

# Pharmacokinetics and Pharmacodynamics of Propofol Microemulsion and Lipid Emulsion after an Intravenous Bolus and Variable Rate Infusion

Kye-Min Kim, M.D.,\* Byung-Moon Choi, M.D.,† Si-Won Park, M.D.,† Soo-Han Lee, Ph.D.,‡ Lane V. Christensen, B.S.,§ Jiaye Zhou, M.S.,|| Byung-Hoon Yoo, M.D.,\* Hye-Won Shin, M.D.,# Kyun-Seop Bae, M.D.,\*\* Steven E. Kern, Ph.D.,†† Sung-Hong Kang, Ph.D.,‡‡ Gyu-Jeong Noh, M.D.§§

**Background:** The aim of this trial was to evaluate the induction and recovery characteristics of microemulsion propofol (Aquafof; Daewon Pharmaceutical Co., Ltd., Seoul, Korea). Pharmacokinetics, pharmacodynamics, and safety profile were investigated. Lipid emulsion propofol (Diprivan®; AstraZeneca, London, United Kingdom) was used as a comparator.

**Methods:** Thirty-one healthy volunteers aged 20–79 yr were given an intravenous bolus of propofol 2 mg/kg, followed by variable rate infusion for 60 min. Each volunteer was studied twice with different formulations at an interval of 1 week. Arterial concentrations of propofol were measured, and Bispectral Index was used as a surrogate measure of propofol effect. The induction and recovery characteristics including bioequivalence were evaluated by noncompartmental analysis. The pharmacokinetics and pharmacodynamics were investigated using a population approach with mixed effects modeling. The rate, severity, and causal relation of adverse events were analyzed.

**Results:** Both formulations were bioequivalent. The observed time to peak effect after a bolus of both formulations was 1.5 min. Plasma concentration of propofol at loss of consciousness, time to loss of consciousness after a bolus, and time to recovery of consciousness after discontinuation of infusion did not show significant differences. The population pharmacokinetics and pharma-

codynamics revealed a variety of differences between two formulations. Aquafof showed similar safety profile to Diprivan®.

**Conclusions:** The efficacy and safety of Aquafof were not different from those of Diprivan® within the dose range in this study.

*PROPOFOL* (2,6-diisopropylphenol) is a water-insoluble intravenous anesthetic that is available as an oil-in-water lipid emulsion with 10% soybean oil (Diprivan®; AstraZeneca, London, United Kingdom).<sup>1</sup> Propofol lipid emulsion has been associated with a variety of drawbacks for which altered lipid emulsion or nonemulsion formulations have been developed.<sup>2</sup>

*Aquafof* (Daewon Pharmaceutical Co., Ltd., Seoul, Korea) is a newly developed microemulsion of propofol. Aquafof is a colorless liquid containing 1% propofol, 8% polyethylene glycol 660 hydroxystearate (Solutol HS 15; BASF Company Ltd., Seoul, Korea) as a nonionic surfactant, and 5% tetrahydrofurfuryl alcohol polyethylene glycol ether (Glycofurol; Roche, Basle, Switzerland) as a cosurfactant (fig. 1). Polyethylene glycol 660 hydroxystearate consists of polyglycol monoesters and diesters of 12-hydroxystearic acid (hydrophobic group) and of approximately 30% free polyethylene glycol (hydrophilic group). Tetrahydrofurfuryl alcohol polyethylene glycol is an approximately equimolar mixture of the polymers tetrahydrofurfuryl alcohol ethylene glycol ether ( $n_1$ -glycofurol) and tetrahydrofurfuryl alcohol diethylene glycol ether ( $n_2$ -glycofurol). Whereas oil-in-water macroemulsions are unstable, which may produce potentially dangerous increases in fat particle sizes and hence may cause fatal pulmonary fat embolism, microemulsion is thermodynamically stable.<sup>3</sup>

Zero-order infusion approaches have been used for most of the pharmacokinetic and pharmacodynamic studies of propofol, which are successfully applied to the target-controlled infusion.<sup>4,5</sup> Pharmacokinetic models derived from studies with a bolus dose or a brief infusion predicted the concentrations during the computer-controlled infusion only poorly.<sup>6,7</sup> Nevertheless, the current study was performed with an intravenous bolus and subsequent variable rate infusion of microemulsion (Aquafof) and lipid emulsion (Diprivan®) to compare their induction and recovery characteristics under the condition closely resembling the clinical setting where anesthesia is induced with an intravenous bolus and maintained with variable rate infusion. The secondary aim of this study was to compare the pharmacokinetics and pharmacodynamics of propofol micro-



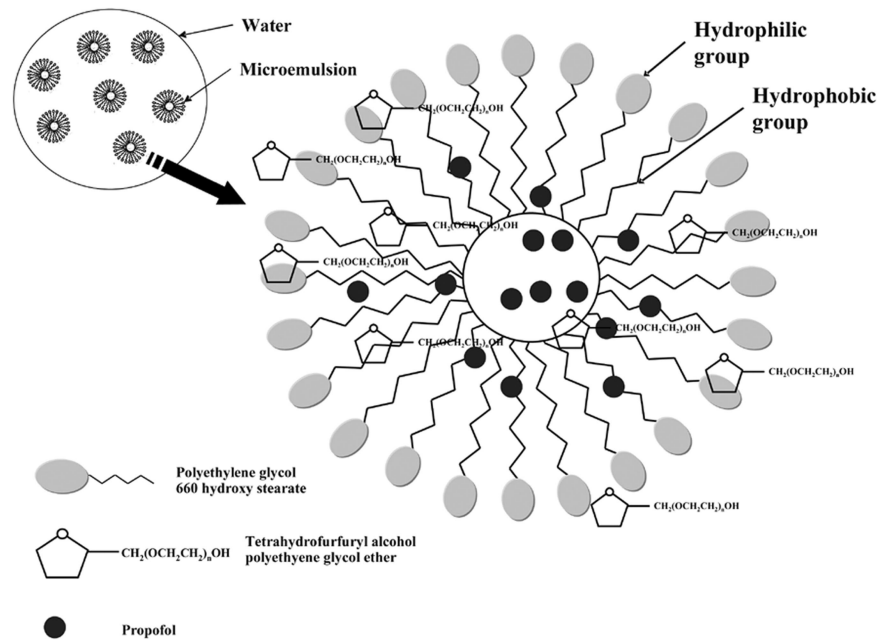
Additional material related to this article can be found on the ANESTHESIOLOGY Web site. Go to <http://www.anesthesiology.org>, click on Enhancements Index, and then scroll down to find the appropriate article and link. Supplementary material can also be accessed on the Web by clicking on the "Article Plus" link either in the Table of Contents or at the top of the Abstract or HTML version of the article.

\* Assistant Professor, Department of Anesthesiology and Pain Medicine, Sanggye Paik Hospital, Inje University College of Medicine, Seoul, Korea. † Resident, Department of Anesthesiology and Pain Medicine, ‡ Postdoctoral Fellow, \*\* Assistant Professor, Department of Clinical Pharmacology and Therapeutics, §§ Professor, Department of Anesthesiology and Pain Medicine and Department of Clinical Pharmacology and Therapeutics, Asan Medical Center, University of Ulsan College of Medicine. § Postdoctoral Fellow, Department of Pharmaceutics and Pharmaceutical Chemistry, || Postdoctoral Fellow, Department of Bioengineering, University of Utah, †† Assistant Professor, Department of Pharmaceutics and Pharmaceutical Chemistry and Department of Anesthesiology, University of Utah College of Pharmacy, Salt Lake City, Utah. # Assistant Professor, Department of Anesthesiology and Pain Medicine, Korea University School of Medicine, Seoul, Korea. ‡‡ Associate Professor, School of Health Administration, Inje University, Kimhae, Korea.

Received from the Department of Anesthesiology and Pain Medicine, Department of Clinical Pharmacology and Therapeutics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea. Submitted for publication August 21, 2006. Accepted for publication January 11, 2007. Supported by a grant (2004-0726) from the Industry Trust Research Service between University of Ulsan College of Medicine and Daewon Pharmaceutical Co., Ltd., Seoul, Korea, and supported in part by a grant (2004-0734) from the Industry Trust Research Service between University of Ulsan College of Medicine and AstraZeneca Korea, Seoul, Korea.

Address correspondence to Dr. Noh: 388-1, Pungnap 2-dong, Songpa-gu, Seoul 138-736, Korea. [nohgj@amc.seoul.kr](mailto:nohgj@amc.seoul.kr). Individual article reprints may be purchased through the Journal Web site, [www.anesthesiology.org](http://www.anesthesiology.org).

**Fig. 1. Illustration of microemulsion formulation of propofol (Aquafol; Daewon Pharmaceutical Co., Ltd., Seoul, Korea). Propofol in microemulsion system is surrounded by a corona of polyethylene glycol 660 hydroxystearate and tetrahydrofurfuryl alcohol polyethylene glycol, and served as the lipid oil core of the microemulsion. The mean particle size of Aquafol measured by dynamic light scattering (ELS-8000; Otsuka Electronics Co., Hirakata, Osaka, Japan) was 30.9 nm (range, 22.1–38.5 nm).**



emulsion and lipid emulsion, using noncompartmental analysis and population analysis with mixed effects modeling. In addition, the safety profiles of the two agents were compared.

## Materials and Methods

### Subjects

After obtaining the approval of the institutional review board of Asan Medical Center (Seoul, Korea) and written informed consent, 31 volunteers participated in this study. The volunteers who had medical problems, abnormal laboratory findings with clinical significance, or evidence of pregnancy were excluded. The subjects were stratified into three age groups (19–40, 41–64, and 65–79 yr), and each group included 5 male and 5 female volunteers.

### Study Design and Procedures

The study was designed as a randomized, open-label, two-period, crossover phase I clinical trial. Each subject received both propofol formulations in a crossover fashion separated by a 7-day washout period, and the order of the drug administration was randomized.

Subjects fasted for 6 h before study drug administration. An 18-gauge angiocatheter was placed in a vein of the antecubital area. A second angiocatheter was placed in the contralateral radial artery for frequent blood sampling. Subjects were monitored with electrocardiography, pulse oximetry, end-tidal carbon dioxide concentration, and invasive blood pressure measurement (Datex-Ohmeda S/5; Planar Systems, Inc., Beaverton, OR) and Bispectral Index (BIS) (Aspect 2000; Aspect Medical Systems, Inc., Newton, MA). The smoothing rate for the measurement of BIS was set at 15 s. With baseline measurements, all of these data

were recorded continually up to 180 min after administration of intravenous bolus dose. Subjects were hospitalized for 24 h after study drug administration.

### Drug Administration

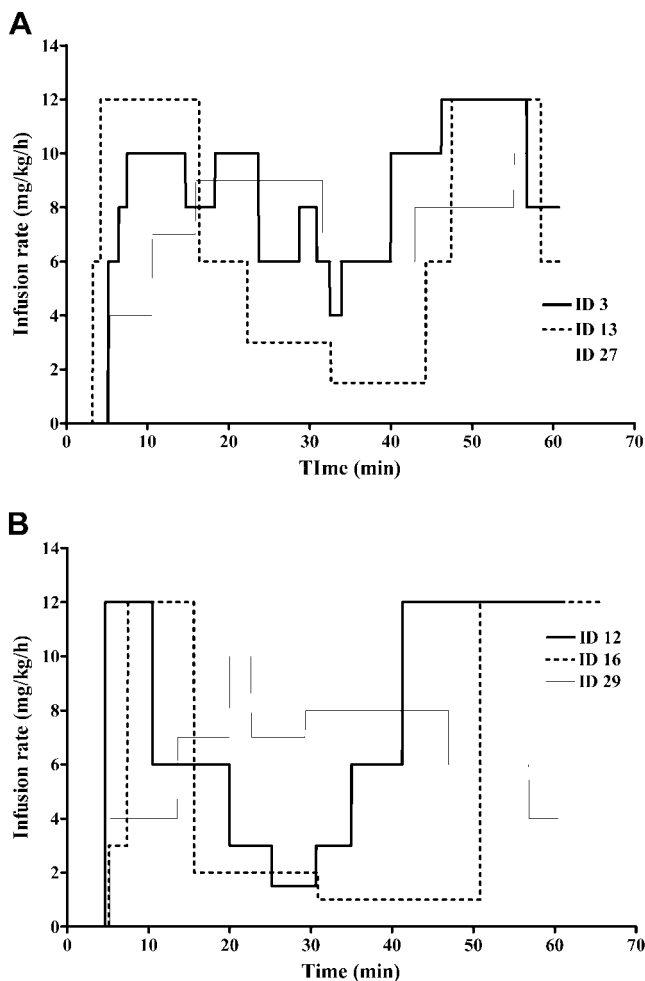
Subjects received an initial intravenous bolus of propofol 2.0 mg/kg over 20 s. Time to loss of consciousness (LOC) was determined every 5 s by the loss of response to verbal command. After observing the lowest BIS value, propofol was infused at variable rates ranging from 0 to 12 mg · kg<sup>-1</sup> · h<sup>-1</sup> for 60 min to produce various BIS values approximately from 20 to 80 (fig. 2). Time to lowest BIS after an initial bolus was determined from the individual data file of BIS, in which BIS values were updated every 5 s. Time to recovery of consciousness (ROC) after discontinuation of infusion was determined by the recovery of response to verbal command.

### Blood Sample Acquisition and Measurement of Propofol Concentration

Samples were collected in ethylenediaminetetraacetic acid (EDTA) tube and centrifuged for 10 min at 3,500 rpm. Plasma was stored at –70°C until assay.

1. Arterial blood samples (4 ml) were taken at preset intervals: 0, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 15, 20, 30, 40, 50, 60, 70, 90, 120, 150 and 180, 240, 300, 600, 720, and 1,200 min after bolus dose of propofol.
2. In addition, arterial samples were drawn when LOC and ROC were observed.

Propofol was isolated from human plasma by extraction using pretreatment with deproteinization and was determined by high-performance liquid chromatography with fluorescence detection. Plasma proteins were pre-



**Fig. 2.** Infusion rates of propofol in representative volunteers. An intravenous bolus of each formulation was given at time 0. (A) Lipid emulsion formulation, (B) microemulsion formulation of propofol. Infusion rate was changed  $7 \pm 4$  (mean  $\pm$  SD) times for lipid emulsion and  $7 \pm 3$  times for microemulsion during study period in all subjects.

cipitated with acetonitrile. The supernatants were analyzed by high-performance liquid chromatography using a Capcell Pak C18 UG120 column and a mixture of methanol and 0.1% trifluoroacetic acid in water (75:25, vol/vol) as a mobile phase. The components of the column effluent were monitored by a fluorometric detector with excitation and emission wavelengths set at 276 and 310 nm, respectively. The lower limit of quantification of propofol was 8 ng/ml. The calibration curve was linear over the range of 8–25,000 ng/ml, with the coefficients of determination ( $R^2$ ) greater than 0.999 for all cases. Intraassay precision values were less than 1.5%. Interassay within-day and between-day precision values were less than 2.5% and 9.3%, respectively. Intraassay accuracy values were 100.8–103.2% of the nominal value. Interassay accuracy values were 98.5–103.7% of the nominal value.

||| US Food and Drug Administration: Guidance for Industry: Statistical Approaches to Establishing Bioequivalence. 1999. Available at: <http://www.fda.gov/cder/guidance/3616fnl.pdf>. Accessed November 8, 2006.

### Noncompartmental Analysis of Pharmacokinetics and Pharmacodynamics

**Pharmacokinetic Analysis.** Pharmacokinetic parameters were calculated by noncompartmental methods (WinNonlin Professional 4.1; Pharsight Corporation, Mountain View, CA). The area under the curve from the time of administration to the last measured concentration ( $AUC_{last}$ ) was calculated by linear trapezoidal integration (linear interpolation). The area under the curve from administration to infinity ( $AUC_{inf}$ ) was calculated as the sum of  $AUC_{last} + C_{last}/\lambda_z$ , with  $C_{last}$  being the last measured concentration and  $\lambda_z$  being the apparent terminal rate constant estimated by unweighted linear regression for the linear portion of the terminal log concentration–time curve. The maximal concentration ( $C_{max}$ ) after an intravenous bolus of study drugs was determined from the observed data. Summary statistics were determined for each parameter.

Analysis of variance was performed with a linear mixed effects model that contained effects for sequence, subject nested within sequence, period, and formulation for logarithmically transformed data. The effect of subject was treated as random effect, and all other effects were treated as fixed effects. In addition,  $P$  values were provided using F statistics ( $P < 0.05$  indicated statistical significance). Ninety percent confidence intervals were constructed for the ratio of geometric means between microemulsion and lipid emulsion for  $AUC_{last}$ ,  $AUC_{inf}$ , and  $C_{max}$ . It was concluded that the two formulations are bioequivalent if these 90% confidence intervals fall within the range of 80–125%.|||

**Pharmacodynamic Analysis.** Time to LOC, BIS at LOC, measured plasma concentration of propofol at LOC, and time to lowest BIS after an intravenous bolus were recorded. After discontinuation of infusion, time to ROC, BIS at ROC, and measured plasma concentration of propofol at ROC were recorded. Time elapse from LOC to lowest BIS was also recorded. Summary statistics were determined for each parameter. Also, we calculated 90% confidence intervals for the difference of these observations between microemulsion and lipid emulsion of propofol, based on an analysis of variance with a linear mixed effects model. A 90% confidence interval was constructed for the difference of arithmetic mean between microemulsion and lipid emulsion for each pharmacodynamic parameter (WinNonlin Professional 4.1).

### Population Pharmacokinetics and Pharmacodynamics

Pharmacokinetic models were fitted using ADVAN 11 subroutine and the first-order conditional estimation procedure of NONMEM<sup>®</sup> V level 1.1, (GloboMax LLC, Elliott City, MD). Pharmacodynamic models were fitted using ADVAN6 subroutine and first-order estimation procedure due to fitting failure of the first-order conditional

estimation procedure of NONMEM<sup>®</sup>. A diagonal matrix was estimated for the different distributions of  $\eta$ 's.

The models were evaluated using statistical and graphical methods. The minimal value of the objective function (equal to minus twice the log likelihood) provided by NONMEM<sup>®</sup> was used as the goodness-of-fit characteristic to discriminate between hierarchical models using the log likelihood ratio test.<sup>8</sup> A *P* value of 0.05, representing a decrease in objective function value of 3.84 points, was considered statistically significant (chi-square distribution, degrees of freedom = 1). The S-plus (MathSoft Inc., Seattle, WA)-based model-building aid Xpose 3.1 was used for graphical model diagnosis.<sup>9</sup> The covariates analyzed were age, sex, weight, height, body surface area,<sup>10</sup> and lean body mass.<sup>11</sup> Covariates significantly influencing the model were added cumulatively until the best description of the data was obtained. A backward elimination step was then performed by fixing the coefficient of each covariate, in turn, to zero. To compare the distribution of  $\eta$ 's to the normal distribution, we calculated the correlation of the points in the normal probability plot, in which the null hypothesis of the test is that the data come from a normal distribution.<sup>12,13</sup>

The median weighted residual and median absolute weighted residual for the final pharmacokinetic models and the individual mean of weighted residuals for the pharmacodynamic models were calculated to examine the quality of prediction for the population. Weighted residual was calculated as (measured - predicted)/predicted.

Based on an analysis of variance with a linear mixed effects model, 90% confidence intervals were constructed for the difference of arithmetic means between microemulsion and lipid emulsion for calculated effect site concentration of propofol at the time of LOC and ROC, and for individually predicted pharmacokinetic parameters of propofol (WinNonlin Professional 4.1).

All of the observations in noncompartmental pharmacodynamic analysis were tested for the difference across any significant categorical covariate in the final pharmacodynamic models, using a *t* test or Mann-Whitney rank sum test as appropriate (SigmaStat for Windows version 3.10; Systat Software, Inc., Point Richmond, CA). An intravenous bolus of propofol 2 mg/kg for both formulations was simulated to calculate the concentrations of plasma, effect site, and rapidly equilibrating and slowly equilibrating compartments over time.

**Pharmacokinetic Analysis.** The interindividual random variability on each of the model parameters ( $V_1$ ,  $k_{10}$ ,  $k_{12}$ ,  $k_{21}$ ,  $k_{13}$ ,  $k_{31}$ ) was modeled using a log-normal model. An additive plus proportional model was used for the residual random variability.

**Pharmacodynamic Analysis.** The pharmacodynamics were described using an effect compartment model in which  $k_{e0}$ , a first-order elimination rate constant char-

acterizing effect site equilibration, is used to estimate the apparent effect site concentrations.<sup>14</sup> The relation of BIS with propofol effect site concentration was analyzed using a sigmoid  $E_{\max}$  model<sup>15</sup>:

$$\text{Effect} = E_0 + (E_{\max} - E_0) \frac{Ce^\gamma}{Ce_{50}^\gamma + Ce^\gamma}, \quad (1)$$

where Effect is BIS,  $E_0$  is the baseline measurement when no drug is present,  $E_{\max}$  is the maximum possible drug effect,  $Ce$  is the calculated effect site concentration of propofol,  $Ce_{50}$  is the effect site concentration associated with 50% maximal drug effect, and  $\gamma$  is the steepness of the concentration-*versus*-response relation.

Interindividual random variability of  $E_{\max}$ ,  $Ce_{50}$ , and  $k_{e0}$  was modeled using a log-normal model. Interindividual random variability of  $E_0$  was modeled using an additive model, and no interindividual variability of  $\gamma$  was assumed. Residual random variability was modeled using an additive error model.

#### *Loss of Consciousness Pharmacodynamics*

Using the observation of LOC and ROC, every calculated effect site concentration of propofol in the final pharmacodynamic model for BIS was joined to 0 (awake) or 1 (sleep). The relation between the probability of LOC and the effect site concentration of propofol was analyzed using a sigmoid  $E_{\max}$  model:

$$\text{Probability of LOC} = \frac{Ce^\gamma}{Ce_{50}^\gamma + Ce^\gamma}, \quad (2)$$

where  $Ce$  is the calculated effect site concentration of propofol,  $Ce_{50}$  is the effect site concentration associated with 50% probability of LOC, and  $\gamma$  is the steepness of the concentration-*versus*-response relation.

The likelihood, *L*, for the observed response, *R* (awake = 0, Sleep = 1) is described by the following equation:

$$\text{Likelihood} = R \times \text{Prob} + (1 - R) \times (1 - \text{Prob}), \quad (3)$$

where Prob is the probability of LOC.

Model parameters were estimated using the option "LIKELIHOOD LAPLACE METHOD = conditional" of NONMEM<sup>®</sup>. Interindividual random variability of  $Ce_{50}$  and  $\gamma$  was modeled using a log-normal model.

#### *Safety Profiles*

Safety profile of study drugs was evaluated by monitoring vital signs, pulse oximetry, end-tidal carbon dioxide concentration, treatment frequency of vasoactive drugs, and adverse events. Clinical laboratory tests were performed within 2 weeks before the administration of the first study drug and 24 h after administration of the second study drug.

Ephedrine or atropine was given if needed to maintain systolic pressure above 80 mmHg and heart rate above 50 beats/min. Each subject was preoxygenated with

**Table 1. Noncompartmental Pharmacokinetic Parameters of Propofol after an Intravenous Bolus of 2 mg/kg Followed by Variable Rate Infusion for 60 min**

	Microemulsion (n = 30)		Lipid Emulsion (n = 30)		Ratio, %*	90% Confidence Interval*
	Mean	SD	Mean	SD		
AUC <sub>last</sub> , min · μg/ml	346.4	90.8	351.8	93.7	98.2	89.8–107.3
AUC <sub>inf</sub> , min · μg/ml	391.9	101.7	398.2	111.1	106.8	89.4–108.0
C <sub>max</sub> , μg/ml	24.8	13.1	26.5	12.5	94.9	80.0–113.6

\* Based on an analysis of variance with a linear mixed effects model that contained effects for sequence, subject nested within sequence, period, and formulation for logarithmically transformed data.

AUC<sub>inf</sub> = area under the curve from administration to infinity; AUC<sub>last</sub> = area under the curve from administration to the last measured concentration; C<sub>max</sub> = maximal concentration.

100% oxygen, and the lungs were manually ventilated with 100% oxygen *via* facemask, to maintain an end-tidal carbon dioxide concentration of 35–45 mmHg. Blood pressure, heart rate, body temperature, and respiratory rate were manually measured at 185, 190, 195, 200, and 210 min (postanesthetic recovery room) and 8 and 24 h (ward) after administration of the bolus dose. Safety data were analyzed using the McNemar test or repeated-measures analysis of variance as appropriate ( $P < 0.05$  indicated statistical significance).

## Results

Thirty-one volunteers (15 male and 16 female) were recruited, and 1 female subject declined to receive microemulsion formulation after receiving lipid emulsion formulation as a first study drug. This subject was replaced and was not included in the noncompartmental pharmacokinetic and pharmacodynamic analyses, but was included in the population analysis of pharmacokinetics and pharmacodynamics and the analysis of safety profile. Weight, height, and age of the volunteers were  $59 \pm 10$  kg,  $163 \pm 10$  cm, and  $47 \pm 19$  yr, respectively (mean  $\pm$  SD). The rate and duration of infusion were  $8.7 \pm 1.6$  mg/min and  $61.2 \pm 2.4$  min for lipid emulsion and  $8.4 \pm 1.8$  mg/min and  $62.1 \pm 4.9$  min for microemulsion, respectively. The total amount of propofol administered was  $530 \pm 96$  mg for lipid emulsion and  $523 \pm 137$  mg for microemulsion. None of these showed significant differences between lipid emulsion and microemulsion of propofol.

### Noncompartmental Analysis of Pharmacokinetics and Pharmacodynamics

**Pharmacokinetic Analysis.** In all subjects, at least 80% of the total AUC was covered by measured concentrations. The arithmetic means of the AUC indicate differences with respect to the extent of absorption of the formulations of approximately 1.5%. The intersubject variability was similar for both formulations (table 1). The analyses of variance did not indicate any differences between formulations for either sequence or period ef-

fects. The 90% confidence intervals for the difference of log-transformed AUC and C<sub>max</sub> are included in the acceptance range for bioequivalence (80–125%).

**Pharmacodynamic Analysis.** A variety of pharmacodynamic endpoints and propofol plasma concentrations at LOC and ROC for both study drugs are found in table 2. When the 90% confidence intervals include 100%, no significant differences between the two formulations are shown for those parameters.

### Population Pharmacokinetics and Pharmacodynamics

**Pharmacokinetic Analysis.** The pharmacokinetics of both study drugs were best described by a three-compartment model. The results of the final pharmacokinetic models of both study drugs are summarized in table 3.

The final model of lipid emulsion included age as a significant covariate for  $k_{10}$ . The following equation describes the final model for lipid emulsion:

$$k_{10} = 0.398 - 0.00165 \times (\text{age} - 44). \quad (4)$$

The final model resulted in an improvement in the objective function (7.32;  $P = 0.0068$ ) compared with the basic model. All of the  $\eta$ 's except  $\eta$  for  $k_{10}$ ,  $k_{12}$ ,  $k_{31}$  of the final pharmacokinetic model were normally distributed. From age 19 to 79 yr, the typical values of  $Cl_1$  of lipid emulsion propofol decreased by approximately 22.5%.

Sex and age were significant covariates for  $k_{21}$  and  $k_{13}$  in the final pharmacokinetic model of microemulsion, respectively. The typical value of  $k_{21}$  was 0.118 for females and 0.0804 for males. The following equation describes  $k_{13}$  in the final model for microemulsion:

$$k_{13} = 0.239 + 0.00158 \times (\text{age} - 44). \quad (5)$$

The final model resulted in an improvement in the objective function (18.23;  $P = 0.0001$ ). All of the  $\eta$ 's of the final pharmacokinetic model were normally distributed. The typical value of  $V_2$  of microemulsion was 27.8 l for males and 18.9 l for females. From age 19 to 79 yr, the typical values of  $V_3$  and  $Cl_3$  of microemulsion increased by approximately 47.5%.

**Table 2. Comparison of Pharmacodynamic Endpoints between Microemulsion and Lipid Emulsion of Propofol after an Intravenous Bolus of 2 mg/kg Followed by Variable Rate Infusion for 60 min**

	Microemulsion (n = 30)		Lipid Emulsion (n = 30)		Ratio, %*	90% Confidence Interval*
	Mean	SD	Mean	SD		
Time <sub>LOC</sub> , min	0.4	0.2	0.3	0.1	120.7	95.3–146.2
BIS <sub>LOC</sub>	94	6	95	4	99.2	97.1–101.2
Cp <sub>LOC</sub> , µg/ml	23.5	13.9	24.6	13.0	96.0	75.1–116.9
Time <sub>lowest BIS</sub> , min	1.5	0.9	1.5	0.9	103.6	87.7–119.4
Lowest BIS	38	13	34	7	107.3	96.6–117.9
ΔTime <sub>LOC-lowest BIS</sub> , min	1.2	0.8	1.1	0.8	99.4	80.9–117.9
Time <sub>ROC</sub> , min	9.3	7.9	10.3	12.1	89.0	50.3–127.7
BIS <sub>ROC</sub>	68	9	69	10	99.7	93.9–105.4
Cp <sub>ROC</sub> , µg/ml	1.3	0.5	1.1	0.3	110.1	95.4–124.9

\* Based on an analysis of variance with a linear mixed effects model that contained effects for sequence, subject nested within sequence, period, and formulation. BIS<sub>LOC</sub> = Bispectral Index at loss of consciousness; BIS<sub>ROC</sub> = Bispectral Index at recovery of consciousness; Cp<sub>LOC</sub> = measured plasma concentration of propofol at loss of consciousness; Cp<sub>ROC</sub> = measured plasma concentration of propofol at recovery of consciousness; ΔTime<sub>LOC-lowest BIS</sub> = time elapse from loss of consciousness to lowest Bispectral Index after an intravenous bolus of propofol 2 mg/kg; Lowest BIS = lowest value of Bispectral Index after an intravenous bolus of propofol 2 mg/kg; Time<sub>LOC</sub> = time to loss of consciousness after an intravenous bolus of propofol 2 mg/kg; Time<sub>lowest BIS</sub> = time to lowest Bispectral Index after an intravenous bolus of propofol 2 mg/kg; Time<sub>ROC</sub> = time to recovery of consciousness after discontinuation of variable rate infusion for 60 min.

Plots for predicted *versus* measured concentrations of propofol for both formulations are shown in figure 3. Ninety percent confidence intervals for the difference of individually predicted pharmacokinetic parameters between microemulsion and lipid emulsion are found in table 4.

**Pharmacodynamic Analysis.** The estimates of population parameters of the final pharmacodynamic models for lipid emulsion or microemulsion of propofol are

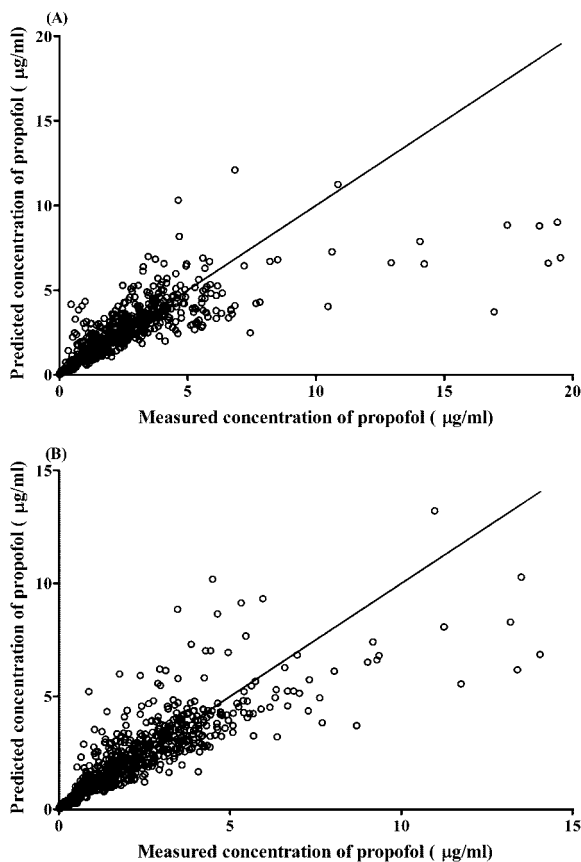
found in table 5. Plots for predicted *versus* observed BIS in the subjects with the lowest and highest absolute values of the individual mean of weighted residuals for lipid emulsion and microemulsion formulation of propofol are shown in figure 4.

Sex was a significant covariate for Ce<sub>50</sub> in the final model of lipid emulsion. The typical value of Ce<sub>50</sub> was 2.62 µg/ml for females and 1.89 µg/ml for males. Objective function value was decreased by 49.4 (*P* < 0.0001),

**Table 3. Population Pharmacokinetic Parameter Estimates (SE) and Interindividual Variability (%CV) of Lipid Emulsion and Microemulsion of Propofol**

Model	Parameter	Estimate (SE, %CV)	
		Lipid Emulsion	Microemulsion
Basic	V <sub>1</sub>	3.80 (0.27, 21.5)	3.53 (0.177, 13.0)
	k <sub>10</sub>	0.394 (0.0348, 13.1)	0.432 (0.0224, 12.2)
	k <sub>12</sub>	0.485 (0.0602, 33.0)	0.625 (0.0719, 37.8)
	k <sub>21</sub>	0.0838 (0.00919, 32.9)	0.0964 (0.0103, 32.1)
	k <sub>13</sub>	0.213 (0.0106, 0.002)	0.244 (0.0171, 15.9)
	k <sub>31</sub>	0.00309 (0.00027, 0.0005)	0.00403 (0.000364, 0.003)
	Additive, σ <sub>1</sub> , ng/ml	12.7 (4.93, —)	16.7 (4.53, —)
Proportional, σ <sub>2</sub> , %		25.1 (0.564, —)	21.5 (0.458, —)
Final	V <sub>1</sub>	3.82 (0.263, 20.4)	3.55 (0.187, 14.6)
	k <sub>10</sub>	θ <sub>1</sub> - θ <sub>2</sub> (age - 44) (8.4)	0.429 (0.0214, 11.0)
		θ <sub>1</sub> 0.398 (0.0364)	
		θ <sub>2</sub> 0.00165 (0.000995)	
	k <sub>12</sub>	0.485 (0.0555, 34.2)	0.629 (0.0682, 37.7)
	k <sub>21</sub>	0.0831 (0.00947, 36.5)	θ <sub>1</sub> - θ <sub>2</sub> × sex (male = 1, female = 0) (27.1)
			θ <sub>1</sub> 0.118 (0.0164)
			θ <sub>2</sub> 0.0376 (0.0171)
	k <sub>13</sub>	0.211 (0.0111, 0.03)	θ <sub>3</sub> + θ <sub>4</sub> × (age - 44) (11.3)
			θ <sub>3</sub> 0.239 (0.0176)
		θ <sub>4</sub> 0.00158 (0.000495)	
k <sub>31</sub>	0.00307 (0.000274, 0.0008)	0.004 (0.000368, 0.003)	
Additive, σ <sub>1</sub> , ng/ml	12.7 (5.89, —)	16.6 (4.44, —)	
Proportional, σ <sub>2</sub> , %	25.1 (0.583, —)	21.5 (0.417, —)	

Interindividual random variability was modeled using a log-normal model. Residual random variability was modeled using additive plus proportional error model. CV = coefficient of variation.



**Fig. 3.** Predicted versus measured concentrations of propofol for lipid emulsion (A) and microemulsion (B) formulation of propofol. The median weighted residual and median absolute weighted residual were  $-0.4\%$  and  $20.3\%$  for lipid emulsion and  $1.4\%$  and  $22.8\%$  for microemulsion, respectively. Weighted residual was calculated as  $(\text{measured} - \text{predicted})/\text{predicted}$ .

compared with the basic model. The  $\eta$ 's of  $k_{e0}$  and  $E_{\max}$  in the final model of lipid emulsion were normally distributed.

In the final model of microemulsion, sex was a significant covariate for  $k_{e0}$  and  $C_{e50}$ . The typical value of  $k_{e0}$  was  $0.167$  for females and  $0.0725$  for males. The typical value of  $C_{e50}$  was  $2.23 \mu\text{g/ml}$  for females and  $1.9 \mu\text{g/ml}$  for males. Objective function value was decreased by

$234.2$  ( $P < 0.0001$ ), compared with the basic model. The  $\eta$ 's of  $k_{e0}$ ,  $E_0$ , and  $E_{\max}$  in the final model of microemulsion were normally distributed.

Simulation of an intravenous bolus of propofol  $2 \text{ mg/kg}$  for both formulations is presented in figure 5. For microemulsion, simulation was performed in males and females ( $k_{e0} = 0.0725$  for males and  $0.167$  for females), but only in males for lipid emulsion ( $k_{e0} = 0.1220$ ).

Because sex was a common significant covariate in the final pharmacodynamic models of both formulations, all of the observations in table 2 were tested for the difference between females and males. For lipid emulsion of propofol, the total amount of propofol administered during study period did not show any significant difference between females (mean  $\pm$  SD:  $513 \pm 107 \text{ mg}$ ) and males ( $562 \pm 85 \text{ mg}$ ), but the time to ROC after discontinuation of infusion was significantly shorter in females (median, 25–75%:  $5.9, 3.8\text{--}7.1 \text{ min}$ ) than in males ( $9.4, 7.1\text{--}14.0 \text{ min}$ ) ( $P = 0.011$ ).

For microemulsion formulation, the time to LOC after an intravenous bolus was significantly shorter in females ( $0.3, 0.2\text{--}0.4 \text{ min}$ ) than in males ( $0.4, 0.3\text{--}0.7 \text{ min}$ ) ( $P = 0.010$ ). Although the total amount of propofol administered during the study period was significantly larger in females ( $596 \pm 152 \text{ mg}$ ) than in males ( $450 \pm 67 \text{ mg}$ ), time to ROC after discontinuation of infusion was significantly shorter in females ( $4.5 \pm 3.3 \text{ min}$ ) than in males ( $14.1 \pm 8.3 \text{ min}$ ) ( $P < 0.001$ ).

#### Loss of Consciousness Pharmacodynamics

The relation between the probability of LOC and effect site concentration of propofol for lipid emulsion and microemulsion formulation and LOC pharmacodynamic parameter estimates are shown in figure 6.

The calculated effect site concentrations of propofol at the time of LOC (mean  $\pm$  SD) were  $1.7 \pm 0.6 \mu\text{g/ml}$  for lipid emulsion and  $1.7 \pm 0.4 \mu\text{g/ml}$  for microemulsion of propofol. The ratio based on an analysis of variance with a linear mixed effects model was  $99.3\%$ . The  $90\%$  confidence interval for the difference between microemul-

**Table 4.** Comparison of Population Pharmacokinetic Parameters between Microemulsion and Lipid Emulsion of Propofol

	Microemulsion (n = 30)		Lipid Emulsion (n = 30)		Ratio, %*	90% Confidence Interval*
	Mean	SD	Mean	SD		
$V_1, \text{ l}$	$3.6^\dagger$	0.4	3.9	0.7	91.7	85.9–97.5
$V_2, \text{ l}$	25.0	10.3	24.8	10.2	100.2	89.1–111.3
$V_3, \text{ l}$	$217.0^\dagger$	38.8	267.0	48.1	81.4	75.1–87.6
$V_{\text{dss}}, \text{ l}$	$245.6^\dagger$	40.8	295.6	54.0	83.1	76.9–89.2
$Cl_1, \text{ l/min}$	1.55	0.27	1.53	0.30	100.6	94.1–107.1
$Cl_2, \text{ l/min}$	$2.40^\dagger$	0.87	2.02	0.60	117.6	103.8–131.4
$Cl_3, \text{ l/min}$	0.87	0.16	0.82	0.15	106.1	99.1–113.2
$t_{1/2\alpha}, \text{ min}$	$0.5^\dagger$	0.1	0.6	0.1	84.9	79.5–90.4
$t_{1/2\beta}, \text{ min}$	$14.9^\dagger$	4.4	16.2	4.6	91.9	85.8–98.0
$t_{1/2\gamma}, \text{ min}$	$276.6^\dagger$	17.5	352.4	12.1	78.6	77.6–79.6

\* Based on an analysis of variance with a linear mixed effects model that contained effects for sequence, subject nested within sequence, period, and formulation.  $^\dagger P < 0.05$  for formulation.

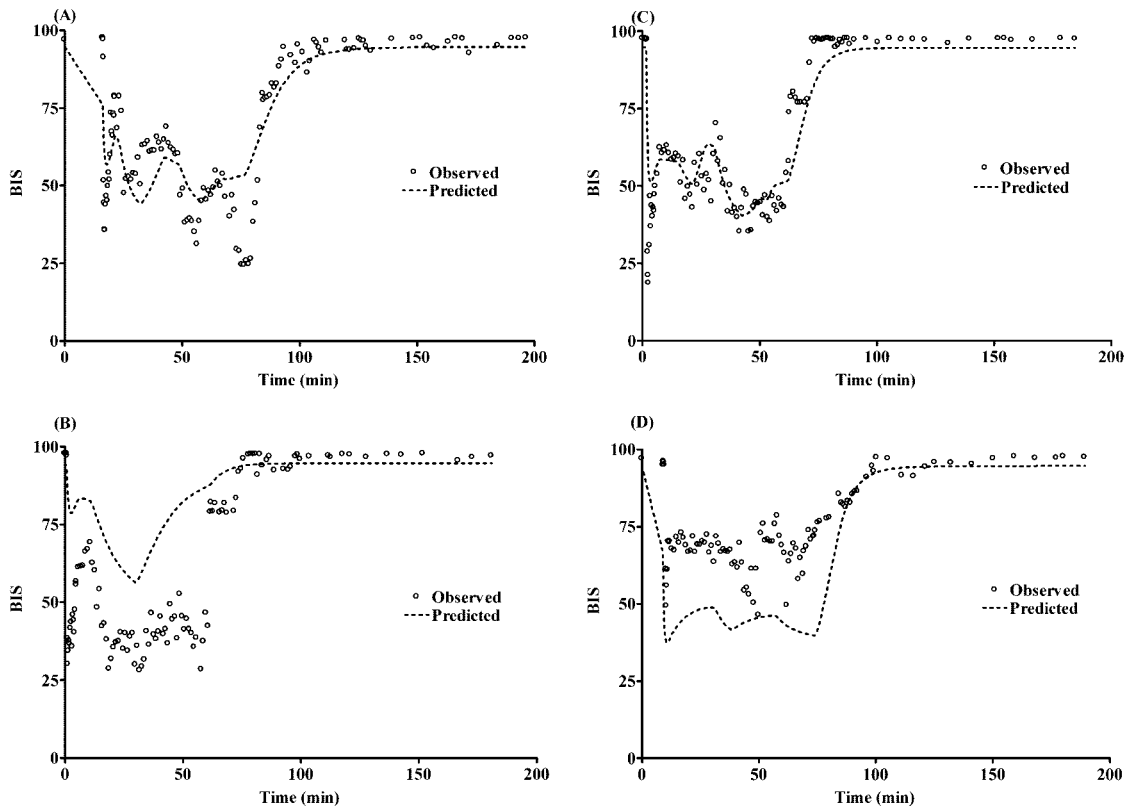
**Table 5. Population Pharmacodynamic Parameter Estimates (SE) and Interindividual Variability (%CV) of Lipid Emulsion and Microemulsion Formulation of Propofol for the Electroencephalographic Bispectral Index**

Model	Parameter	Estimate (SE, %CV)	
		Lipid Emulsion	Microemulsion
Basic	$k_{e0}, \text{min}^{-1}$	0.116 (0.00631, 21.7)	0.114 (0.0157, 41.5)
	$Ce_{50}, \mu\text{g/ml}$	2.27 (0.182, 24.1)	2.05 (0.0764, 27.6)
	$E_0^*$	94.3 (0.804, —)	95.4 (8.22, —)
	$E_{\text{max}}$	37.8 (3.98, 29.7)	22.9 (7.2, 68.9)
	$\gamma \dagger$	3.65 (0.38, —)	2.78 (0.29, —)
	$\sigma^2 \ddagger$	95.7 (11.6, —)	97.9 (9.13, —)
Final	$k_{e0}, \text{min}^{-1}$	0.122 (0.0203, 29.5)	$\theta_1 - \theta_2 \times \text{sex}$ (32.4) $\theta_1$ 0.167 (0.0168) $\theta_2$ 0.0945 (0.0378)
	$Ce_{50}, \mu\text{g/ml}$	Female 2.62 (0.392, 46.6) Male 1.89 (0.305, 21.1)	Female 2.23 (0.201, 25.6) Male 1.9 (0.292, 29.9)
	$E_0^*$	94.7 (1.14, —)	94.7 (0.902, —)
	$E_{\text{max}}$	37.2 (4.41, 52.4)	30.5 (5.71, 47.0)
	$\gamma \dagger$	3.41 (0.375, —)	3.39 (0.709, —)
	$\sigma^2 \ddagger$	93.9 (10.9, —)	91.5 (8.37, —)

\* Interindividual random variability was modeled using additive model. † No interindividual random variability was assumed; interindividual random variability of other structural model parameters was modeled using a log-normal model. ‡ Residual random variability was modeled using an additive error model. CV = coefficient of variation.

sion and lipid emulsion was 89.8–108.9%. The calculated effect site concentrations of propofol at the time of ROC (mean ± SD) were  $2.2 \pm 0.7 \mu\text{g/ml}$  for lipid emulsion and  $2.2 \pm 0.8 \mu\text{g/ml}$  for microemulsion of

propofol. The ratio based on an analysis of variance with a linear mixed effects model was 96.5%. The 90% confidence interval for the difference between microemulsion and lipid emulsion was 83.8–109.8%.



**Fig. 4. Predicted versus observed Bispectral Index (BIS) in the subjects with the lowest (A and C) and the highest (B and D) absolute values of the individual mean of weighted residuals for lipid emulsion (A: subject 4, 0.5%; B: subject 21, 25.6%) and microemulsion (C: subject 6, 0.6%; D: subject 27, 43%) formulation of propofol. The median (minimum, maximum) of the individual mean of weighted residuals was  $-7.7\%$  ( $-25.6\%$ ,  $14.2\%$ ) for lipid emulsion and  $-0.5\%$  ( $-20.1\%$ ,  $43.1\%$ ) for microemulsion. Weighted residual was calculated as (measured – predicted)/predicted.**



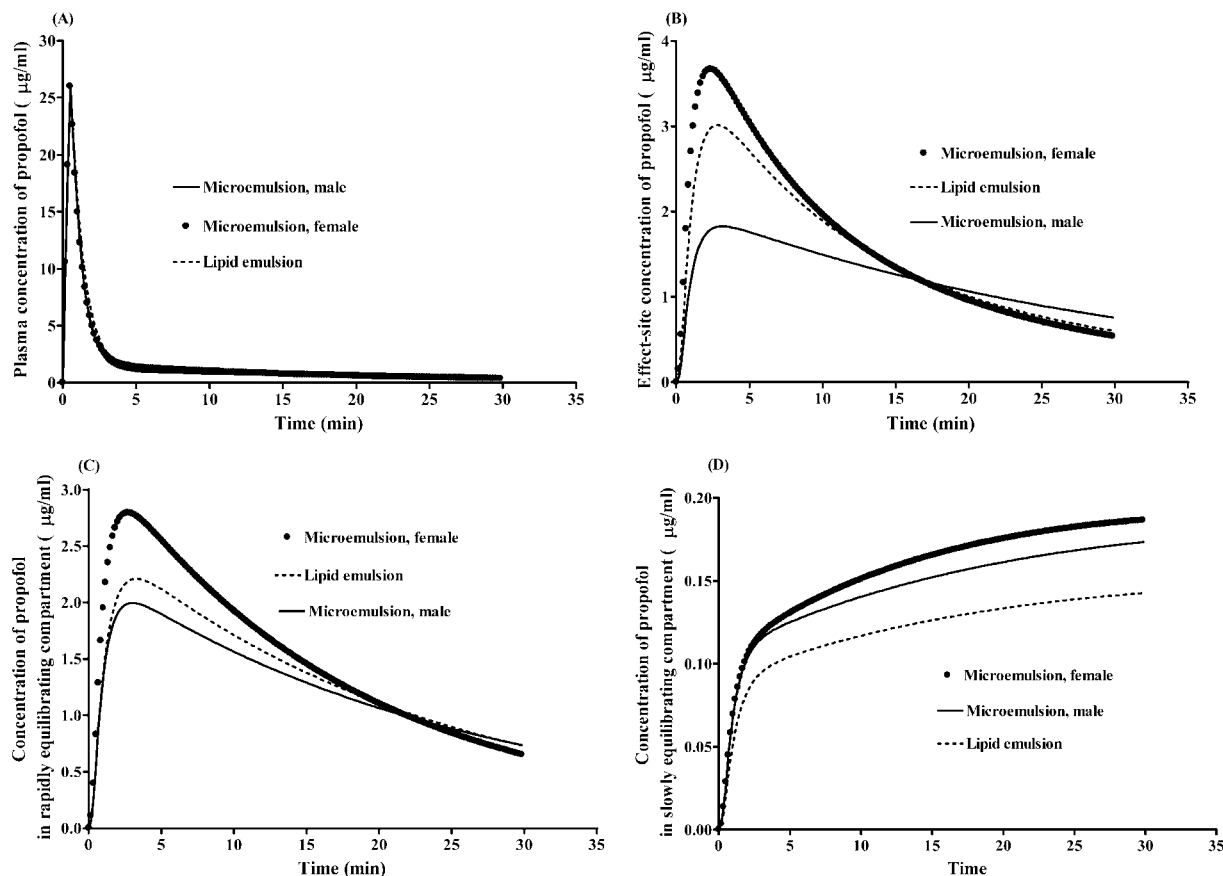


Fig. 5. Simulation of an intravenous bolus of propofol 2 mg/kg for lipid emulsion and microemulsion of propofol in a subject whose age, body weight, and height are 44 yr, 65 kg, and 170 cm, respectively. (A) Predicted plasma concentration, (B) predicted effect site concentration, (C) predicted concentration in rapidly equilibrating compartment, (D) predicted concentration in slowly equilibrating compartment.

### Safety Profiles

Overall, a total of 50 adverse events were reported in 31 subjects during study period. Eighteen (58.1%) of 31 subjects experienced adverse events after lipid emulsion dosing, and 14 (46.7%) of 30 subjects experienced adverse events after microemulsion dosing.

The adverse events after lipid emulsion dosing were mild ( $n = 17$ ), moderate ( $n = 7$ ), and severe ( $n = 1$ ). The adverse events after microemulsion dosing were mild ( $n = 18$ ), moderate ( $n = 5$ ), and severe ( $n = 2$ ). No serious adverse event occurred for either formulation. The adverse events after lipid emulsion dosing had probable ( $n = 20$ ), possible ( $n = 1$ ), unlikely ( $n = 1$ ), and no ( $n = 3$ ) causal relation to the study drug. The adverse events after microemulsion dosing had probable ( $n = 24$ ) and unlikely ( $n = 1$ ) causal relation to the study drug. All of the adverse events completely resolved without sequelae. The frequency and severity of the adverse events and the causal relation of adverse events to study drugs did not show significant differences between lipid emulsion and microemulsion. The number of subjects per each adverse event, including the frequency of concurrent treatments, is found in table 6.

Arterial oxygen saturation was maintained at or above

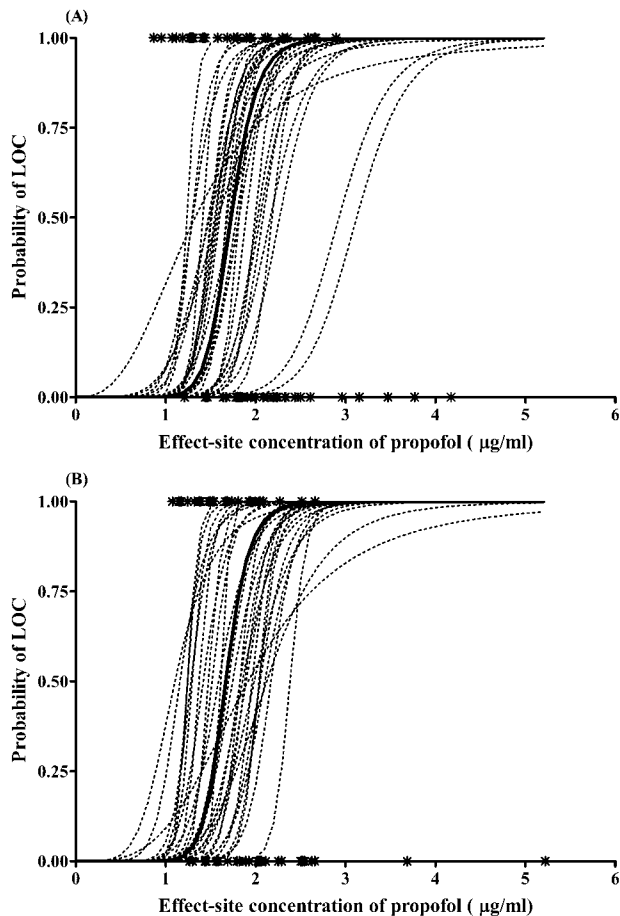
95% throughout study period in all subjects. Blood pressure, heart rate, body temperature, respiratory rate, and clinical laboratory tests did not show significant differences between lipid emulsion and microemulsion.

### Discussion

#### Noncompartmental Analysis of Pharmacokinetics and Pharmacodynamics

AquaSol and Diprivan<sup>®</sup> were bioequivalent. Regardless of formulations, time to peak effect after an intravenous bolus, which was assessed by BIS, was 1.5 min. Morey *et al.*<sup>3</sup> reported that significantly greater doses of propofol were required to induce anesthesia with propofol microemulsions irrespective of surfactant concentration or type than with propofol macroemulsion. However, the clinical characteristics at induction and recovery, including bolus and cumulative doses, were not different between microemulsion and lipid emulsion in this study.

Individually predicted  $V_3$  and hence  $V_{dss}$  of microemulsion were significantly smaller than those of lipid emulsion. Individually predicted half-lives were shorter in microemulsion than in lipid emulsion. These findings suggest that propofol in microemulsion is less exten-



**Fig. 6.** The relation between the probability of loss of consciousness (LOC) and the effect site concentration of propofol for lipid emulsion (A) and microemulsion formulation (B). The estimates of  $Ce_{50}$  (the effect site concentration of propofol associated with 50% probability of LOC) with SE and interindividual variability presented as % coefficient of variation are 1.73  $\mu\text{g/ml}$  (0.07, 22.0%) for lipid emulsion and 1.67  $\mu\text{g/ml}$  (0.07, 20.9%) for microemulsion. The estimates of  $\gamma$  (the steepness of the concentration-*vs.*-response relation) with SE and interindividual variability presented as % coefficient of variation are 11.8 (1.13, 50.4%) for lipid emulsion and 12.7 (1.43, 54.4%) for microemulsion. The mean  $Ce_{95}$  (the effect site concentration of propofol associated with 95% probability of LOC) with SD is  $2.22 \pm 0.44 \mu\text{g/ml}$  for lipid emulsion and  $2.11 \pm 0.44 \mu\text{g/ml}$  for microemulsion. Interindividual random variability was modeled using a log-normal model. \* Effect site concentrations of propofol at LOC and ROC.

sively distributed to peripheral tissues and is more rapidly disposed than propofol in lipid emulsion. We speculated that the former may be attributed to a relatively lower tissue/blood partition coefficient of microemulsion system as a propofol vehicle, and the latter may be explained by higher concentration of free propofol in aqueous phase, faster spontaneous destabilization of the microemulsion nanodroplets to release propofol, and relatively smaller size of the microemulsion nanodroplets.

#### Population Pharmacokinetics and Pharmacodynamics

The metabolic clearance of lipid emulsion was decreased with increasing age, which is the same finding as

**Table 6.** Number of Subjects per Each Adverse Event

	Lipid Emulsion (n = 31)	Microemulsion (n = 30)
Involuntary movement	6	6
Hypotension (ephedrine)	1(0)	5 (4)
Bradycardia (atropine)	4(5)	2 (0)
Apnea	2	3
Excitement	5	2
Headache (acetaminophen)	1(2)	2 (0)
Cough	1	1
Euphoria	0	1
Anemia	2	0
Increase of LD	0	1*

Dosing frequency of ephedrine, atropine, and acetaminophen is presented in parentheses. All adverse events except headache, increase of lactate dehydrogenase (LD), and anemia occurred during administration of propofol lipid emulsion or microemulsion.

\* Baseline LD: 206 U/l; LD at 1 day after administration of microemulsion of propofol: 291 U/l.

in previous studies.<sup>16,17</sup> Unlike lipid emulsion, the effects of age on the pharmacokinetic characteristics of microemulsion were equal increases of  $V_3$  and  $Cl_3$  with increasing age. Hence, age is not a factor influencing the rate of change in the amount of drug in the slowly equilibrating compartment.

The lack of weight being a significant covariate in this study is probably due to the small weight distribution in our population, which is a classic problem among volunteer studies. In general, a weight-independent model is difficult to apply in a target-controlled infusion system, and the clinical population of patients mostly requires a weight-dependent model.

For lipid emulsion, faster recovery of consciousness in females may be explained by the higher typical value of  $Ce_{50}$ , which suggests that females may be pharmacodynamically more resistant to the effect of propofol on the central nervous system than males. Gan *et al.*<sup>18</sup> found that females awoke significantly faster after discontinuation of the infusion of lipid emulsion formulation. Ward *et al.*<sup>19</sup> concluded that pharmacokinetic differences were primarily responsible for sex differences. In this study, we did not find any pharmacokinetic characteristic of lipid emulsion propofol to explain faster emergence for females.

Slower onset of sleep in males receiving microemulsion formulation may be partly explained by the higher volume of rapidly equilibrating compartment of microemulsion in males than in females, which in turn causes a lower peak effect site concentration of propofol. The rate of decrease in the effect site concentration of propofol is higher in females receiving microemulsion than in males receiving microemulsion (fig. 5). The effect site concentrations of propofol after approximately 17 min after an intravenous bolus are lower in females receiving microemulsion than in males receiving microemulsion. These findings are attributed to the higher  $k_{e0}$  of microemulsion in females, which may partly explain faster emergence in females. For micro-

emulsion, the higher typical value of  $Ce_{50}$  in females should be regarded as a factor for faster sleep and emergence, which is the same finding as in lipid emulsion. Females seem to be more resistant to the effect of propofol on the central nervous system regardless of formulations. For microemulsion formulation, a combination of pharmacokinetic and pharmacodynamic factors is responsible for the sex difference.

#### *Loss of Consciousness Pharmacodynamics*

In a previous study, the plasma concentration necessary for 50% of the participants to be awake at steady state condition was 1.68  $\mu\text{g/ml}$ , and an age effect on the steady state plasma  $C_{50}$  of propofol for being asleep was observed.<sup>20</sup> In this study, the effect site concentration of propofol associated with 50% probability of LOC was 1.73  $\mu\text{g/ml}$  for lipid emulsion and 1.67  $\mu\text{g/ml}$  for microemulsion, but an age or formulation effect was not observed. There was little difference of the concentrations (plasma or effect site) of propofol associated with 50% probability of loss of consciousness between steady state and non-steady state conditions.

#### *Safety Profiles*

Based on information on toxicologic data provided by BASF,  $LD_{50}$  of polyethylene glycol 660 hydroxystearate is 3.16 g/kg for male mice and 5 g/kg for female mice. Tetrahydrofurfuryl alcohol polyethylene glycol is used as a solvent in parenteral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material. Our previous preclinical studies of tetrahydrofurfuryl alcohol polyethylene glycol revealed that the approximate lethal dose in rats was more than 4 g/kg, no-observed-effect level, and approximate lethal doses in beagle dogs were 1 and 5 g/kg, respectively (June 28, 2003, single intravenous dose toxicity study of tetrahydrofurfuryl alcohol polyethylene glycol in rats, study No. B03069, intravenous dose-escalation study of tetrahydrofurfuryl alcohol polyethylene glycol in beagle dogs, study No. B03071, Sun-Hee Kim, Ph.D., and Zai-Zhi Huang, Ph.D., Biototech Co., Ltd., Ochang, Korea). Nine men with liver cirrhosis and nine other hospital patients with normal liver function were each injected intravenously with approximately 6.5 g tetrahydrofurfuryl alcohol polyethylene glycol. No overt adverse events were reported in any of the subjects.<sup>21</sup> There are no available data or literature to clearly indicate no observed effect level of these materials in humans, which should be carefully studied in other well-designed clinical trials. However, we found that the adverse events caused by microemulsion were not different from those by lipid emulsion with respect to type, incidence, and

severity of adverse events. Along with the evidence of bioequivalence and the pharmacodynamic endpoints in table 2, this suggests that microemulsion is therapeutically equivalent with lipid emulsion.##

In conclusion, the clinical characteristics at induction and recovery did not show significant differences between Aquafol (microemulsion) and Diprivan<sup>®</sup> (lipid emulsion). Aquafol and Diprivan<sup>®</sup> were bioequivalent. Population pharmacokinetic and pharmacodynamic modeling revealed a variety of differences between the two formulations. Aquafol showed a safety profile similar to that of Diprivan<sup>®</sup>.

The authors thank Sook-Kyung Seo, M.P.H. (Unit Manager, Medical Records Department, Asan Medical Center, Seoul, Korea), and Yoo-Mi Kim, M.P.H. (Researcher, Department of Health Care Industry, Korea Health Industry Development Institute, Seoul, Korea), for the preparation of data used in this study. They also thank Yun-Ah Kim, B.S. (Researcher, Clinical Research Center, Asan Medical Center), for the measurement of propofol concentration.

## References

- Han J, Davis SS, Washington C: Physical properties and stability of two emulsion formulations of propofol. *Int J Pharm* 2001; 215:207-20
- Baker MT, Naguib M: Propofol: The challenges of formulation. *ANESTHESIOLOGY* 2005; 103:860-76
- Morey TE, Modell JH, Shekhawat D, Grand T, Shah DO, Gravenstein N, McGorray SP, Dennis DM: Preparation and anesthetic properties of propofol microemulsions in rats. *ANESTHESIOLOGY* 2006; 104:1184-90
- Schnider TW, Minto CF, Gambus PL, Andresen C, Goodale DB, Shafer SL, Youngs EJ: The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. *ANESTHESIOLOGY* 1998; 88:1170-82
- Gepts E, Camu F, Cockshott ID, Douglas EJ: Disposition of propofol administered as constant rate intravenous infusions in humans. *Anesth Analg* 1987; 66:1256-63
- Coetzee JF, Glen JB, Wium CA, Boshoff L: Pharmacokinetic model selection for target controlled infusions of propofol: Assessment of three parameter sets. *ANESTHESIOLOGY* 1995; 82:1328-45
- Vuyk J, Engbers FH, Burm AG, Vletter AA, Bovill JG: Performance of computer-controlled infusion of propofol: An evaluation of five pharmacokinetic parameter sets. *Anesth Analg* 1995; 81:1275-82
- Beal S, Sheiner L: *NONMEM User's Guides Part V Introductory Guide*. San Francisco, NONMEM Project Group, University of California, 1992, p 48
- Jonsson EN, Karlsson MO: Xpose: An S-PLUS based population pharmacokinetic/pharmacodynamic model building aid for NONMEM. *Comput Methods Programs Biomed* 1999; 58:51-64
- Green B, Duffull SB: What is the best size descriptor to use for pharmacokinetic studies in the obese? *Br J Clin Pharmacol* 2004; 58:119-33
- Bouillon T, Shafer SL: Does size matter? *ANESTHESIOLOGY* 1998; 89:557-60
- Shapiro S, Wilk M, Chen H: A comparative study of various tests for normality. *J Am Stat Assoc* 1968; 63:1343-72
- Royston P: Estimating departure from normality. *Stat Med* 1991; 10:1283-93
- Hull CJ, Van Beem HB, McLeod K, Sibbald A, Watson MJ: A pharmacodynamic model for pancuronium. *Br J Anaesth* 1978; 50:1113-23
- Holford NH, Sheiner LB: Understanding the dose-effect relationship: Clinical application of pharmacokinetic-pharmacodynamic models. *Clin Pharmacokinet* 1981; 6:429-53
- Kirkpatrick T, Cockshott ID, Douglas EJ, Nimmo WS: Pharmacokinetics of propofol (Diprivan) in elderly patients. *Br J Anaesth* 1988; 60:146-50
- Schuttler J, Ihmsen H: Population pharmacokinetics of propofol: A multicenter study. *ANESTHESIOLOGY* 2000; 92:727-38
- Gan TJ, Glass PS, Sigl J, Sebel P, Payne F, Rosow C, Embree P: Women emerge from general anesthesia with propofol/alfentanil/nitrous oxide faster than men. *ANESTHESIOLOGY* 1999; 90:1283-7
- Ward DS, Norton JR, Guivarc'h PH, Litman RS, Bailey PL: Pharmacodynamics and pharmacokinetics of propofol in a medium-chain triglyceride emulsion. *ANESTHESIOLOGY* 2002; 97:1401-8
- Schnider TW, Minto CF, Shafer SL, Gambus PL, Andresen C, Goodale DB, Youngs EJ: The influence of age on propofol pharmacodynamics. *ANESTHESIOLOGY* 1999; 90:1502-16
- Bury RW, Breen KJ, Desmond PV, Raymond K, Mashford ML: Disposition of intravenous glycofurool: Effect of hepatic cirrhosis. *Clin Pharmacol Ther* 1984; 36:82-4

## European Medicines Agency (EMA): Note for Guidance on Investigation of Bioavailability and Bioequivalence. Available at: <http://www.emea.eu.int/pdfs/human/ewp/140198en.pdf>. Accessed January 2, 2007.