatures were monitored and maintained at 37°C throughout the study with a heating blanket and heating lamps as needed. Once access to the vascular compartment was obtained, each animal was anticoagulated with

an intravenous bolus injection of heparin (100 units/kg of body weight).

Instrumentation for electroencephalographic monitoring was accomplished by preparing the skin over the fronto-occipital regions bilaterally and placing four cutaneous electrodes (Aspect Medical, Framingham, MA). Four channels of the electroencephalogram were amplified and digitally recorded using an Aspect A1000 electroencephalogram machine. Digitized raw electroencephalographic waveform data and Bispectral Index Scale (BIS) values were collected electronically.

Hemorrhage Protocol

After instrumentation, the animals underwent a 30-min stabilization period before initiation of the hemorrhage protocol. After the stabilization period, the unbled control animals underwent another 30-min period that served as a sham hemorrhage period.

The hemorrhage protocol was designed to ensure that each animal was at an equivalent degree of metabolic compromise from hemorrhagic shock before initiation of the propofol infusion. This was accomplished by using an isobaric hemorrhage model before drug infusion, as described by Wiggers.¹¹

Animal were bled *via* an arterial line feeding through a computer-controlled roller pump. Shed blood was stored in a reservoir placed on a scale. Shed-blood volume was measured by weight. *Via* a second arterial line, mean arterial blood pressure readings were continuously acquired by the computer controlling the roller pump. Blood was removed at a rate required to achieve a linear decrease in the mean arterial blood pressure to a target pressure over a 20-min period. Blood was then removed or reinfused by the servo-controlled roller pump to maintain the target pressure.

The arterial blood pressures were measured with a pressure transducer (Utah Medical, Midvale, UT). A computerized data acquisition system recorded the mean arterial blood pressure, systolic and diastolic arterial pressures, heart rate, and shed-blood volume every 5 s.

Arterial blood samples for determining pH, PO_2 , PCO_2 , bicarbonate, glucose, potassium, hematocrit, glucose, and lactate were measured using blood gas and chemistry analyzers (Stat Profile 1 Analyzer, Nova Biomedical, Waltham, MA and YSI Model 2700 Select Biochemistry Analyzer, Yellow Springs Instrument Company, Yellow Springs, OH) after hemorrhage, before the propofol infusion, and on completion of the propofol infusion. Metabolic and hemodynamic parameters for each group were compared at these time points using an unpaired two-tailed Student *t* test. To account for multiple comparisons and maintain the probability of a type I error below 0.05, *P* values less than 0.025 were considered significant.

Propofol Administration and Assay

A series of pilot studies were performed to determine the appropriate target mean arterial blood pressure, the endpoint of the hemorrhage protocol, and propofol infusion rate that would achieve near maximal drug effect but allow the animal subjects to survive the study period. Previous work in our laboratory examining the influence of blood loss on remifentanyl pharmacology, an isobaric hemorrhage model was developed where the target mean arterial blood pressure was 40 mmHg and the hemorrhage protocol was terminated after 48 ml/kg had been removed. After hemorrhage, swine were administered remifentanyl $10 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 10 min. All animals survived.³

Starting with these hemorrhage model indices, a series of pilot studies ($n = 5$) were performed. A target mean arterial blood pressure of 50 mmHg until 30 ml/kg of blood was removed followed by a 10-min propofol infusion at $200 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ allowed animals to survive the study protocol and achieved near-maximal drug effect. Subsequently, 16 animals were randomly assigned to two groups, the experiment shock group and the control group.

The propofol infusion ($200 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 10 min) was administered intravenously at a constant rate on completion of the hemorrhage protocol using a syringe pump (Medfusion 2010i, Medex Inc, Duluth, GA). At this time, the roller pump was turned off so that no additional blood was removed or reinfused during the period where propofol samples were collected. During and following the infusion, 3-ml arterial blood samples were obtained at preset intervals, with more rapid sampling during the infusion and immediately after termination of the infusion. A baseline sample was collected before the infusion. Samples were collected at 4, 8, 10, 11, 12, 13, 14, 15, 17.5, 20, 25, 30, 40, 60, and 180 min after the start of the infusion.

Propofol plasma concentrations were measured using a gas chromatography mass spectrometer technique described in work by Ibrahim *et al.*¹² with a quantitation limit of 50 ng/ml.

Pharmacokinetic Analysis

The concentration *versus* time data for both groups were analyzed using several techniques. First, a two-stage approach was used to estimate the individual pharmacokinetic parameters for a three-compartment model using pharmacokinetic modeling software (NONMEM, University of California San Francisco, San Francisco, CA). Second, an exploration of pharmacokinetic parameter-covariate relationships was made. Third, the control and shock groups were combined to build a population model using nonlinear mixed effect modeling software (NONMEM). Covariates demonstrating a strong correlation with pharmacokinetic parameters were introduced into the population model in an effort to im-

prove the model's ability to predict propofol plasma concentrations.

Two-stage Analysis

A two-stage approach implemented in NONMEM was performed to estimate the mean pharmacokinetic parameters for each group. The first stage involved fitting a three-compartment mammillary model to the propofol concentration *versus* time data to estimate the pharmacokinetic parameters for each animal. The triexponential equation for each animal was parameterized in terms of distribution volumes and clearances. The second stage of the two-stage approach was to calculate the average of the pharmacokinetic parameters to obtain mean population estimates for each group. The shock and control groups were then compared with an unpaired two-tailed Student *t* test. Six comparisons were made between groups (one for each pharmacokinetic parameter). To maintain the probability of a type 1 error at 0.05 for this multiple comparison analysis, a *P* value less than 0.0083 was considered significant for each individual comparison.

Exploration of Parameter-Covariate Relationships

The feasibility of using hemodynamic covariates to improve the overall model was studied. The individual pharmacokinetic parameter estimates from the two-stage analysis were regressed independently on each covariate as advocated by Maitre *et al.*¹³ Covariate parameters measured on completion of the propofol infusion included shed-blood volume, heart rate, mean arterial blood pressure, and cardiac index. This step was intended to identify useful relationships between model parameters and covariates and to characterize the shape of these relationships.

Nonlinear Mixed Effects Model Analysis

In contrast to the two-stage approach, propofol concentration *versus* time data for both the shock and control groups were combined and used to construct a single, three-compartment population pharmacokinetic model using NONMEM. Data from both groups were simultaneously analyzed to provide an estimate of typical values for the parameters along with an estimate of the parameter's interindividual variability. Interindividual variability was modeled using a log-normal error model:

$$\theta_{\text{individual}} = \theta_{\text{typical}} e^{\eta_{\text{individual}}}$$

where $\theta_{\text{individual}}$ is the true value of a pharmacokinetic parameter (V_1 , Cl_1 , *etc.*) in the individual, θ_{typical} is the population mean estimate, and $\eta_{\text{individual}}$ is the between-subject variance whose distribution was estimated with a mean of zero and a variance of ω^2 . Estimates of ω obtained in NONMEM are similar to the coefficient of variation used in standard descriptive statistics.

The performance of this population model was evaluated in terms of its ability to predict individual animal

blood concentrations in both groups. The model was quantitatively assessed in terms of a weighted residual (WR), the difference between a measured blood concentration (C_m) and the model-predicted concentration (C_p) in terms of C_p . Thus, WR was defined as: $WR = (C_m - C_p)/C_p$. Using this definition, the WRs for the population model were computed at every measured data point for all animals in the combined shock and control group.

Using the WR data, the overall accuracy of the model was determined by computing the median absolute weighted residual (MDAWR), defined as: $MDAWR = \text{median } [|WR_1|, |WR_2|, \dots, |WR_n|]$, where n is the total number of samples in the study population. Using this formula, the MDAWR for the population models were computed. The median weighted residuals (MDWR), a measure of model bias, were also computed. The accuracy and bias of each model was also visually assessed by plotting (1) the C_m/C_p versus time and (2) C_m versus C_p .

Model Expansion with Covariate Effects

After obtaining the best population model without covariates, the influence of shed-blood volume, heart rate, mean arterial blood pressure, and cardiac index on population model performance were evaluated. Guided by the initial regression analysis exploring the relationships between model parameters and subject covariate, an improved population model was built in a stepwise fashion in which the individual covariate effects on each model parameter were incorporated into the model and the resulting expanded model was examined for significant improvement. A change in the objective function ($-2 \times$ the log likelihood) of at least four was viewed as sufficient justification to include an additional parameter in the model (in the form of a covariate or covariate plus a constant, which represented the addition of two model parameters). An iterative process was used where various models were tested both forward (starting with no covariates) and backward (starting with all covariates) to confirm that the observed improvement was not a result of covariate correlation. A series of MDAWRs, MDWRs, C_m/C_p versus time plots, and C_m versus C_p plots were generated for each model to assess the extent of model improvement.

Pharmacodynamic Analysis

The pharmacologic effect of propofol was characterized by examining the influence of propofol on the BIS, which has been established as a surrogate measure of propofol effect in humans.¹⁴⁻¹⁶ The BIS was calculated using the Aspect A1000 machine, software version 3.1.

Data from pilot studies were used to compare the BIS profile over time during the study period between control and shock animals in the absence of propofol. This

was done to assess the effect of hemorrhagic shock alone on the BIS.

In unbled animals, the propofol infusion did not produce an appreciable decrease in the BIS, which hindered a pharmacodynamic analysis. An additional set of experiments were performed with the goal of administering propofol to achieve the same effect in the BIS observed in the shock group. DePaepe *et al.* reported that increasing the propofol dose by 2.5-fold in unbled rats led to an equipotent effect in the electroencephalogram observed in bled rats.⁵ Therefore, eight additional swine weighing between 28.0 and 43.0 kg (mean weight, 34.1 kg) were instrumented in an identical fashion as described above; after a 30-min stabilization period and 30 min sham hemorrhage period, each pig received a propofol infusion of $500 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 10 min (an increase of 2.5-fold over $200 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). The experimental protocol for this additional group was identical to the control group described above.

Parametric Modeling of the Concentration-Effect Relationship

The pharmacodynamic analysis was performed in three steps.¹ Plots of the raw data (plasma propofol levels vs. BIS) were made for each individual animal and the hysteresis between drug concentration and effect noted.² Because plots of the concentration-effect relationship were sigmoid in shape, an inhibitory effect sigmoid model (*i.e.*, Hill equation) was used to model the relationship parametrically.¹⁷ Using pharmacodynamic modeling software (WinNonLin, Version 3.1, Pharsight Corporation, Chelsea, MI), the equation:

$$E = E_0 - (E_0 * C_e^\gamma / (C_e^\gamma + C_{50}^\gamma)),$$

where E is the predicted effect, E_0 is the baseline effect level, C_e is the effect site concentration, γ is a measure of curve steepness, and C_{50} is the plasma concentration that produces 50% of maximal effect, was fit to each individual animal. This analysis yielded a set of pharmacodynamic parameters and an apparent effect site concentration-effect (BIS) curve for each individual animal. These plots were reviewed to ensure that the apparent effect site concentration versus BIS data represented a collapsing of the hysteresis noted in the raw plasma propofol concentration versus BIS data.³ Using individual pharmacodynamic parameters, model estimates of the effect site concentration versus drug effect were plotted over a range of 0.2-100 $\mu\text{g}/\text{ml}$ for each animal. Individual pharmacodynamic parameters from the shock and control groups were compared with an unpaired two-tailed t test. Because four comparisons were made in this analysis, P values of less than 0.0125 were considered significant to maintain the probability of a type I error at 0.05.

Computer Simulations

Computer simulations using a combined pharmacokinetic/pharmacodynamic model for each study group were performed to illustrate the influence of blood loss on propofol's pharmacologic behavior in swine. The first simulation compared differences in the peak effect site concentration between the shock and control models after a bolus (8 mg/kg body weight) and a continuous infusion ($400 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) of propofol. Simulation doses were selected to achieve an effect site concentration near the C_{50} for the control pharmacokinetic/pharmacodynamic model. The second simulation determined the total dose required to deliver a 1-h computer-controlled infusion targeted to the C_{50} for both control and shock group models. Simulations were performed using drug infusion simulation software (Stanpump, Stanford University, Palo Alto, CA). The simulations used pharmacokinetic parameters derived from the control and shock groups where each group received a 10-min infusion of propofol at $200 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Linear pharmacokinetics were assumed across propofol dose. The simulations used the pharmacodynamic parameters derived from the control and shock groups; the control group received a 10-min infusion of propofol at $500 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and the shock group received a 10-min infusion of propofol at $200 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$.

Results

Summary of Pilot Studies

Pilot studies revealed that the dose of propofol and the extent of hemorrhage had to be reduced for animals to survive the 3-h study protocol from what we had previously reported in studies examining the influence of blood loss on intravenous opioid pharmacology.^{2,3} Animals bled in an isobaric fashion to 50 mmHg until 30 ml/kg of blood had been removed survived the 10-min propofol infusion and the remainder of the 3-h study protocol. Additional pilot studies were performed to assess the influence on the BIS of blood loss in the absence of propofol. Isobaric hemorrhage did not change the BIS[®] throughout the duration of the study protocol.

Effect of Hemorrhagic Shock on Hemodynamic and Metabolic Parameters

Before initiation of the hemorrhage protocol, there was no difference in the hemodynamic and metabolic profile between the shock and control groups. Animals subjected to the isobaric hemorrhagic shock protocol required 43 ± 7 min (mean \pm SEM) to reach the target shed-blood volume of 30 ml/kg. Bled animals developed a hemodynamic and metabolic profile consistent with hemorrhage shock. In comparison with control animals, bled animals developed (1) an increase in heart rate, plasma lactate levels, and plasma glucose levels; and (2)

Table 1. Hemodynamic and Metabolic Parameters before and Immediately after Propofol Infusion

Parameter	Control Group			Hemorrhage Group		
	Before Propofol Infusion Column 1	After Propofol Infusion Column 2	Change from before to after Propofol Infusion Column 3	Before Propofol Infusion Column 4	After Propofol Infusion Column 5	Change from before to after Propofol Infusion Column 6
Heart rate (beats/min ⁻¹)	112 \pm 8	103 \pm 7†	9 \pm 2	168 \pm 7‡	174 \pm 14§	-6 \pm 11
Central venous pressure (mmHg)	6.0 \pm 0.4	6.0 \pm 0.4	0.0 \pm 0.3	3.8 \pm 0.6‡	3.6 \pm 0.8§	0.1 \pm 0.3
Pulmonary artery occlusion pressure (mmHg)	4.4 \pm 0.3	4.0 \pm 0.3	0.4 \pm 0.2	4.9 \pm 1.4	6.1 \pm 1.4	-1.3 \pm 0.7
Cardiac index (L \cdot min ⁻¹ \cdot m ² ⁻¹)	5.0 \pm 0.5	4.9 \pm 0.5	0.1 \pm 0.2	2.6 \pm 0.1‡	2.6 \pm 0.2§	0.1 \pm 0.2
Mean arterial blood pressure (mmHg)	115 \pm 6	101 \pm 6†	13 \pm 2	56 \pm 3‡	52 \pm 4§	4 \pm 5
Systemic vascular resistance index (dynes \cdot sec \cdot cm ⁻⁵)	1,769 \pm 94	1,587 \pm 89†	181 \pm 36	1,615 \pm 70	1,547 \pm 168	68 \pm 140
Arterial pH	7.473 \pm .019	7.479 \pm .017	-0.006 \pm 0.022	7.441 \pm 0.022	7.379 \pm 0.032§	0.062 \pm 0.023
Plasma lactate (mmol \cdot L)	1.4 \pm 0.3	1.8 \pm 0.5	-0.5 \pm 0.5	3.0 \pm 0.5‡	5.8 \pm 1.5	-2.8 \pm 1.1
Plasma glucose (mg \cdot dL)	68 \pm 10	60 \pm 11	3 \pm 5	149 \pm 26‡	150 \pm 36	-1 \pm 21

Data are presented as mean \pm SEM.

* $P < 0.02$ for comparisons between the change before and after the propofol infusion between groups (column 3 vs. column 6). † $P < 0.02$ for comparisons between before and after the propofol infusion in the control group (column 1 vs. column 2). ‡ $P < 0.02$ for comparisons between the shock and control groups before the propofol infusion (column 1 vs. column 4). § $P < 0.02$ for comparisons between the shock and control groups after the propofol infusion (column 2 vs. column 5).

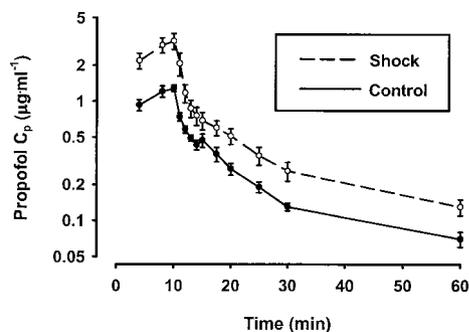


Fig. 1. Mean propofol plasma concentration *versus* time data. **Solid circles** = mean plasma level for control animals; **open circles** = mean plasma level for shock animals.

a decrease in central venous pressure, mean arterial blood pressure, and cardiac index (column 1 *vs.* column 4 in table 1).

Effect of Propofol on Hemodynamic and Metabolic Parameters

After the propofol infusion, bled animals continued to have a hemodynamic and metabolic profile consistent with hemorrhage shock (column 2 *vs.* column 5 in table 1). The propofol infusion produced a decrease in the heart rate, mean arterial blood pressure, and systemic vascular resistance index in the unbled control animals (column 1 *vs.* column 2 in table 1), but it did not produce significant changes in any of these hemodynamic parameters in the shock group. A comparison of the magnitude of change in each hemodynamic and metabolic parameter from before to immediately after the propofol infusion is presented in columns 3 and 6 of table 1. The propofol infusion produced no change in any of the hemodynamic and metabolic parameters between the hemorrhage and control groups. Changes in the mean arterial blood pressure and systemic vascular resistance index tended to be larger in the control group but were not significant. Changes in the plasma lactate level tended to be larger in the shock group but were not significant.

Pharmacokinetic Analysis

The infusion of propofol administered in this protocol resulted in time *versus* concentration curves character-

istic of brief intravenous infusions. The mean propofol concentrations in the shock and control groups are contrasted in figure 1. The shock group exhibited higher concentrations throughout the experiment.

Two-stage Analysis

The raw concentration *versus* time data were described by a three-compartment model. A set of pharmacokinetic parameters was estimated from the plasma propofol concentration *versus* time data for each individual animal. A summary of the pharmacokinetic parameter estimates by group is presented in table 2. A comparison of the pharmacokinetic parameters between the control and shock groups revealed slower intercompartmental clearances in the shock group.

Exploration of Parameter-Covariate Relationships

Plots of the individual parameter estimates *versus* the covariates revealed several potentially useful relationships. Some of the most pronounced relationships were found between the rapid distribution clearance (Cl_2) and the cardiac index and Cl_2 and the shed-blood volume. Selected parameter-covariate relationships are presented in figure 2.

Nonlinear Mixed Effects Model Population Analysis

Propofol concentration *versus* time data from both the shock and control groups were combined to construct a three-compartment population pharmacokinetic model (simple model) as shown in table 3. The performance of the *simple* population model with no covariates is presented in table 4. Model performance parameters from the simple model were used as a baseline for comparison with covariate expanded population models.

Model Expansion with Covariate Effects

The covariate pharmacokinetic parameter relationships that were most promising were introduced into the population model. Sixty-five evaluations were made exploring the influence of individual covariates (*e.g.*, cardiac index, shed-blood volume, and mean arterial blood pressure) and constants (*e.g.*, intercept terms from the regression analysis) on improving the accuracy of the population model. Population model performance was

Table 2. Summary of Pharmacokinetic Parameter Estimates by Group

Parameter	Control Group	Shock Group	P Value
Volumes (l)			
Central compartment (V_1)	4.7 ± 1.0	3.5 ± 0.7	0.352
Rapidly equilibrating peripheral compartment (V_2)	16.7 ± 3.6	7.4 ± 1.3	0.031
Slowly equilibrating peripheral compartment (V_3)	231.9 ± 63.5	164.8 ± 49.3	0.442
Clearance ($l \cdot \text{min}^{-1}$)			
Elimination clearance (Cl_1)	1.6 ± 0.3	0.8 ± 0.2	0.032
Fast distribution clearance (Cl_2)	4.6 ± 0.9	1.0 ± 0.2	0.002
Slow distribution clearance (Cl_3)	1.9 ± 0.3	0.9 ± 0.2	0.004

Data are presented as mean ± SEM. A P value < 0.0083 is considered significant.

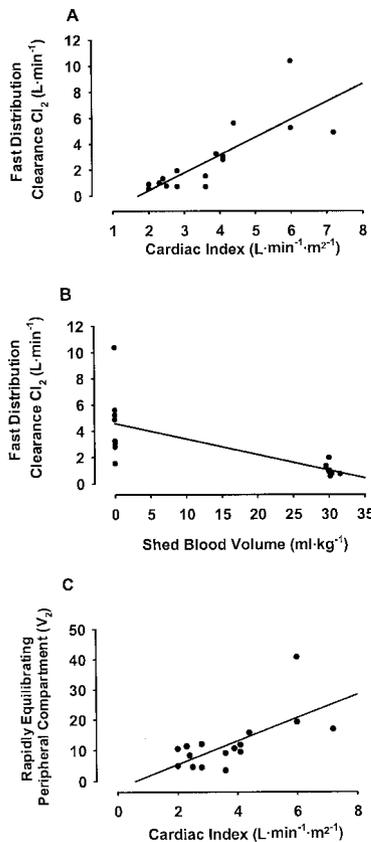


Fig. 2. (A) Plot of the fast distribution compartment clearance (Cl_2) versus cardiac index. (B) Plot of the fast distribution compartment clearance (Cl_2) versus the shed-blood volume. (C) Plot of the rapidly equilibrating peripheral compartment volume (V_2) versus the cardiac index.

improved by scaling all parameters either to cardiac index or to the shed-blood volume using relationships identified during the parameter versus covariate analysis. The parameter values for the covariate modified population models are presented in table 3.

Scaling clearances and volumes to cardiac index or shed-blood volume resulted in an improvement in the objective function, MDAWR, and MDWR. These results, including the MDAWR tenth and ninetieth percentile values, are shown in table 4. The performance of the simple and cardiac index enhanced population models are compared graphically in figure 3. The cardiac index modified population model improved estimates of

Table 4. MDAWR, Tenth and Ninetieth MDAWR Percentiles, MDWR, and Negative Two Times the Log Likelihood (Objective Function) for Selected Population Models

	Simple	All Parameters Scaled to CI	All Parameters Scaled to SBV with k
MDAWR, %	37.2	28.6	22.7
Tenth percentile, %	6.2	6.1	3.3
Ninetieth percentile, %	123.4	59.3	60.8
MDWR, %	15.1	4.6	0.4
Objective function	-768	-826	-883

CI = cardiac index; k = constant; MDAWR = mean absolute residuals; MDWR = mean weighted residuals; SBV = shed-blood volume.

propofol levels in both the shock and control animals. The underestimation of the plasma propofol levels over time in the shock group using the simple model was improved with the cardiac index enhanced population model.

Pharmacodynamic Analysis

The $200 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ propofol infusion for 10 min produced a decrease in the BIS that returned to baseline within 30 min of the infusion in all of the animals in the shock group, but it had minimal effect on the BIS in the control group (fig. 4, A). In the additional set of experiments, propofol at $500 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 10 min administered to unbled swine resulted in a decrease in the BIS in seven of the eight animals, similar to that observed in the shock group (fig. 4, B). The magnitude of the propofol-induced decrease in BIS was similar for the control ($500 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) and shock ($200 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) groups, but the shock group demonstrated an earlier drop in the BIS during the propofol infusion.

Parametric Modeling of the Concentration-Effect Relationship

The pharmacodynamic parameters for each group are presented in table 5. E_0 and γ were similar in both groups. The C_{50} was 2.7-fold less in the shock group. The k_{e0} demonstrated an increasing trend with shock, but the difference was not significant. One animal in the control group did not demonstrate any change in the BIS during the propofol infusion and was not included in the

Table 3. Simple and Covariate Expanded Population Models

	Simple	All Parameters Scaled to CI	All Parameters Scaled to SBV with k
V_1 (L)	2.4 [0, 1.28]	$(-0.2 * CI) + 4.8$ [0.7, 0.96]	$(-0.4 * SBV) + 4.7$ [0.1, 1.64]
V_2 (L)	9.1 [0, 0.43]	$(3.8 * CI)$ [1.0, 0.35]	$(-0.3 * SBV) + 16.7$ [1.3, 0.21]
V_3 (L)	113.0 [0, 0.55]	$(8.4 * CI)$ [12.3, 0.51]	$(-2.3 * SBV) + 232.7$ [14.3, 0.46]
Cl_1 ($L \cdot \text{min}^{-1}$)	1.2 [0, 0.58]	$(0.2 * CI)$ [0.1, 0.40]	$(-0.02 * SBV) + 1.6$ [0.1, 0.34]
Cl_2 ($L \cdot \text{min}^{-1}$)	1.1 [0, 0.64]	$(1.3 * CI)$ [0.2, 0.73]	$(-0.1 * SBV) + 4.6$ [0.7, 0.20]
Cl_3 ($L \cdot \text{min}^{-1}$)	1.0 [0, 0.56]	$(0.3 * CI)$ [0.1, 0.38]	$(-0.3 * SBV) + 1.9$ [0.2, 0.23]

Values in brackets are the SEM and coefficients of variation for the interindividual error estimate (η).

CI = cardiac index; k = constant; SBV = shed-blood volume.

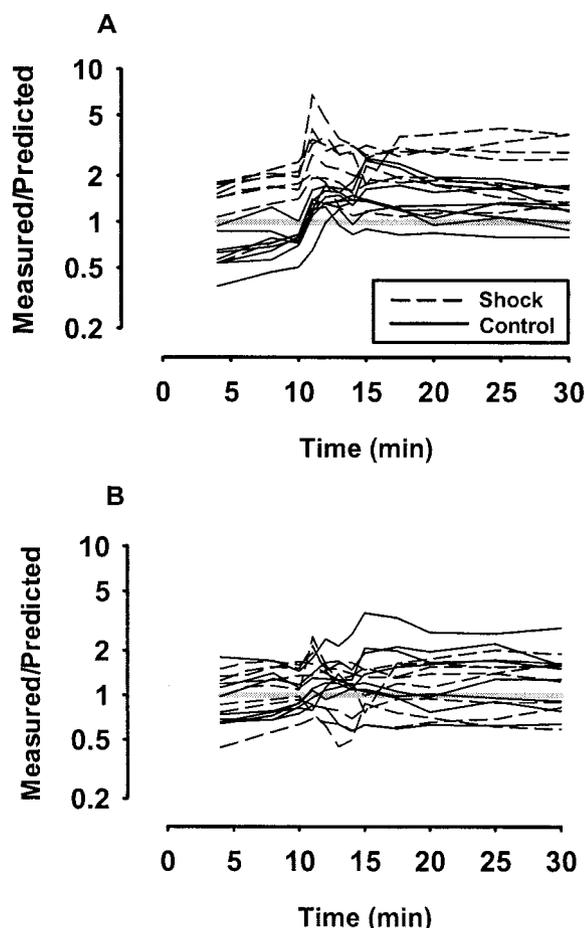


Fig. 3. The measured over predicted plots for the population models using all animals from both the control and shock groups. (A) Each line represents the performance of the simple population model when applied to an individual pig over time. (B) Each line represents the performance of the population model with all parameters scaled to cardiac index when applied to an individual pig over time. A pig with plasma concentrations perfectly predicted by the model is represented by a straight line at 1 (gray line). Solid lines = control group; dashed lines = shock group.

pharmacodynamic analysis. The concentration-effect relationship for each animal as characterized by the pharmacodynamic model over a propofol effect site concentration range of 0.2–100 $\mu\text{g}/\text{ml}$ is presented in figure 5.

Computer Simulations

Simulations using combined pharmacokinetic/pharmacodynamic models for each study group revealed differences in the clinical pharmacology of propofol between bled and unbled swine. The simulation of a propofol bolus (10 mg/kg) and of a propofol infusion (500 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) maintained for 60 min for both study groups are presented in figure 6. The simulations of the bolus dose yielded peak effect site propofol concentrations of 12.4 and 4.4 $\mu\text{g}/\text{ml}$ for the shock and control groups, respectively. To put these peak effect site values in pharmacodynamic perspective, the C_{50} for the shock and control groups have been added to the plots in

figure 6. In unbled (control) swine, the propofol bolus yielded a peak effect site concentration that briefly approximated the control C_{50} . By contrast, simulation of the same bolus administered to bled swine generated a peak effect site concentration that exceeded the shock C_{50} for 28 min.

The simulation of the 60-min infusion yielded steady-state effect site propofol concentrations of 9.7 and 4.9 $\mu\text{g}/\text{ml}$ for the shock and control groups, respectively. In unbled swine, the infusion required 44 min to exceed the control C_{50} . With the same dose administered to bled swine, the shock C_{50} was attained within 4 min, and by the end of the infusion the effect site concentration exceeded the shock C_{50} sixfold and persisted above the shock C_{50} for 37 min after termination of the infusion.

In the second set of simulations, we simulated a target-

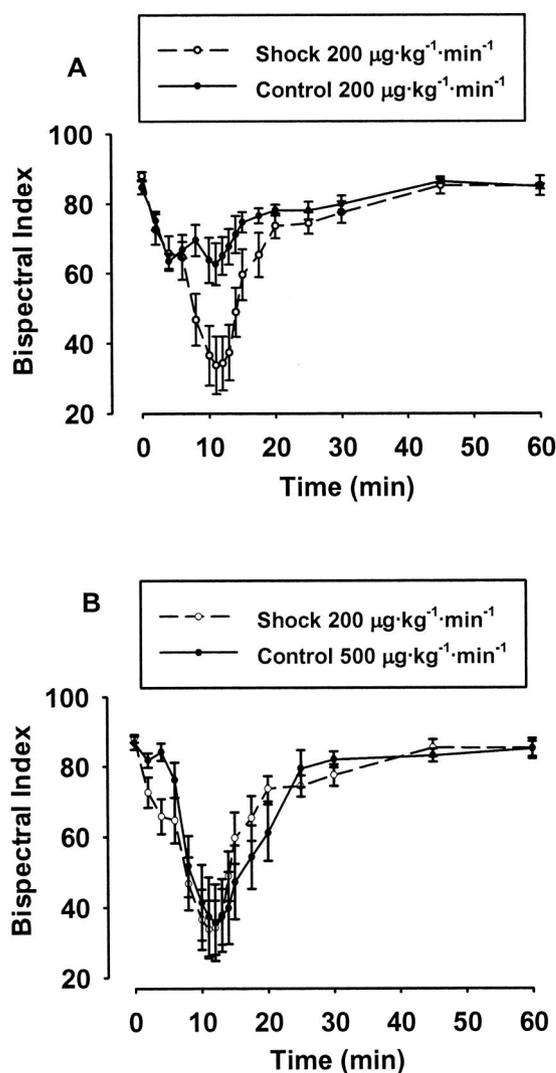


Fig. 4. Mean Bispectral Index Scale (BIS) changes versus time during and after a propofol infusion for shock and control animals. (A) Plot of bled and unbled animals receiving 200 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 10 min. (B) Plots of bled animals receiving 200 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and unbled animals receiving 500 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Solid circles = mean BIS measurements for control animals; open circles = mean BIS measurements for shock animals.

Table 5. Pharmacodynamic Parameters

Parameter	Control Group	Shock Group	P Values
E_0	85.3 ± 2.6	81.9 ± 2.0	0.27
γ	9.8 ± 3.9	8.2 ± 2.9	0.72
EC_{50} ($\mu\text{g} \cdot \text{ml}^{-1}$)	4.6 ± 0.6	1.7 ± 0.3	< 0.01
k_{e0}	0.12 ± 0.01	0.16 ± 0.02	0.18

Data are presented as mean ± SEM. A P value < 0.0125 is considered significant.

E_0 = baseline BIS; γ = a measure of curve steepness; EC_{50} = effect-site concentration that produces 50% of maximal effect on the BIS; k_{e0} = elimination constant from the effect site compartment.

controlled infusion using the pharmacokinetic parameters for each group. The target was set at the C_{50} value for each group. We found a fivefold decrease (35.0 mg/kg to 6.4 mg/kg for the control and shock models, respectively) in the amount of propofol required to maintain the C_{50} for 60 min in the shock group.

Discussion

We examined the effect of hemorrhagic shock on the pharmacology of propofol. We hypothesized that severe blood loss would alter the pharmacokinetics and pharmacodynamics of propofol. Our results confirmed this hypothesis. The essential finding of this study was that a lower dose of propofol was required to achieve the same effect in shock. This was a function of both the pharmacokinetic and pharmacodynamic changes observed in the shock state. We found that when compared with control animals, the same propofol dose resulted in (1) higher plasma levels in shock because of slower clearances, and (2) greater effect in shock because of greater end organ sensitivity (e.g., lower C_{50}). A compelling

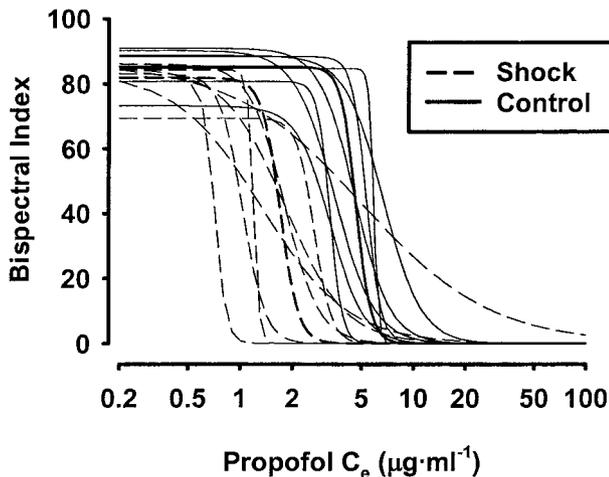


Fig. 5. The concentration–effect relationship for each animal as characterized by the pharmacodynamic model. *Solid lines* = control animals over a propofol plasma concentration range of 0.2–100 $\mu\text{g}/\text{ml}$; *dotted lines* = shock animals over the same range; *bold lines* = the mean pharmacodynamic model for each group. The horizontal axis is on the log scale.

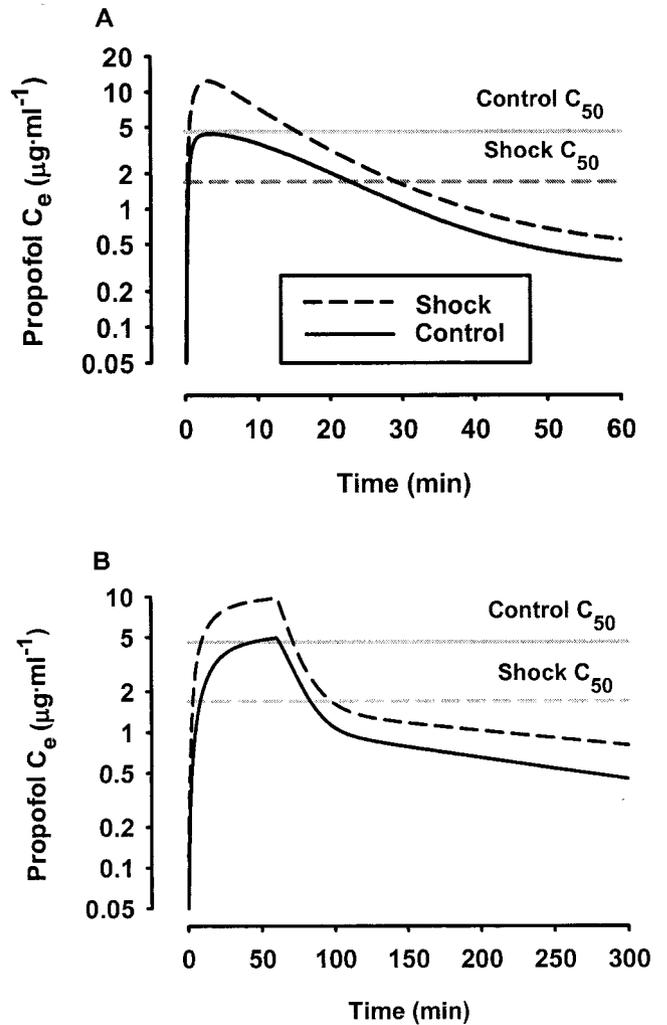


Fig. 6. Simulation of the plasma propofol concentration that results from a (A) 10-mg/kg bolus and (B) 500 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ infusion for 60 min in control and shock animals. *Gray lines* = effect site concentration that produces 50% of maximal effect on the BIS for the shock (*dashed*) and control (*solid*) swine.

example of these changes was demonstrated in the pilot studies where bled animals receiving a higher dose infusion of propofol were unable to survive the study protocol.

In addition to confirming the study performed by De Paepe *et al.*,⁴ this work makes a few important additions to this line of investigation. First, with a more severe hemorrhage (e.g., 30 vs. 17 ml/kg) in different species, the hemorrhage-induced pharmacokinetic changes are similar. Second, equivalent doses can lead to dramatically different plasma propofol levels and increased drug effect. Third, this work confirms the somewhat unusual finding presented by De Paepe *et al.* that the potency of propofol is increased in a setting of hemorrhagic shock.

Influence of Hemorrhagic Shock and Propofol on Cardiovascular Performance

Before initiating this study, we performed a series of pilot studies to determine the extent of hemorrhage and

the dose of propofol that our animal preparation would tolerate to complete our study protocol. It is interesting to point out that in previous work with opioids, we administered large doses (fentanyl at $10 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 5 min and remifentanyl for $10 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 10 min) with the goal of eliciting a measurable response in the processed electroencephalogram in swine bled to a mean arterial blood pressure of 40 mmHg. However, when this same approach was taken with propofol, the animals suffered cardiovascular collapse before completing the study protocol. Results from these pilot studies confirm what previous investigators have reported regarding the hemodynamic effects of propofol^{18,19} and illustrate the potentially serious consequence of using selected intravenous sedative hypnotics known to suppress the cardiovascular system in patients suffering from hemorrhagic shock.

As a result of our pilot studies, we reduced the severity of hemorrhagic shock and the propofol dose so that animals would survive the duration of the study protocol. Although reduced in severity, the hemorrhage model still introduced large variations in cardiovascular parameters. These included a 47% decrease in the cardiac index, an estimated 43% decrease in blood volume assuming a vascular volume of 70 ml/kg, and a 51% decrease in the mean arterial blood pressure. As investigators have suggested with other intravenous anesthetics,²⁰⁻²² we suspected that these changes in cardiovascular function would be large enough to alter the pharmacokinetic profile of propofol.

In addition to evaluating the implications of hemorrhagic shock on propofol pharmacokinetics, we also compared the influence of propofol *itself* on cardiovascular function between the control and shock groups. We found that a propofol infusion of $200 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, in the absence of hemorrhage, produced a small decrease in the mean arterial blood pressure (12%) and systemic vascular resistance (10%) with no observed change in the cardiac index or any other of the metabolic or hemodynamic parameters presented in table 2. These results were consistent with what other authors have reported as the hemodynamic consequences of a bolus dose and/or a continuous infusion of propofol in dogs and pigs.²³⁻²⁶ We next examined what influence a continuous infusion of propofol would have on the hemodynamics in the setting of hemorrhagic shock. We found no significant change in the metabolic or hemodynamic profile in the bled animals from before to after the propofol infusion, suggesting that the cardiovascular impact of propofol was diminished in an already depressed hemodynamic state during hemorrhagic shock.

Influence of Hemorrhagic Shock on Propofol Pharmacokinetics

Based on our study of fentanyl and remifentanyl pharmacokinetics during shock, we anticipated that propofol

plasma levels would be higher in shock. Inspection of the raw data confirmed our hypothesis. In shock animals, peak propofol plasma levels were over twofold higher and remained higher throughout the study period when compared with those of control animals.

Our pharmacokinetic parameters for propofol in the control group were similar to what has been reported in swine,²⁷ rodents,⁵ and humans,^{28,29} and, in the shock group, with what has been reported in bled rodents.⁵ The pharmacokinetic modeling techniques also confirmed our hypothesis. As expected, the noncovariate-adjusted mixed effects population model performed poorly. Without incorporating covariates into the population model, the model underestimated the plasma values observed in the shock group and overestimated the plasma values observed in the control group. In keeping with our findings with fentanyl² and remifentanyl,³ incorporating shed-blood volume, mean arterial blood pressure, or cardiac index improved the mixed effects population model accuracy substantially.

Our pharmacokinetic results for propofol were similar to those reported by De Paepe *et al.*⁵ They removed 17 ml/kg of blood over 30 min in rodents and reported a 60% decrease in the central compartment volume and a 31% decrease in central clearance. By comparison, we removed 30 ml/kg over an average of 43 min in swine and reported a 78 and 52% decrease in the fast and slow distribution clearances, respectively. A more complete comparison of other pharmacokinetic parameters is difficult because the work presented by De Paepe *et al.* has been parameterized differently from what we have reported.

Propofol has a large volume of distribution (*e.g.*, 300 l in humans²⁸) and exhibits rapid distribution to peripheral tissues after intravenous injection. We reported a large decrease in the clearance from the rapid and slow equilibrating peripheral compartments as a consequence of moderate hemorrhage. As demonstrated by Upton *et al.*, changes in cardiac output can significantly alter the pharmacokinetic profile of propofol.²¹ We found a 48% decrease in the cardiac index between shock and control animals and suggest that this decrease contributed to the reduction in propofol intercompartmental clearances.

We hypothesized that hemorrhagic shock would reduce clearance and suggested that this is a consequence of decreased hepatic perfusion. Previous work has established that propofol undergoes both hepatic and extrahepatic clearance,^{30,31} and that hepatic clearance accounts for a majority of the total propofol clearance.³² Propofol has a hepatic extraction ratio near 0.8³² and hence should clear propofol as quickly as it is presented to the liver. Thus, it is plausible that a reduction in hepatic perfusion alone could account for the observed reduction in total clearance. However, the contribution of extrahepatic sites to propofol clearance during hemorrhagic shock remains unclear.

Influence of Hemorrhagic Shock on Propofol Pharmacodynamics

Perhaps the most interesting finding of this study was that hemorrhagic shock increased end-organ sensitivity to propofol in swine. This is similar to what DePaepe *et al.*⁵ described in rodents and unlike what we have reported with remifentanyl in hemorrhagic shock.³ Our pharmacokinetic analysis revealed that after equivalent dosing, the mean propofol plasma concentration in the shock group increased 2.5-fold over the control group, suggesting that pharmacokinetics changes alone were responsible for the observed changes in drug effect. However, we also reported a 64% reduction in the C_{50} , indicating that pharmacodynamic changes contribute to the observed changes in dose response.

The mechanism of how hemorrhagic shock increases the potency of propofol is unclear. A potential mechanism may be the result of increased circulating endorphins that act in a synergistic fashion with propofol. Several researchers have demonstrated a decrease in the propofol dose requirements in the presence of opioids.^{33,34} For example, Pavlin *et al.* reported a 46% reduction (6.1 to 3.3 $\mu\text{g}/\text{ml}$) in the C_{50} of propofol with the coadministration of alfentanil in the presence of nitrous oxide.³³ Kazama *et al.* reported a 44% reduction in the propofol plasma concentration, in which 50% of patients did not respond to skin incision with the coadministration of fentanyl.³⁴ With this synergistic relationship in mind, investigators have demonstrated large increases in circulating β endorphins during hemorrhagic shock in a variety of models that include primates,³⁵ rats,³⁶ and dogs.³⁷ In an isobaric hemorrhage model in rats with a target mean arterial blood pressure of 40 mmHg, Molina demonstrated a fourfold increase in circulating β endorphins.³⁶ We suggest that the endogenous opioid interaction with propofol may play a role in the observed increase in propofol potency.

Computer Simulations

To highlight the clinical significance of our findings, we performed a series of simulations using combined pharmacokinetic/pharmacodynamic models for each study group (shock and control). In the first set of simulations, equivalent dosing of propofol led to a more rapid onset and prolonged duration of effect in bled *versus* unbled animals. In the second set of simulations, we demonstrated a marked decrease in the amount of propofol required to achieve an equivalent effect between bled and unbled swine. These simulations demonstrate how the combined changes in both the pharmacokinetics and pharmacodynamics mandate substantial dosage reduction to avoid hemodynamic toxicity and prolonged effect in the setting of hemorrhagic shock. These findings support the practice of moderating the dose of propofol or avoiding it all together when caring for patients who have suffered significant blood loss.

Study Limitations

Several limitations to this line of investigation have been discussed in previous work.^{2,3,5} For example, controlled, unresuscitated hemorrhagic shock is not typical of clinical practice, in which resuscitation is usually under way and ongoing hemorrhage may not be controlled before the administration of an intravenous anesthetic. Furthermore, many differences exist among species in (1) how they exhibit their response to hemorrhagic shock, such as differences in splenic red cell reserve and dissimilar hemoglobin p50s; and (2) the dosing requirements needed to achieve a desired clinical effect.

Another limitation of this study is related to our pharmacodynamic analysis. We used the BIS as a surrogate measure of propofol effect in swine. To our knowledge, BIS monitoring has undergone no formal validation in swine for scientific use. However, the BIS is derived from cerebral electrical activity, and components such as burst suppression or spectral edge have been used as surrogate measures of drug effect in swine.³⁸⁻⁴¹ One criticism of using measures of electroencephalographic activity as surrogates of drug effect in swine is that they have a thick skull that may attenuate the electroencephalographic signal. To account for this potential limitation, we used smaller swine. Although it is true that the electroencephalogram in swine has not been mapped to the clinical domain (and never will be), it is unquestionably a high-resolution surrogate measure of drug effect in swine. Plots of the concentration *versus* effect (BIS as a processed measure of electroencephalographic activity) demonstrate that quite convincingly.

An additional limitation of our pharmacodynamic analysis was that one animal from the control group failed to develop a response in the BIS after the administration of propofol. The BIS did not decrease during the propofol infusion, but the plasma propofol levels were similar to those levels observed in the other control group animals that did develop a BIS response.

Another limitation was that we administered propofol in the presence of isoflurane. One concern is that isoflurane would alter the concentration effect relationship of propofol as measured by the BIS and should be acknowledged when interpreting our pharmacodynamic profile of propofol in bled and unbled swine. No previous studies have investigated the dose response of isoflurane on the BIS in swine. However, the dose response of isoflurane on the BIS has been well established for humans¹⁵ and has been used as a measure of isoflurane effect in goats⁴² and horses.⁴³ As noted previously, we performed a series of pilot studies that demonstrated no significant effect from isoflurane on the BIS over the time course of the hemorrhage protocol used in this study.

In summary, we studied the influence of moderate blood loss on the pharmacologic behavior of propofol in swine. We found that hemorrhagic shock altered both

the pharmacokinetics and pharmacodynamics of propofol, demonstrating that less propofol is required to achieve a desired effect. Simulations using a combined pharmacokinetic/pharmacodynamic model constructed from these results indicated that the dose required to reach a target propofol effect site concentration is reduced 5.4-fold in moderate hemorrhagic shock. Although care should be taken in extrapolating results from animal studies to clinical practice, our results and simulations support the wise practice of moderating the dose of propofol administered to patients in hemorrhagic shock.

The authors are grateful for the propofol assay work performed by Sang Park, Ph.D., Research Scientist with the Analytical Facility, Department of Anesthesiology, University of Washington, Seattle, Washington.

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