

Influence of Hemorrhagic Shock on Remifentanyl

A Pharmacokinetic and Pharmacodynamic Analysis

Ken B. Johnson, M.D.,* Steven E. Kern, Ph.D.,† Elizabeth A. Hamber, M.D.,‡ Scott W. McJames, M.S.,§
Kateljine M. Kohnstamm, B.S.,|| Talmage D. Egan, M.D.¶

Background: Hemorrhagic shock is known to alter significantly the pharmacokinetics of fentanyl, an opioid that requires delivery to the liver for metabolism. The authors hypothesized that the pharmacokinetics and pharmacodynamics of remifentanyl, an esterase metabolized opioid that does not require delivery to a metabolic organ, would be altered less by hemorrhagic shock than those of fentanyl.

Methods: Sixteen pigs were assigned randomly to control and shock groups. The shock group was bled using an isobaric hemorrhage model. Remifentanyl $10 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ was infused for 10 min to both groups. Arterial samples were collected for remifentanyl concentration assay. Pharmacokinetic parameters were estimated using a three-compartment model. The electroencephalogram spectral edge was used as a measure of drug effect. The pharmacodynamics were characterized using a sigmoid inhibitory maximal effect model.

Results: Remifentanyl blood levels were higher in the shocked group. The central clearance was slower and the central compartment was smaller in shocked animals. No difference between groups was observed in the magnitude or time course of the remifentanyl-induced decrease in spectral edge.

Conclusions: Hemorrhagic shock altered the pharmacokinetics of remifentanyl, suggesting that less remifentanyl would be required to maintain a target plasma concentration. However, because of its rapid metabolism, the impact of hemorrhagic shock on the concentration decline of remifentanyl after termination of the infusion was minimal. Hemorrhagic shock did not alter the pharmacodynamics of remifentanyl.

ANESTHESIOLOGISTS have long recognized the need to moderate the dose of opioids for patients who have significant blood loss before or during surgery. However, the scientific rationale for moderating doses of opioids during hemorrhagic shock is not well established.

Prior work in our laboratory investigated the influence of severe blood loss on the pharmacokinetics of fentanyl in a porcine isobaric hemorrhagic shock model. We found that after a 5-min fentanyl infusion, plasma levels

in shocked swine were twofold higher than in controls.¹ Using a compartmental model to estimate pharmacokinetic parameters, we found that hemorrhagic shock reduced the central compartment volume and clearance. As described by Hughes *et al.*,² we performed computer simulations of the context-sensitive half-time (the time required to achieve a 50% decrease in plasma concentration after termination of an infusion) as a means of understanding the clinical impact of shock on the pharmacokinetics of fentanyl. Our kinetic simulations revealed a prolonged context-sensitive half-time in shocked animals for fentanyl infusions longer than 100 min. We concluded that the shock-induced changes in pharmacokinetic parameters were primarily caused by alterations in the rapid distribution of fentanyl during and shortly after the infusion and a reduction in fentanyl clearance. Based on the known decrease in hepatic perfusion and function in isobaric shock models,³⁻⁸ we speculated that fentanyl metabolism in the liver was compromised, resulting in the prolonged context-sensitive half-time.

In view of these results for fentanyl, we investigated the influence of hemorrhagic shock on the pharmacokinetics and pharmacodynamics of remifentanyl, an esterase metabolized opioid that does not require delivery to a metabolic organ for metabolism. Our hypothesis was that the distribution characteristics of remifentanyl would be changed in a fashion similar to what we observed with fentanyl (a reduction in the central compartment volume and steady state distribution volume). Furthermore, we hypothesized that because the metabolism of remifentanyl is rapid and independent of hepatic perfusion, the shock-induced changes in clearance would be less marked and would not produce as great an effect on the context-sensitive half-times as observed with fentanyl. Finally, based on our clinical observation that reduced doses of opioid appear to be adequate despite the pharmacokinetic changes we have documented, we hypothesized that the pharmacodynamics of remifentanyl would not be substantially altered by hemorrhagic shock.

Methods and Materials

Experimental Design

Experiments were performed on commercial farmed pigs of either sex. The study was approved by the Institutional Animal Care and Use Committee at the University of Utah. Animals were randomly assigned to ei-

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* Interim Instructor, † Research Assistant Professor, § Research Associate, || Research Fellow, ¶ Associate Professor, Department of Anesthesiology, University of Utah School of Medicine. ‡ Anesthesiologist, St. Mary's Health Services, Grand Rapids, Michigan.

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Address reprint requests to Dr. Johnson: Department of Anesthesiology, University of Utah School of Medicine, Salt Lake City, Utah 84132. Address electronic mail to: kjohnson@anesth.med.utah.edu. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

ther 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 remifentanil infusion. Animals in the control group were instrumented in an identical fashion to the shock group and maintained in an anesthetized ventilated state for 60 min before receiving the remifentanil infusion. This was performed to ensure that both groups would receive the remifentanil infusion after near equivalent times under anesthesia.

Animal Preparation

Swine weighing between 21 and 31 kg were commercially obtained and quarantined for 6 days in a temperature- and light-controlled environment. Animals had access to food and water *ad libitum*. Anesthesia was induced with an intramuscular injection of 1.7 mg/kg tiletamine HCl and 1.7 mg/kg zolazepam. Intravascular access was obtained from an ear vein. Muscle relaxation was achieved with an intravenous injection of succinylcholine (1.5 mg/kg).

The animal's tracheas were 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 fraction of inspired oxygen 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 oxygen saturation by pulse oximetry above 95% and the end-tidal carbon dioxide at 38 ± 2 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 carbon dioxide partial pressure at 40 ± 2 mmHg.

A continuous level of anesthesia was achieved with isoflurane and intermittent bolus doses of pancuronium (0.1 mg/kg). Expired isoflurane levels were monitored and kept at 1.0 minimum alveolar concentration equivalent for swine.⁹ Subcutaneous electrocardiograph electrodes were placed, and the electrocardiograph was monitored throughout the study.

The left femoral artery was cannulated with a 16-gauge arterial sheath using sterile technique 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

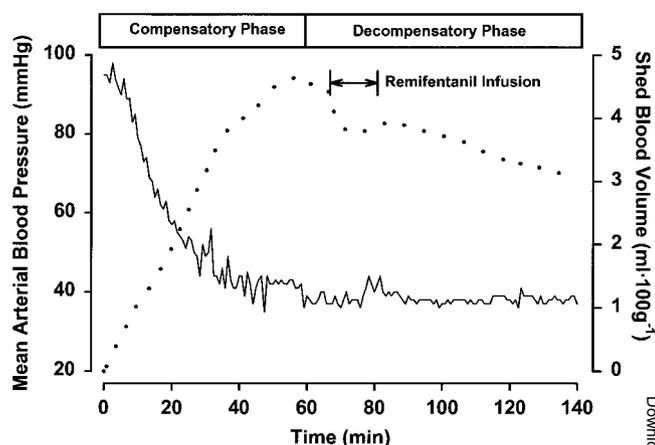


Fig. 1. Typical time course of mean arterial blood pressure (solid line) and shed blood volume (dotted line) changes during an isobaric hemorrhage to 40 mmHg.

heparin (100 U/kg body weight) and allowed to stabilize for 10 min before starting the protocol.

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 electroencephalographic machine. Digitized raw electroencephalographic waveform data and processed electroencephalographic values were collected electronically.

Remifentanil ($10 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) was administered intravenously at a constant-rate infusion using a syringe pump (model number AS40a; Baxter, Deerfield, IL) for 10 min. During and after 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. During the infusion, samples were collected every 2 min. After the infusion was stopped, samples were collected at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 7.5, 10, 15, 20, 30, 40, 50, and 65 min.

Hemorrhage Protocol

The hemorrhage protocol was designed to ensure that each animal was at an equivalent degree of metabolic compromise from hemorrhagic shock before initiating the remifentanil infusion. This was accomplished by using an isobaric hemorrhage model and tracking the progression of the lactic acidemia before drug infusion.

Animals in the hemorrhage group were bled in an isobaric fashion using a computer-controlled algorithm based on a modified Wiggers' isobaric hemorrhage model.¹⁰ The arterial blood pressures were measured with a pressure transducer (Utah Medical, Midvale, UT). Blood was removed and stored in a citrated bag at a rate required to achieve a mean arterial blood pressure (MABP) of 40 mmHg over 20 min. Blood was then removed or reinfused by a servo-controlled peristaltic

pump to maintain the target pressure as shown in figure 1. With the blood reservoir bag on a scale, shed blood volume was determined from the weight.

The compensatory phase of hemorrhagic shock was defined as the time during which blood had to be removed to maintain the MABP at 40 mmHg. The decomensatory phase of hemorrhagic shock was defined as the time period during which blood had to be reinfused to maintain the MABP at 40 mmHg. A computerized data acquisition system recorded the MABP, systolic and diastolic arterial pressures, heart rate, and shed blood volume every 5 s. The peak shed blood volume (PSBV) was defined as the maximum amount of blood removed during the isobaric hemorrhage process.

Arterial blood samples for pH, oxygen partial pressure, carbon dioxide partial pressure, 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) at 25% intervals of the estimated PSBV and at the actual PSBV. Sampling times were based on an estimated PSBV of 45 ml/kg body weight.

The remifentanyl infusion was initiated once the animals reached the actual PSBV manifested by (1) the need to reinfuse shed blood to maintain the MABP at 40 mmHg for at least 5 min, and (2) a plasma lactate level greater than 2 mM. Metabolic (plasma lactate, plasma glucose, and arterial pH) and hemodynamic parameters (heart rate, MABP, and cardiac output) were recorded at the time of infusion. Metabolic and hemodynamic parameters for each group were compared at the time of blood reinfusion using an unpaired two-tailed Student *t* test. *P* values less than 0.05 were considered significant.

Blood Sampling Processing and Concentration Assay

Because of the metabolic pathway of remifentanyl, special processing was necessary to prevent continued metabolism of remifentanyl after sample collection. The process consisted of inhibition of remifentanyl hydrolysis in whole blood by the addition of 20 μ l of 50% citric acid per milliliter of blood immediately after collection. Samples were agitated for 1 min and then immediately stored at -20°C until the time of assay. Remifentanyl blood concentrations were measured by a high-pressure liquid chromatography assay with ultraviolet detection with a quantitation limit of 1 ng/ml.¹¹

Pharmacokinetic Analysis

The concentration-*versus*-time data for both groups was analyzed using several techniques. First, estimates of the individual pharmacokinetic parameters for a three-compartment model were made using a two-stage approach using pharmacokinetic modeling software (Win-

NonLin; Pharsight Corporation, Mountain View, CA). Second, an exploration of pharmacokinetic parameter-covariate relations was made. Third, the control and shock groups were combined to build a population model using nonlinear mixed-effect modeling software (NONMEM; University of California-San Francisco, San Francisco, CA). Covariates demonstrating a strong correlation with pharmacokinetic parameters were introduced into the population model in an effort to improve the model's ability to predict remifentanyl blood concentrations. Finally, computer simulations based on the mean of individual pharmacokinetic parameters for each group were performed to provide more clinically relevant meaning to the analysis. Linear pharmacokinetic were assumed for the purposes of these analyses.

Two-stage Analysis. A two-stage approach implemented in WinNonLin was performed to estimate the mean pharmacokinetic parameters for each group. The first stage involved fitting a three-compartment mammillary model to the remifentanyl concentration-*versus*-time data to estimate the pharmacokinetic parameters for each animal. The triexponential equation for each animal was parameterized in terms of clearances and apparent distribution volumes. The second stage 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. *P* values less than 0.05 were considered significant.

Exploration of Parameter-Covariate Relations. The feasibility of using hemodynamic and metabolic 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.*¹² Covariate parameters included a mean of the following parameters during the drug infusion: shed blood volume, heart rate, MABP, cardiac index, plasma lactate levels, arterial pH and plasma glucose levels. This step was intended to identify useful relations and to characterize the shape of these relations between model parameters and covariates.

Nonlinear Mixed-effects Model Analysis. In contrast to the two-stage approach, remifentanyl concentration-*versus*-time data for both the shock and control groups were combined and used to construct a three-compartment population pharmacokinetic model using NONMEM. NONMEM simultaneously analyzed the entire population's data and provided an estimate of typical values for the parameters along with an estimate of the parameter's interindividual variability. Interindividual variability on each parameter 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 in the individual, θ_{typical}

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is the population mean estimate, and $\eta^{\text{individual}}$ is a random variable whose distribution is estimated by NONMEM with a mean of zero and a variance of ω^2 . The estimates of ω obtained with NONMEM are similar to the coefficient of variation often used in standard descriptive statistics. Residual error was modeled assuming a log-normal distribution.

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 weighted residuals (WRs), 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 NONMEM 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 WR (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 constructed by NONMEM were computed. The median WRs, a measure of model bias, were also computed. The performance of each model was also visually assessed by plotting the C_m/C_p versus time and examining the plots for accuracy and bias.

Model Expansion with Covariate Effects. After obtaining the best NONMEM model without covariates, the influence of shed blood volume, heart rate, MABP, cardiac index, plasma lactate, arterial pH, and plasma glucose were evaluated. Guided by the initial regression analysis exploring the relations 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. The objective function was defined as negative two times the log likelihood. A change in the objective function of at least 4 was viewed as sufficient justification to include an additional parameter in the model (in the form of a covariate or covariate plus a constant that represented the addition of two model parameters). A total of 63 different models were tested. The 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, median WRs, and C_m/C_p -versus-time plots were generated for each model to assess the extent of model improvement. Those covariate combinations with the largest reduction in the MDAWR are presented in tabular and graphical form.

Computer Simulations. Computer simulations using the pharmacokinetic parameters obtained from the two-stage approach provided an illustration of the predicted decline in blood concentration in the shock and control groups when remifentanyl is administered by infusion. These simulations were used to predict the time necessary to achieve a 50 or 80% decrease in drug concentration after termination of a variable-length infusion targeted to a constant drug concentration in blood as described by Hughes *et al.*² The simulations are based on Euler's solution to the three-compartment model with a step size of 1 s. Four simulations were performed for a 30-kg pig: a 50% and 80% decrement time for both the shock and control groups.

Pharmacodynamic Analysis

Spectral Edge Analysis. The pharmacologic effect of remifentanyl was characterized by examining the influence of remifentanyl on the spectral edge frequency as described by Scott *et al.*,^{13,14} who used spectral edge as a surrogate measure of opioid effect with fentanyl, sufentanil, and alfentanil. The spectral edge was calculated by the Aspect A1000 machine. The spectral edge was determined by calculating the area under the power-versus-frequency histogram and identifying the frequency below which 95% of the total area is found.¹⁵

Because we were concerned that shock itself in the absence of remifentanyl might alter the electroencephalographic waveform, pilot studies were conducted to exclude this possibility. The isobaric hemorrhagic shock protocol elicited no significant change in the spectral edge when compared with normotensive animals under identical anesthetic conditions.

Parametric Modeling of the Concentration-Effect Relation. Because plots of the concentration-effect relation were sigmoid in shape, an inhibitory sigmoid E_{max} equation (*i.e.*, Hill equation) was used to model the relation parametrically.¹⁶ Using WinNonLin, the equation

$$E = E_0 - (E_0 - E_{\text{max}}) \times [C_b^{\gamma} / (C_b^{\gamma} + EC_{50}^{\gamma})]$$

where E is the predicted effect, E_0 is the baseline effect level, E_{max} is the maximal effect, C_b is the blood concentration, γ is a measure of curve steepness, and EC_{50} is the blood concentration that produces 50% of maximal effect, was fit to the effect-versus-plasma concentration data.

Computer Simulations. Computer simulations were performed using the full pharmacokinetic-pharmacodynamic model from the study to illustrate the clinical application of the estimated parameters. The first simulation was intended to illustrate the time to peak concentration and magnitude and duration of effect for a bolus and infusion of remifentanyl using typical human dosages of remifentanyl. The first simulation estimated remifentanyl blood levels after bolus administration (1 $\mu\text{g}/\text{kg}$ body weight) followed by an infusion

Table 1. Hemodynamic and Metabolic Parameters in Control and Hemorrhaged Animals Just before Remifentanyl Infusion

Parameter	Control Group	Hemorrhage Group
Heart rate	127 ± 5.6	217 ± 8.7*
Mean arterial blood pressure	82 ± 4.5	39.7 ± 1.0*
Cardiac index	5.1 ± 0.3	1.7 ± 0.3*
Plasma lactate	1.3 ± 0.2	7.5 ± 1.0*
Plasma glucose	78 ± 6.3	155 ± 4.4
Arterial pH	7.45 ± 0.02	7.33 ± 0.04†

Data are presented as mean ± SEM.

* $P < 0.001$. † $P < 0.01$.

($0.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) using parameters derived from the control and shock groups. The second simulation, intended to illustrate dosing requirements of an equipotent infusion, was a simulation of the total dose required to deliver a 1-h computer-controlled infusion targeted to the blood EC_{50} for both control and shock groups. Simulations were performed using drug infusion simulation software (Stanpump; Stanford University, Palo Alto, CA).

Results

Effect of Hemorrhagic Shock on Metabolic Parameters

Animals subjected to the isobaric hemorrhagic shock protocol developed a lactic acidemia once the PSBV was achieved when compared with control animals. A comparison of mean heart rate, cardiac index, MABP, plasma lactate levels, plasma glucose levels, and arterial pH is presented in table 1. Cardiac index data were not available in two of the shock animals because of technical problems. An example of the typical changes in blood pressure and shed blood volume during the isobaric hemorrhage is presented in figure 1. The average shed blood volume at the time of drug administration was $48 \pm 2.2 \text{ ml/kg}$ body weight. The average shed blood volume returned during the 10-min infusion of remifentanyl to maintain the MABP at 40 mmHg was $4.1 \pm 1.0 \text{ ml/kg}$ body weight.

Pharmacokinetic Analysis

The infusion of remifentanyl administered in this protocol resulted in time-versus-concentration curves characteristic of brief intravenous infusions. The mean remifentanyl concentrations in the shock and control groups are contrasted in figure 2. The shock group reached higher peak concentrations and exhibited higher levels throughout the experiment. The shock group also exhibited greater pharmacokinetic variability.

Two-stage Analysis. The raw concentration-versus-time data were adequately described by a three-compartment model. The two-stage compartmental analysis revealed a smaller central compartment volume (V_1), a smaller peripheral compartment (V_2), and a slower rate

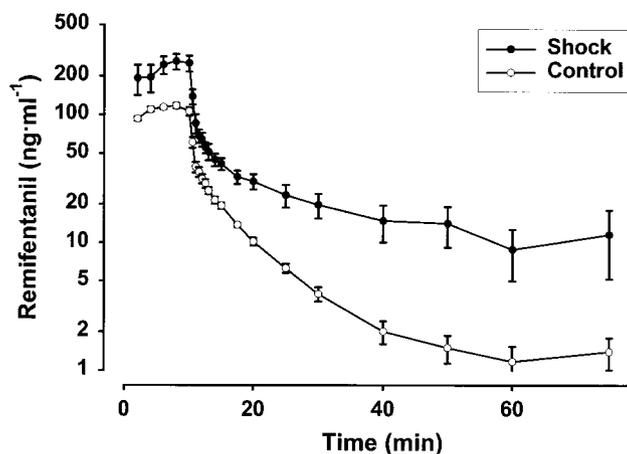


Fig. 2. Mean remifentanyl blood concentration-versus-time data. The open circles represent the mean blood level for normotensive animals, and the solid circles represent the mean blood level for shocked animals.

of clearance from the central compartment (Cl_1) in the shocked animals. All other pharmacokinetic parameters for the shocked and control groups were not different. The two-stage three-compartment model parameters for each group are shown in table 2.

Exploration of Parameter-Covariate Relations

Plots of the individual parameter estimates versus the covariates revealed several potentially useful relations. The most pronounced relations were found between the central compartment clearance and shed blood volume, MABP, or cardiac index. The results of these linear regressions, including the coefficients of determination (*i.e.*, r^2) are presented in table 3. Selected parameter-covariate relations are presented in figure 3.

Nonlinear Mixed-effects Model Population Analysis. The simple (*i.e.*, no covariates) population model parameters are presented in table 4. The performance of the NONMEM population model with no covariates (*i.e.*, simple model) is presented graphically in figure 4. Measured blood remifentanyl levels are plotted along with

Table 2. Mean and Standard Error of Individual Parameter Estimates (Two-stage Approach)

Parameter	Control Group	Hemorrhage Group
Volumes (l)		
Central	1.4 ± 0.3	0.7 ± 0.1*
2nd peripheral	3.7 ± 0.8	1.4 ± 0.5*
3rd peripheral	25.1 ± 12.6	12.6 ± 7.2
Steady state	30.2 ± 13.1	14.7 ± 7.1
Clearance (l/min)		
Central	1.9 ± 0.1	0.8 ± 0.1†
Intercompartmental 1	0.8 ± 0.1	0.5 ± 0.1
Intercompartmental 2	0.4 ± 0.1	0.5 ± 0.2
Half-lives (min)		
α	2.6 ± 0.4	2.7 ± 0.4
β	0.2 ± 0.1	0.4 ± 0.1
γ	0.1 ± 0.0	0.1 ± 0.0

Data are presented as mean ± SEM.

* $P < 0.05$. † $P < 0.01$.

Table 3. Linear Regression Analysis of Selected Covariates versus Individual Pharmacokinetic Parameter Estimates

	Intercept	Slope	r ²	P Value
V ₁ versus MABP	0.2	0.015	0.30	0.026
V ₁ versus SBV	1.4	-0.015	0.30	0.027
V ₁ versus CI	0.4	0.204	0.30	0.041
Cl ₁ versus MABP	0.0	0.021	0.65	<0.001
Cl ₁ versus SBV	1.9	-0.025	0.86	<0.001
Cl ₁ versus CI	0.5	0.250	0.68	<0.001

V₁ = central compartment volume; Cl₁ = clearance from central compartment; MABP = mean arterial blood pressure; SBV = shed blood volume; CI = cardiac index.

the population model estimates for the control group (fig. 4A) and the shock group (fig. 4B). The simple population model underestimated measured blood concentrations in the shocked animals and overestimated them in the control animals. In figure 4C, a C_m/C_p-versus-time plot demonstrates a wide range of variability in the population model's overestimate of remifentanyl concentrations in shocked animals and, by contrast, and a more narrow range of variability in the population

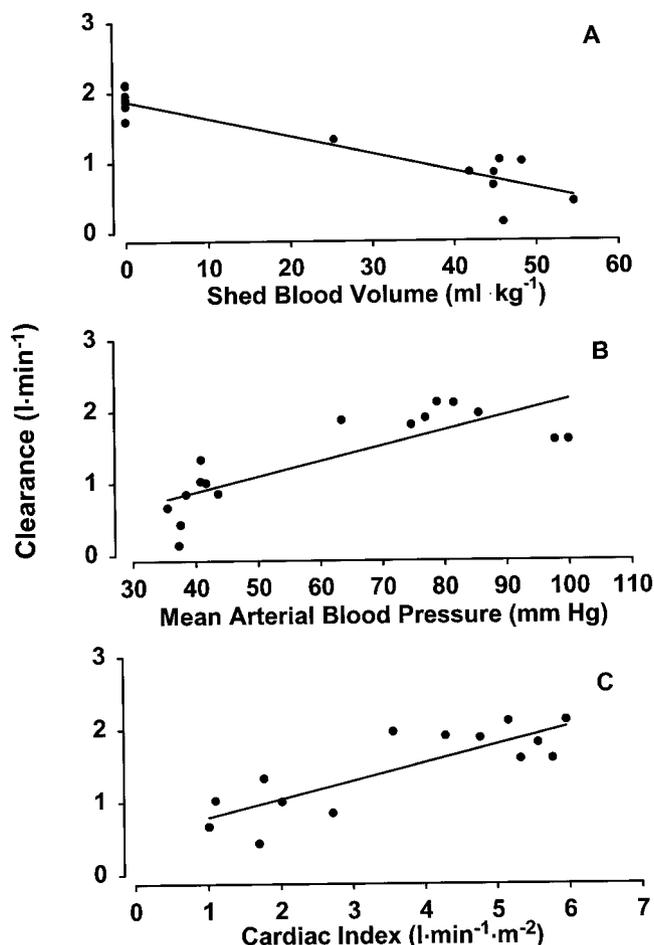


Fig. 3. (A) A plot of the central compartment clearance versus shed blood volume. (B) A plot of central compartment clearance versus mean arterial blood pressure. (C) A plot of the central compartment clearance versus cardiac index.

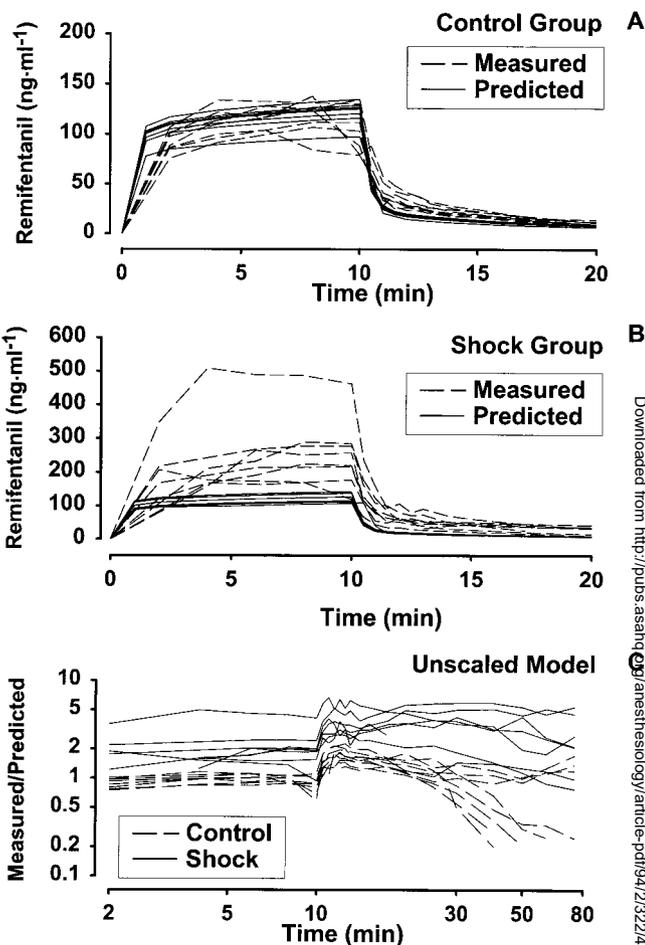


Fig. 4. Measured (dashed lines) and population model estimate (solid lines) of remifentanyl blood levels for the control group (A) and the shock group (B) using the simple NONMEM model. (C) The measured over predicted plot for the population model using all animals from both the control and shock groups. Each line represents the performance of the simple NONMEM population model when applied to an individual pig. A pig whose blood concentrations were perfectly predicted by the model would be represented by a straight line at 1. Solid lines represent shock animals, and dashed lines represent control animals.

model's underestimate of remifentanyl concentrations in control animals.

Model Expansion with Covariate Effects. Sixty-three evaluations were made exploring the influence of (1) individual covariates, (2) combinations of covariates, and (3) intercept terms from the parameter-covariate analysis on improving the accuracy of the population model. Optimal population model performance was achieved by scaling the central compartment clearance and volume to the shed blood volume covariate, as was suggested by the initial exploration of the parameter-versus-covariate relations. An intercept term for both the central compartment clearance and volume improved the model. Combinations of other covariates did not improve the model. Although scaling clearance to the cardiac index covariate yielded a lower objective function value, it did not improve the model bias or MDAWR

Table 4. Simple and Final Covariate Expanded NONMEM Population Models

Model	Simple	Central Compartment Clearance and Volume Scaled to SBV with a Constant
Central compartment volume (l)	0.9	$(0.015 \times \text{SBV}) + 0.37$
2nd peripheral compartment volume (l)	2.0	8.3
3rd peripheral compartment volume (l)	12.9	1.96
Central compartment clearance (l/min)	1.8	$(0.025 \times \text{SBV}) + 0.13$
Intercompartmental clearance 1 (l/min)	0.4	0.32
Intercompartmental clearance 2 (l/min)	0.4	0.24

SBV = shed blood volume.

as great as the shed blood volume covariate. The parameter values for the shed blood volume-scaled NONMEM model are presented in table 4.

Scaling the central compartment clearance and volume to shed blood volume resulted in an improvement in the objective function from 1,512 to 1,305 and an improvement in the MDAWR and median WR. These results, including the MDAWR 10th and 90th percentile values, are shown in table 5. The performance of the best covariate enhanced model is presented graphically in figure 5. Measured remifentanyl levels are plotted along with the population model estimates of blood levels for the shock group (fig. 5A) and the control group (fig. 5B). Here, the population model demonstrated improved estimates of measured remifentanyl levels in both the shocked and control animals as manifest by an improvement in the bias and MDAWR. In figure 5C, a C_m/C_p versus-time plot demonstrates a narrowing in the range of variability in the population model's estimate of remifentanyl in all animals. The results of some other covariate models that were evaluated merit attention. Although heart rate, cardiac index, and plasma lactate demonstrated favorable relations to pharmacokinetic parameters in the regression analysis, these covariates did not improve the population model.

Computer Simulations. The context sensitive half-time simulations demonstrated that hemorrhagic shock produced only minimal changes in the pharmacokinetic behavior of remifentanyl. The time required to achieve a 50% decrease in the remifentanyl blood level after termination of an infusion was nearly identical for both groups and was independent of infusion duration (fig. 6). The time required to achieve an 80% decrease in

remifentanyl blood levels was longer for the shock group (6.6 min) when compared with the control group (3.3 min)

Pharmacodynamic Analysis

Spectral Edge Analysis. The remifentanyl infusion produced a large decrease in the spectral edge that returned to baseline within 30 min of the infusion for both the control and shock groups (fig. 7). The timing and magnitude of the remifentanyl-induced decrease in spectral edge was not significantly different between control and shock groups. The differences in these parameters between these groups were not significant.

Parametric Modeling of the Concentration-Effect Relation. Similar to the timing and magnitude of the decrease in spectral edge during the remifentanyl infusion, there was no significant difference between EC_{50} values for the shock and the control groups, respectively. The pharmacodynamic parameters for each group are presented in table 6. The concentration-effect relation for each animal as characterized by the pharmacodynamic model is shown in figure 8.

Computer Simulations. The computer simulation revealed differences in the clinical pharmacology of remifentanyl between the control and shock groups. The simulation of a typical remifentanyl bolus dose ($1 \mu\text{g}/\text{kg}$) followed by a remifentanyl infusion ($0.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) for both study groups is presented in figure 9. The simulation of the bolus dose yielded a peak remifentanyl blood concentration of 28 and 15 ng/ml for the shock and control groups, respectively. The simulation of the infusion yielded a peak remifentanyl blood concentration of 9 and 6 ng/ml for the shock and control groups, respectively.

Table 5. Median Absolute Weighted Residuals (MDAWR), 10th and 90th MDAWR Percentiles, Median Weighted Residuals (MDWR), and NONMEM Objective Function Values for Selected NONMEM Population Models

	Median (%)	10th Percentile (%)	90th Percentile (%)	MDWR (%)	Objective Function
Simple	66	9	346	62	1,512
Cl_1 scaled to MABP with k	31	6	113	18	1,381
Cl_1 scaled to CI with k	40	7	135	25	1,194
Cl_1 scaled to SBV with k	32	5	85	10	1,329
Cl_1 and V_1 scaled to SBV with k	32	3	100	14	1,305

Cl_1 = central compartment clearance; MABP = mean arterial blood pressure; k = constant; CI = cardiac index; SBV = shed blood volume; V_1 = central compartment volume.

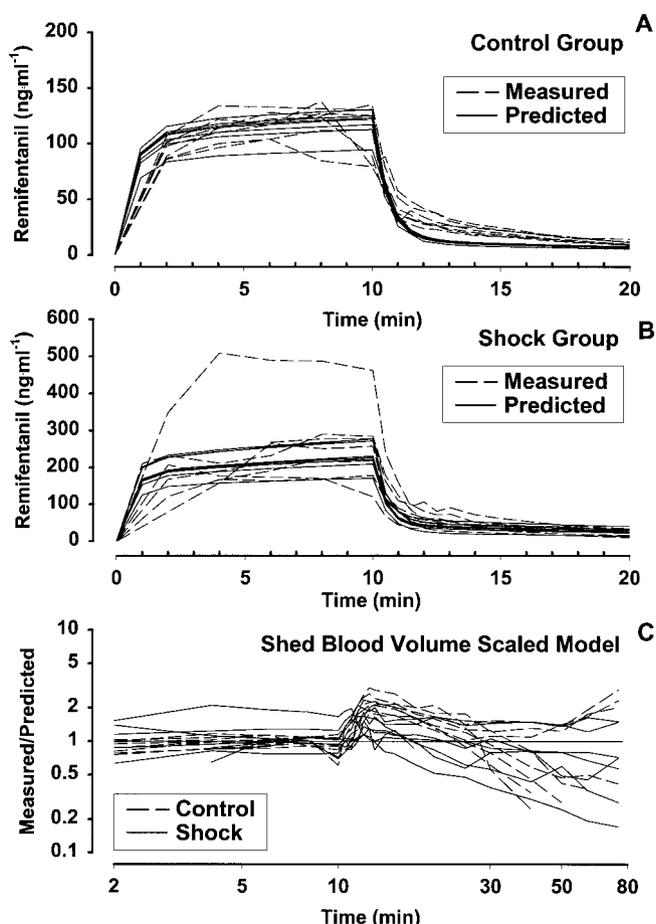


Fig. 5. Measured (dashed lines) and covariate (shed blood volume) adjusted population model estimates (solid lines) of remifentanil blood levels for the control group (A) and the shock group (B). (C) The measured over predicted plot for the shed blood volume adjusted population model using all animals from both the control and shock groups. Each line represents the performance of the shed blood volume adjusted population model when applied to an individual pig. A pig whose blood concentrations were perfectly predicted by the model would be represented by a straight line at 1. Solid lines represent shock animals, and dashed lines represent control animals.

These results suggested that during shocked conditions, conventional dosing would result in elevated remifentanil blood concentrations, leading to a more pronounced opioid effect. Further simulations were performed examining the difference between the total dose required to maintain the EC₅₀ with shock group pharmacokinetic parameters and the total dose required to maintain the EC₅₀ with control group pharmacokinetic parameters for 60 min. Because there was no difference in the EC₅₀ between the shock and control groups, the target EC₅₀ was the average of all EC₅₀ measurements (24 ng/ml). The total dose required to maintain the EC₅₀ with the control group parameters was larger than the dose required to maintain the EC₅₀ with the shock group parameters (114 vs. 74 μg/kg, respectively).

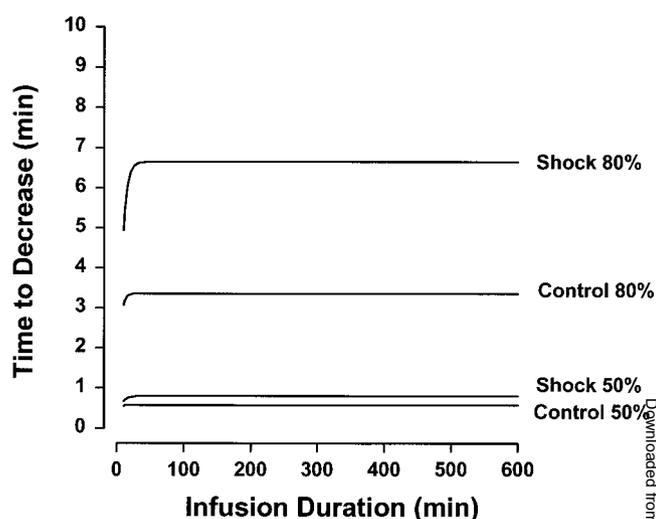


Fig. 6. A simulation of the time necessary to achieve a 50 or 80% decrease in remifentanil blood concentration after variable length intravenous infusions of remifentanil. These simulations were performed using the two-stage three-compartment model parameters.

Discussion

We examined the effect of hemorrhagic shock on the pharmacokinetics and pharmacodynamics of remifentanil. We hypothesized that severe blood loss would alter the pharmacokinetics but not the pharmacodynamics of remifentanil. Our hypothesis was confirmed. The most important findings of this study were threefold. First, severe hemorrhage decreased the central compartment volume and clearance, resulting in elevated remifentanil blood concentrations. Second, when these kinetic differences were examined for clinical relevance through the use of a context-sensitive half-time computer simulation, minimal impact was observed. Finally, severe hemorrhage did not significantly change the pharmacodynamics (*i.e.*, potency) of remifentanil.

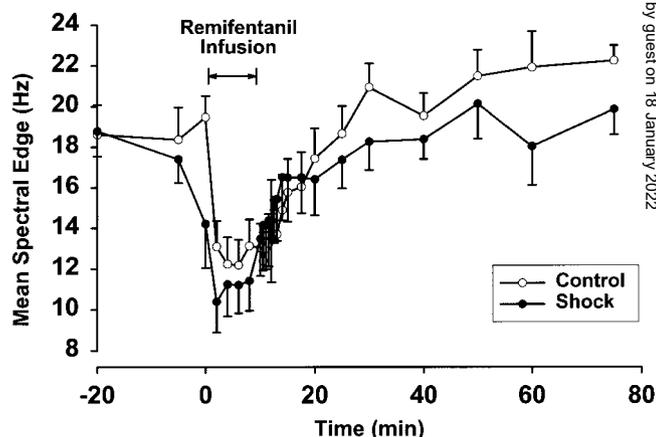


Fig. 7. Mean spectral edge changes versus time during the remifentanil infusion. The open circles represent the mean spectral edge measurements for the control animals, and the solid circles represent the mean spectral edge measurements for the shocked animals.

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Table 6. Pharmacodynamic Parameters

Parameter	Control Group	Hemorrhage Group	P Values
E_0 (Hz)	22.5 ± 0.8	20.3 ± 1.2	0.12
E_{max} (Hz)	13.8 ± 1.5	11.1 ± 1.1	0.13
γ	5.6 ± 0.9	5.6 ± 1.1	0.98
EC_{50} (ng/ml)	25 ± 3	23 ± 4	0.62

Data are presented as mean ± SEM.

E_0 = baseline spectral edge effect level; E_{max} = maximal spectral edge effect; γ = a measure of curve steepness; EC_{50} = effect-site concentration that produces 50% of maximal spectral edge effect.

Influence of Hemorrhagic Shock on Remifentanyl Pharmacokinetics

Based on our study of fentanyl pharmacokinetics during shock, we anticipated remifentanyl blood levels would be higher in shock. Inspection of the raw data confirmed our hypothesis. In shocked animals, peak remifentanyl blood levels were more than twofold higher and remained higher throughout the study period when compared with control animals.

The pharmacokinetic modeling techniques also confirmed our hypothesis. The two-stage compartmental analyses demonstrated a decrease in the central compartment volume and clearance in shocked animals. As expected, the non-covariate-adjusted mixed-effects population model performed poorly. In keeping with our findings regarding fentanyl, incorporating shed blood volume, MABP, or cardiac index improved the mixed-effects population model accuracy substantially.

Kinetic simulations of the context-sensitive half-time were also consistent with our hypothesis. Unlike our findings with fentanyl, where hemorrhagic shock prolonged the context-sensitive half-time with long infusions, the context-sensitive half-time of remifentanyl was only minimally effected by hemorrhagic shock. Youngs and Shafer,¹⁷ in their analysis of how pharmacokinetic parameters influence a range of decrement times, identified a subset of key pharmacokinetic parameters that impact decrement times for fentanyl, sufentanyl, and alfentanil. As one would intuitively expect, they found that an increase in the central compartment volume or a decrease in central compartment clearance prolonged the context-sensitive half-time. We hypothesized that hemorrhagic shock would decrease the central compartment volume and decrease the central compartment clearance, and our pharmacokinetic analysis confirmed this hypothesis. Thus, based on the work of Youngs and Shafer,¹⁷ we speculated that hemorrhagic shock might introduce two opposing influences on the context-sensitive half-time: a reduced central compartment volume that would shorten the context-sensitive half-time and a decreased central compartment clearance that would lengthen the context-sensitive half-time.

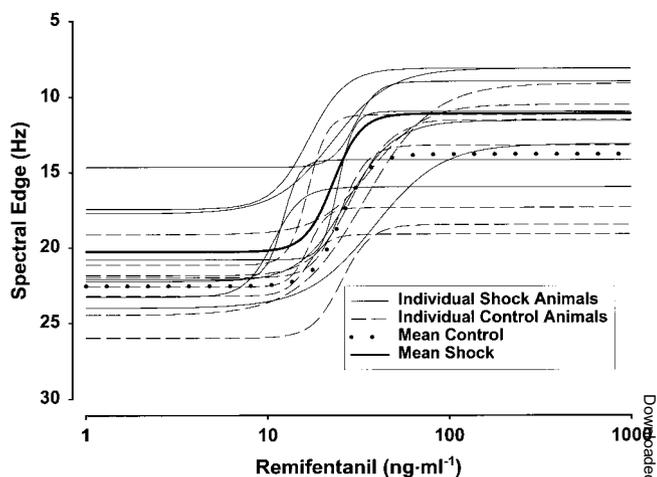


Fig. 8. The concentration–effect relation for each animal as characterized by the pharmacodynamic model. The solid lines represent the control animals over a remifentanyl blood concentration range of 1–1,000 ng/ml. The dotted lines represent the shocked animals over the same range. The bold lines portray the mean pharmacodynamic model for each group. The horizontal axis is on the log scale.

Influence of Hemorrhagic Shock on Remifentanyl Pharmacodynamics

Before beginning our study, we examined the effect of severe blood loss on the electroencephalogram spectral edge in three pilot animals that did not receive remifentanyl. We anticipated that hemorrhagic shock would not significantly change the electroencephalogram waveform because compensatory mechanisms such as cerebral blood flow autoregulation are at work to preserve brain function.¹⁸ We found no change in the spectral edge throughout our hemorrhage protocol, and, specifically, no change was noted during the phase in isobaric hemorrhage, where we planned to administer remifentanyl. In addition, we found that during the 10 min just after reaching the PSBV, the time that would have corresponded to the remifentanyl infusion, no shed blood was returned to maintain the MABP at 40 mmHg.

The dose of remifentanyl we used produced a large decrease in the spectral edge in both the shocked and control animals, suggesting that sufficient drug had been administered to elicit maximum drug effect. Plots of the spectral edge–versus–plasma concentration revealed minimal hysteresis, and thus modeling of an “effect compartment” was unnecessary.

The simulations presented in figure 9A were consistent with the pharmacokinetic profile observed in our raw data. Remifentanyl blood levels were consistently higher in the bolus and infusion simulations using parameters derived from the shock group when compared with the simulations using parameters derived from the control group. In these simulations, we administered doses of remifentanyl typical of clinical practice in humans. However, the blood levels reached were well below the EC_{50} for remifentanyl except for the bolus dose of remifentanyl

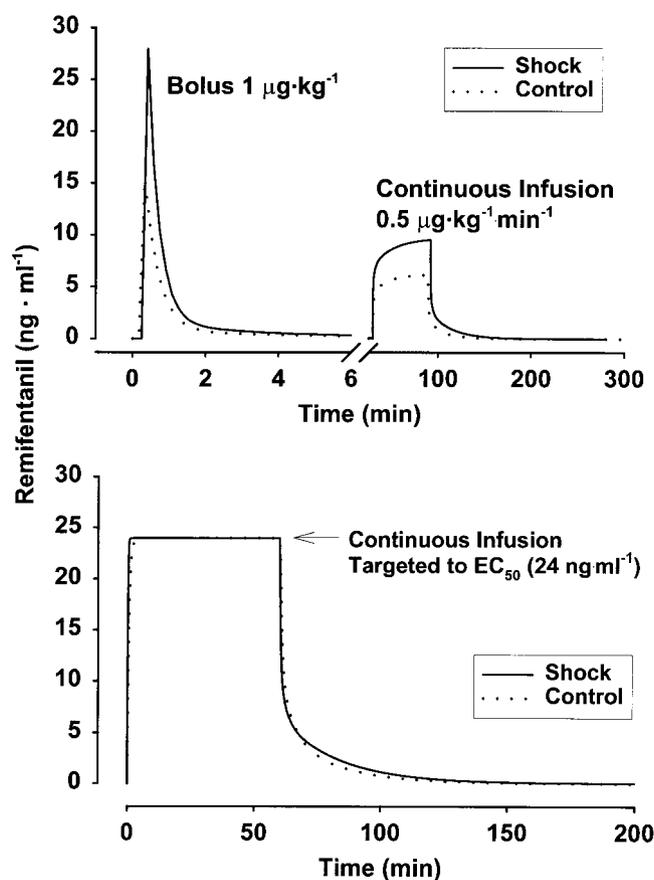


Fig. 9. (Top) Simulation of plasma concentrations (C_p) that result from equipotent bolus and infusion of remifentanil using the pharmacokinetic model. (Bottom) The plasma concentration that results from a 1-h computer-controlled infusion targeted to an EC_{50} of 24 ng/ml for normotensive (dotted line) and shocked (solid line) animals.

using the shock kinetics. It is important to point out that analgesic effects are typically observed at concentrations well below those required for spectral edge changes. For example, with fentanyl, analgesic effects are achieved with plasma concentrations between 1 and 3 ng/ml, but the EC_{50} for electroencephalographic changes does not occur until plasma concentrations of 6.9 ng/ml are reached.¹⁹

Possibly the most unique finding of our pharmacodynamic analysis was that hemorrhagic shock did not significantly change the potency of remifentanil. No prior data are available in pigs examining the EC_{50} of remifentanil, but our results were remarkably similar to what has been reported for humans (19.5 ng/ml).²⁰ Shocked animals demonstrated no significant shift in the EC_{50} , suggesting that a near equivalent remifentanil concentration would be required to achieve the same degree of spectral edge suppression. However, as demonstrated by the simulation of the dose necessary to target the EC_{50} for the two study groups, the pharmacokinetic differences result in a much lower dosage requirement during shock. This simulation examined kinetics and economic issues, not pharmacodynamic ones.

Limitations of the Study

A shortcoming of our study relates to the use of an isobaric hemorrhage model in swine to mimic what a patient in hemorrhagic shock might experience. Several issues that relate to species and type of hemorrhage model must be considered when interpreting our data. Isobaric hemorrhage models are often criticized as being far removed from a typical clinical scenario, in part because severe blood loss associated with trauma or surgery does not occur as a controlled hemorrhage over time with a target MABP, but rather as an uncontrolled hemorrhage with a highly variable MABP.²¹ Hemorrhagic shock is a dynamic process involving dramatic changes in cardiovascular and metabolic states that vary with time, species, and laboratory, and we felt it was important to examine the effects of remifentanil at an equivalent stage of physiologic compensation. This was best achieved with an isobaric model. This model permitted us to consistently administer remifentanil at the onset of cardiovascular decompensation as manifest by the transition from removal to reinfusion of blood to maintain the target MABP. Achieving a consistent pathophysiologic end point using hemorrhage models that better simulate hemorrhage associated with trauma or surgery (*i.e.*, isovolemic or uncontrolled hemorrhage models) is difficult.

The difference in how species exhibit their response to shock should be considered. Although, in general, pigs are thought to be pharmacologically and cardiovascularly similar to humans, they do have some splenic erythrocyte reserve that can introduce variability into the progression of the shock-induced metabolic demise. A splenectomy performed several days before the experiment has been shown to produce a more stable shock model for some experimental purposes.²² Swine also have a dissimilar hemoglobin P_{50} for oxygen that is 50% higher than that for human hemoglobin (*e.g.*, 36 vs 26 mmHg).²³ This becomes an issue when the oxygen delivery plays a critical role in maintaining the metabolic integrity required for drug biotransformation. It should also be noted that patients suffering from severe blood loss who require surgery are usually undergoing some form of fluid resuscitation before receiving an anesthetic. Hence, future studies investigating the influence of resuscitation after severe hemorrhage on the pharmacodynamics and pharmacokinetics of anesthetics are warranted, as well as the examination of other drug classes such as the sedative hypnotics.

We presented an approach using a population model with and without hemodynamic covariates to explore covariate effects on model performance. We introduced these model covariates as physiologic state variables. The rationale for choosing these parameters was that during severe hemorrhagic shock, one or more of these parameters would change in a similar fashion to shock-induced changes in pharmacokinetic parameters. How-

ever, there is no question that the hemodynamic variables we used as covariates can be influenced by other physiologic states. For example, we acknowledge that in physiologic states other than hemorrhagic shock, changes in MABP may not represent the same magnitude of change in pharmacokinetic parameters for remifentanyl that they did in hemorrhagic shock.

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