Anesthesiology 2005; 103:718–29 © 2005 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

AQUAVAN® Injection, a Water-soluble Prodrug of Propofol, as a Bolus Injection: A Phase I Dose-escalation Comparison with DIPRIVAN® (Part 1)

Pharmacokinetics

Ekaterina Gibiansky, Ph.D., Michel M. R. F. Struys, M.D., Ph.D.,† Leonid Gibiansky, Ph.D.,‡ Ann L. G. Vanluchene, M.D.,§ James Vornov, M.D., Ph.D.,‖ Eric P. Mortier, M.D., D.Sc.,# Eric Burak, Ph.D.,** Luc Van Bortel, M.D., Ph.D.††*

Background: **AQUAVAN® Injection (AQ) (GPI 15715; Guilford Pharmaceutical Inc., Baltimore, MD) is a water-soluble prodrug of propofol (Propofol$_{GPI}$). This study aimed to explore the pharmacokinetics of AQ, Propofol$_{GPI}$, and formate (a metabolite of AQ) and to compare them with the pharmacokinetics of propofol lipid emulsion (Propofol$_{D}$).**

Methods: **After ethics committee approval, 36 healthy volunteers were randomly allocated into six cohorts (male/female: 3/3) and given a single bolus of AQ (5, 10, 15, 20, 25, or 30 mg/kg). For comparison, an equipotent dose (as measured by the Bispectral Index) of Propofol$_{D}$ was given to the same subjects 1 week later. For both drugs, blood samples were collected (1–480 min) to analyze AQ, Propofol$_{GPI}$, Propofol$_{D}$, and formate concentrations. Noncompartmental pharmacokinetic analyses were performed for all analytes. A population compartmental model was developed for AQ and Propofol$_{GPI}$ using NONMEM. The models were evaluated using simulations and bootstraps.**

Results: **The noncompartmental pharmacokinetic comparison revealed different dispositions of Propofol$_{GPI}$ and Propofol$_{D}$. The maximum plasma concentration was lower for Propofol$_{GPI}$ than for Propofol$_{D}$ at equipotent doses, and apparent clearance and distribution volume were much higher for Propofol$_{GPI}$ than for Propofol$_{D}$. Formate concentrations were similar when injecting both drugs and were not higher than baseline. Compartmental modeling revealed that the pharmacokinetic behavior of AQ and its liberated Propofol$_{GPI}$ was best described by a nonlinear, six-compartment model, composed of two three-compartment models connected to each other by hydrolysis of AQ to Propofol$_{GPI}$.**

Conclusions: **Propofol$_{GPI}$ showed different noncompartmental pharmacokinetics from Propofol$_{D}$, hereby revealing the influence of the formulation. The combined model for AQ and Propofol$_{GPI}$ was best modeled by a nonlinear, six-compartment model.**

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 "ArticlePlus" link either in the Table of Contents or at the top of the Abstract or HTML version of the article.

PROPOFOL is an intravenous anesthetic–hypnotic agent that is marketed throughout the world as a lipid emulsion formulation under numerous trade names. Although propofol has a favorable pharmacokinetic and pharmacodynamic profile for the induction and maintenance of the hypnotic component of anesthesia,[1] known disadvantages associated with the emulsion formulation of propofol are pain on injection[2] and high lipid intake during long-term sedation in the intensive care unit.[3,4] Also, propofol is known to cause dose-related respiratory and hemodynamic depression.[1]

AQUAVAN® Injection (GPI 15715; Guilford Pharmaceuticals, Baltimore, MD) is a water-soluble prodrug of propofol and is intended to eliminate the disadvantages associated with the current lipid emulsion formulation of propofol by delivering propofol as a water-soluble prodrug. As seen in figure 1, AQUAVAN® Injection is chemically described as a phosphono-O-methyl prodrug of propofol. It undergoes hydrolysis by alkaline phosphatases liberating propofol (hereafter referred to as Propofol$_{GPI}$) as an active metabolite together with formaldehyde and phosphate. Formaldehyde is rapidly converted to formate.

The prodrug approach leads to rapid liberation of the active drug. In rats, Schywalsky *et al.* [5] concluded that, compared with the known propofol formulations, Propofol$_{GPI}$ showed a longer half-life, an increased volume of distribution, a delayed onset, a sustained duration of action, and an apparent greater potency with respect to plasma concentration. Recently, simulations from the first phase I study in nine volunteers receiving a constant-rate infusion of 290, 580, or 1,160 mg AQUAVAN® Injection over 10 min showed that, compared with DIPRIVAN® (propofol; AstraZeneca, London, United Kingdom; hereafter referred to as Propofol$_{D}$), the bolus dose of AQUAVAN® Injection produced a longer time to peak Propofol$_{GPI}$ plasma concentration.

The aim of this phase I, open-label, single-bolus dose,

* Head, Pharmacometrics, and Principal Scientist, ‖ Director, Clinical Research, Guilford Pharmaceuticals Inc., Baltimore, Maryland. † Professor in Anesthesia and Research Coordinator, § Staff Anesthesiologist, # Professor in Anesthesia and Chair, Department of Anesthesia, Ghent University Hospital. ‡ Former position: Senior Statistician, Emmes Corporation, Rockville, Maryland. Current position: Principal Scientist, Metrum Research Group, Avon, Connecticut. ** Former position: Director of DMPK, Guilford Pharmaceuticals Inc., Baltimore, Maryland. Current position: Pharmacokineticist, Rib-X Pharmaceuticals, New Haven, Connecticut. †† Professor, Clinical Pharmacology and Pharmacotherapy, Heymans Institute of Pharmacology, Ghent University and Head of Drug Research Unit Ghent, Ghent University Hospital.

Received from the Ghent University Hospital, Department of Anesthesia, Gent, Belgium. Submitted for publication September 29, 2004. Accepted for publication June 23, 2005. Supported in part by a grant from Guilford Pharmaceuticals Inc., Baltimore, Maryland, and departmental and institutional funding from the Ghent University Hospital, Gent, Belgium. Presented in part as a poster at the Euroanaesthesia meeting, Lisbon, Portugal, June 5–8, 2004.

Address reprint requests to Dr. Struys: Department of Anesthesia, Ghent University Hospital, De Pintelaan 185, B-9000, Gent, Belgium. Address electronic mail to: michel.struys@ugent.be. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

Copyright © by the American Society of Anesthesiologists. Unauthorized reproduction of this article is prohibited.

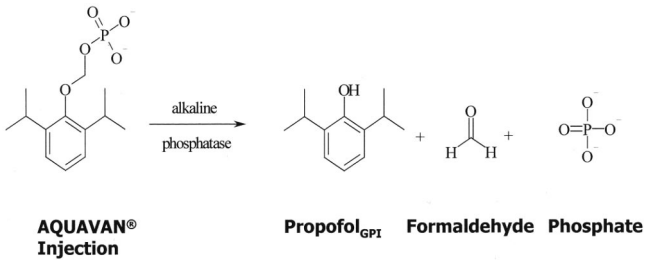


Fig. 1. Structure of AQUAVAN® Injection.

dose-escalation study was to explore the noncompartmental pharmacokinetics of AQUAVAN® Injection, Propofol$_{GPI}$, and formate and to compare Propofol$_{GPI}$ with Propofol$_{D}$. In addition, population compartmental pharmacokinetic modeling was conducted for AQUAVAN® Injection and Propofol$_{GPI}$.

Materials and Methods

Clinical Protocol

After local ethics committee (Ghent University Hospital, Gent, Belgium) approval and written informed consent were obtained, 36 healthy volunteers (18 males and 18 females) aged between 18 and 45 yr with a normal medical history were enrolled. For 1 week before the study, subjects were to follow a diet with limited amounts of alcohol and caffeine. Ingestion of caffeine, alcohol, products containing aspartame (aspartame may increase formate concentrations), or use of paracetamol within 24 h before study drug administration resulted in ineligibility.

In this crossover study, six cohorts of six volunteers (three men and three women) each received a single bolus dose of AQUAVAN® Injection starting with 5 mg/kg (called cohort 1) and increased with steps of 5 mg/kg up to 30 mg/kg (called cohort 6). After a washout period of 7 days, each subject received a comparator dose of the standard lipid emulsion propofol (DIPRIVAN®; Propofol$_{D}$) targeted to produce the same peak electroencephalographic effect that had been observed after the AQUAVAN® Injection dose, as measured by the minimal Bispectral Index. More methodologic details are given in the accompanying pharmacodynamic article.[6] AQUAVAN® Injection was administered manually, as quickly as possible (within 10 s). Propofol$_{D}$ was administered at the recommended infusion rate (50 mg/min)[7] *via* a standard infusion pump to avoid overshoot of clinical effect. The same procedures (monitoring, blood sampling, and others) were followed for both treatment phases.

Sample Acquisition, Handling, and Processing

A 20-gauge arterial catheter was inserted in the arteria radialis of the dominant arm for arterial blood sampling. All volunteers received an ipsilateral venous catheter in a large forearm vein for venous blood sampling and a contralateral venous catheter for drug and fluid administration.

To study the pharmacokinetics of AQUAVAN® Injection, Propofol$_{GPI}$, and Propofol$_{D}$, arterial samples were collected at the following nominal times: predose (baseline) and at 1, 2, 4, 7, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 100, 120, 140, 160, 180, 200, 240, 280, 320, 360, 420, and 480, For formate analysis, venous samples were drawn at screening, predose (baseline), and at frequent time points starting at 5 min through 482 min after drug administration and at checkout (1,440 min). As per protocol, urine was collected throughout the study for AQUAVAN® Injection analysis.

Drug Assay

Analysis of plasma AQUAVAN® Injection was performed using reverse-phase high-performance liquid chromatography with tandem mass spectrometric detection (Agilent 1100 Series high-performance liquid chromatography in line with a Micromass Quattro ULTMIA; Agilent Technologies, Palo Alto, CA). The analytical range of this method was 5–1,000 ng/ml, with coefficients of variation of 10.5, 3.2, and 2.9% in the low, medium, and high parts of the concentration range, respectively.

Analysis of plasma Propofol$_{GPI}$ and Propofol$_{D}$ was performed using a reverse-phase high-performance liquid chromatography with fluorescence detection, modified from the method of Plummer.[8,9] The analytical range of this method was 5–2,000 ng/ml, with a coefficient of variation of 3.9%.

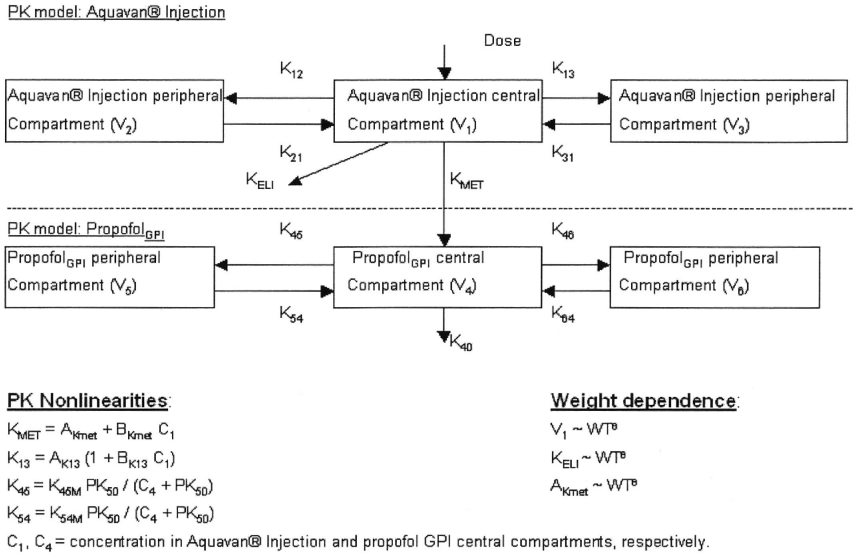
Concentrations of formate in human plasma were determined using high-resolution gas chromatography with mass spectrometric detection over a concentration range of 15.0–150.1 μg/ml, with precision of 3.6% coefficient of variation. For the pool used in the validation, blank human plasma samples from two donors were pooled together. Fifty-four replicates of the pool were analyzed to evaluate the endogenous concentration of formate. The endogenous concentration of formate in the pool was 24.69 μg/ml.[10]

Urine samples were analyzed for AQUAVAN® Injection using a validated high-performance liquid chromatography with mass spectrometric detection. The linear range of the assay was 9.98–997.75 ng/ml. The lower limit of quantification was 9.98 ng/ml.

Pharmacokinetic Analysis

Noncompartmental Analysis. Arterial plasma pharmacokinetic parameters of AQUAVAN® Injection and Propofol$_{GPI}$ were determined for each subject and summarized for each dosing group using standard noncompartmental techniques[11] and the software program WinNonlin version 3.1 (Pharsight Corp., Mountain View, CA). The following parameters were obtained: peak

Copyright © by the American Society of Anesthesiologists. Unauthorized reproduction of this article is prohibited.



PK Nonlinearities:

$K_{MET} = A_{Kmet} + B_{Kmet}\ C_1$

$K_{13} = A_{K13}\ (1 + B_{K13}\ C_1)$

$K_{45} = K_{45M}\ PK_{50} / (C_4 + PK_{50})$

$K_{54} = K_{54M}\ PK_{50} / (C_4 + PK_{50})$

Weight dependence:

$V_1 \sim WT^a$

$K_{ELI} \sim WT^a$

$A_{Kmet} \sim WT^a$

C_1, C_4 = concentration in Aquavan® Injection and propofol GPI central compartments, respectively.

Fig. 2. Population pharmacokinetic (PK) compartmental model for AQUAVAN® Injection and Propofol$_{GPI}$.

plasma concentration (C_{max}), time to C_{max} (T_{max}), area under the curve (AUC) from time 0 to the last quantifiable concentration (AUC_{0-t}), clearance (CL), volume of distribution (Vd), and terminal elimination phase half-life ($T_{1/2}$). For Propofol$_{GPI}$, CL and Vd are presented as apparent values (CL/F and Vd/F, where F is a bioavailability fraction) and were computed based on AQUAVAN® Injection dose adjusted for differences in molecular weight of AQUAVAN® Injection and its Propofol$_{GPI}$. For comparison of propofol pharmacokinetics from the two treatments, noncompartmental parameters were also calculated for Propofol$_D$ for each subject and were summarized by group that corresponded to AQUAVAN® Injection dose groups. Clearance (CL or CL/F) was calculated as Dose/AUC_{0-inf}, and volume of distribution (Vd or Vd/F) was calculated as CL/λ_z. The apparent terminal phase rate constant (λ_z) was determined using unweighted linear regression analysis on at least three log-transformed concentrations visually assessed to be on the linear portion of the terminal log concentration–time curve but not including the peak concentration. In general, objective selection of points included in the estimation of half-life required selection of those points that maximized the R^2 for the linear regression. For Propofol$_{GPI}$, the dose of propofol equivalent to the mole amount of the AQUAVAN® Injection dose was used in the calculation of CL/F and Vd/F. F shows that our knowledge of CL and V is relative, and they should not be compared to Propofol$_D$.

To test whether there is an increase in formate concentrations after administration of AQUAVAN® Injection, C_{max} values were summarized for each dosing group of both treatments.

Urine data were used to obtain the following AQUAVAN® Injection parameters: amount excreted, cumulative amount excreted, and fraction of dose excreted.

Population Pharmacokinetic Modeling of AQUAVAN® Injection and Propofol$_{GPI}$.

Model Description and Development. Concentrations of AQUAVAN® Injection and Propofol$_{GPI}$ were modeled simultaneously using NONMEM.[12] Four- to six-compartment models (two or three compartments for each compound) with linear and nonlinear distribution and elimination were examined. Hydrolysis of AQUAVAN® Injection to Propofol$_{GPI}$ was modeled by transferring drug from the central compartment of AQUAVAN® Injection into the central compartment of Propofol$_{GPI}$ (fig. 2). The model was parameterized in terms of rate constants (K_{12}, K_{21}, K_{13}, K_{31}, K_{14}, K_{10}, K_{45}, K_{54}, K_{46}, K_{64}, K_{40}) and volumes of AQUAVAN® Injection and propofol central compartments (V_1, V_4). First, linear models were tested. Then, dependencies of individual parameters on AQUAVAN® Injection dose were examined to access the linearity of the model. To model nonlinear behavior, parameters that exhibited dose dependence were presented as a sum of concentration-independent (constant) and concentration-dependent terms. The shape of parameter dependence on dose guided the selection of the parameter dependence on concentration. The process was repeated until all random effects dependencies on AQUAVAN® Injection dose were replaced by the parameter dependencies on AQUAVAN® Injection or Propofol$_{GPI}$ concentrations. More information on the modeling history and the raw data can be found on the ANESTHESIOLOGY Web site, in the Web Enhancement section, at http://www.anesthesiology.org. The differential equations and NONMEM representation are described in the appendix. Interindividual variability of the parameters was assumed to be log-normally distributed and was described by the exponential error model: $P_i = P_{TV} \cdot e^{\eta i}$, where P_i is the parameter value (rate constants and volumes of distribution) in the ith subject, P_{TV} is the typical value of the parameter in the

Copyright © by the American Society of Anesthesiologists. Unauthorized reproduction of this article is prohibited.

population, and η is a random variable with a mean of 0 and a variance of ω.[2] Individual variability is reported as ω, the SD of η in the log domain, which is approximately the coefficient of variation in the standard domain. Residual error was also described by the exponential model (implemented as an additive error in the model for logarithm of plasma AQUAVAN® Injection and $Propofol_{GPI}$ concentrations). Initially, the first-order estimation method was used for the analysis. After the best model was selected, the parameters of the model were reestimated using the first-order conditional estimation method.

The objective function value, diagnostic goodness-of-fit plots, and distributions of random effects guided model selection. The significance level $\alpha = 0.01$ was used for the likelihood ratio test. This corresponded to the change of $\Delta = 6.63$ in the value of the objective function for one additional parameter included in the model.

After the best model without covariates was determined, weight and sex covariates were added to all interindividual random effect parameters. Then, insignificant dependencies were excluded from the model one by one, starting from the least influential ones. Significance was defined by the likelihood ratio test with the significance level $\alpha = 0.01$.

Model Evaluation. The predictive performance of the population model was evaluated through the graphical analysis, leverage analysis, and bootstrap simulations as follows.

Graphical Analysis. The final population model with the final parameter estimates was used to predict concentrations of AQUAVAN® Injection and $Propofol_{GPI}$. Goodness-of-fit plots were evaluated for systematic bias. Plots of individual random effects *versus* covariates were evaluated to check for unaccounted dependencies on covariates. Correlation of individual random effects was investigated to check the adequacy of their correlation structure.

Leverage Analysis. All subjects were randomly allocated into 10 groups, each consisting of roughly 10% of the total number of subjects. Excluding subjects from 1 of 10 groups from the full data file created 10 new data sets. The final pharmacokinetic model was fitted to each of the resulting data files, and the model parameters were compared with the estimates and confidence intervals obtained from the fit of the full data file. The leverage analysis technique was used to evaluate whether selected subjects exerted a strong contribution or "leverage" on the model. Hereby, it is accepted that exclusion of small fraction of subjects at a time should not significantly influence the parameter estimates. Similarity of the parameter estimates for the full data set and for each of the leverage analysis data subsets ensures that none of the subjects exhibit unduly strong influence on the population model.

Bootstrap Analysis. One thousand bootstrap data sets were created by sampling the data from the original data set (by subject, with replacement). The final pharmacokinetic model was fitted to each of the resulting data sets. The bootstrap analysis examined the overall distribution of the parameters, confirmed the absence of local minima, and identified 95% confidence intervals of the parameter estimates. The distributions of model parameters were compared with the estimates and confidence intervals obtained from the fit of the original data set.

Percent Prediction Error and Absolute Percent Prediction Error for the Model. Hereby, percent prediction error (PPE) is defined as PPE = (Observed − Predicted)/Predicted × 100%, and absolute percent prediction error (APPE) is defined as APPE = Abs(PPE). Using PPE and APPE, summary measures, defined as median PPE and median APPE for both population and individual predictions, for AQUAVAN® Injection and $Propofol_{GPI}$ separately were calculated.

Model Predictions. After having obtained the final pharmacokinetic model for AQUAVAN® Injection, the influence of the nonlinearities in the AQUAVAN® Injection metabolism and distribution rate constants were assessed. To do so, the nonlinearities were excluded from the final model one by one, and the simplified models were compared with the full model. In addition, the contribution of the alternative routes of elimination from AQUAVAN® Injection were assessed by comparing the final model with a model without an alternative route of elimination.

The model was used to investigate the pharmacokinetics of AQUAVAN® Injection and $Propofol_{GPI}$ for a typical 70-kg subject.

Results

An exploratory analysis of the data indicated the short half-life of both AQUAVAN® Injection and $Propofol_{GPI}$.

Thirty-six subjects (18 men and 18 women, all white) contributed 575 arterial samples of AQUAVAN® Injection and $Propofol_{GPI}$. Their age and weight ranged from 19 to 43 yr and from 54 to 84 kg, respectively. There were no clinically important differences in demographics (age, sex, weight, height, body mass index, smoking history, alcohol consumption) and baseline data among the dose groups.

Noncompartmental Analysis in Plasma

All arterial samples were included in the calculations. Plasma concentrations of AQUAVAN® Injection rapidly declined after bolus administration (fig. 3). The initial rapid decline was followed by a slower terminal phase with a half-life of 1.01–1.49 h. Arterial concentrations of $Propofol_{GPI}$ increased rapidly (median T_{max} of 3–7.2 min) (fig.

Copyright © by the American Society of Anesthesiologists. Unauthorized reproduction of this article is prohibited.

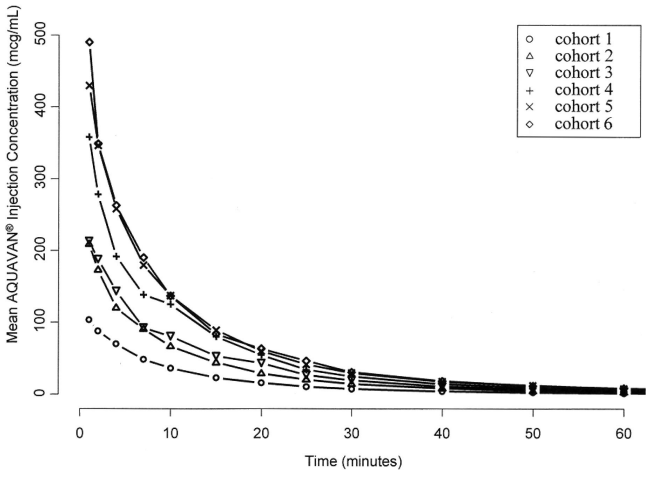


Fig. 3. Observed plasma concentration–time points of AQUAVAN® Injection. Data are mean of cohort.

4, top). Rapid initial decrease after peak was followed by a slower terminal phase with a half-life of 2.84–4.89 h. The summaries of pharmacokinetic parameters for AQUAVAN® Injection and $Propofol_{GPI}$ for each dose group are presented in tables 1 and 2, respectively. Mean systemic exposure (AUC_{0-t}) and peak concentrations (C_{max}) of AQUAVAN® Injection and $Propofol_{GPI}$ were

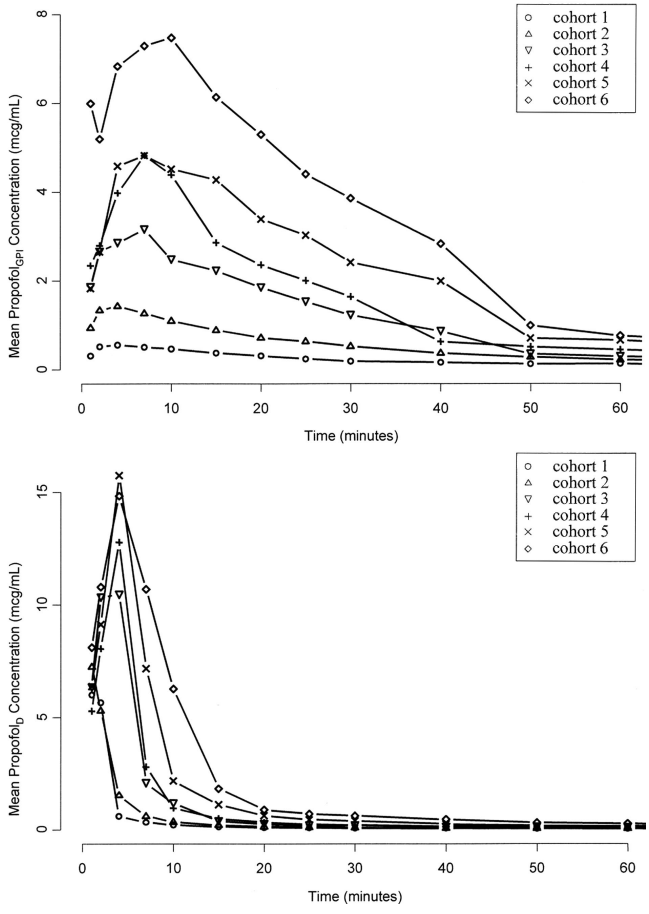


Fig. 4. Observed plasma concentration–time points of $Propofol_{GPI}$ and $Propofol_D$. Data are mean of cohort.

similar between men and women. Exposure to AQUAVAN® Injection increased slightly less than dose proportionally: For a 6-fold increase in dose, mean C_{max} and AUC_{0-t} of AQUAVAN® Injection increased 5- and 4-fold, respectively, in the arterial plasma. $Propofol_{GPI}$ exposure increased faster than dose: mean C_{max} and AUC_{0-t} of propofol increased 13- and 11-fold, respectively, in arterial plasma.

For $Propofol_D$ (fig. 4, bottom), the average doses administered (in the groups corresponding to AQUAVAN® Injection dose groups) ranged from 1.0 to 5.1 mg/kg. Administration time lasted from 0.9 to 9.4 min. The summary of pharmacokinetic parameters of $Propofol_D$ is presented in table 3.

When comparing $Propofol_{GPI}$ and $Propofol_D$, peak plasma concentrations of $Propofol_D$ were higher than those from $Propofol_{GPI}$, with the mean ratio of C_{max} values decreasing from 12 at the lowest dose to 2 at the highest dose group. Decline of plasma concentrations was slower and AUC values were higher for $Propofol_{GPI}$ than for $Propofol_D$. Ratios of mean propofol AUC ($Propofol_{GPI}$ to $Propofol_D$) ranged between 1.5 and 2.1 for all dose groups (except the lowest dose group, with a ratio of 1.1) with no apparent relation to dose.

Formate concentration–time profiles (venous) were flat across all dose groups regardless of the treatment. The C_{max} and exposure values were similar for both male and female volunteers. There was no trend toward increasing formate exposure with increasing doses of $Propofol_D$ or AQUAVAN® Injection. Peak concentrations and exposure were consistent across all dose groups studied (table 4).

Urine Data

After administration of AQUAVAN® Injection, samples (< 5%) from nine subjects showed measurable concentrations of AQUAVAN® Injection. The majority (eight samples) of measurable concentrations were from the first collection interval (0–3 h) and from the higher doses (25 and 30 mg/kg). The fraction of unchanged AQUAVAN® Injection excreted in urine was less than 0.02%, indicating insignificant excretion of unchanged AQUAVAN® Injection in urine.

Compartmental Population Pharmacokinetic Modeling

Model Description. The data obtained within the first 125 min after the dose administration were used in the analysis. The final population pharmacokinetic arterial model was a six-compartment model that consisted of two three-compartment blocks that described AQUAVAN® Injection and $Propofol_{GPI}$, respectively (fig. 2). The pharmacokinetics of AQUAVAN® Injection (compartments 1–3) was described by linear elimination of nonmetabolized drug and nonlinear metabolism to $Propofol_{GPI}$. The rate of metabolism increased linearly

Copyright © by the American Society of Anesthesiologists. Unauthorized reproduction of this article is prohibited.

Table 1. Mean (SD) Arterial Pharmacokinetic Parameters of AQUAVAN® Injection

Cohort No.	Dose, mg/kg	C_{max},* μg/ml	AUC_{0-t}, μg · h/ml	CL, l · h^{-1} · kg^{-1}	Vd, l/kg	$T_{1/2}$, h
1	5	103	19.4	0.267	0.386	1.01
		(8.1)	(4.2)	(0.06)	(0.10)	(0.24)
2	10	209	37.0	0.273	0.501	1.26
		(17)	(4.2)	(0.03)	(0.14)	(0.26)
3	15	216	44.4	0.354	0.754	1.49
		(40)	(10)	(0.09)	(0.21)	(0.30)
4	20	358	63.4	0.323	0.722	1.52
		(41)	(12)	(0.05)	(0.25)	(0.32)
5	25	430	78.9	0.323	0.694	1.49
		(55)	(11)	(0.05)	(0.14)	(0.16)
6	30	490	83.3	0.364	0.848	1.62
		(42)	(9.5)	(0.04)	(0.16)	(0.26)

* Observed maximum plasma concentration (C_{max}) was at the first sampling time (1 min) because of bolus administration.

AUC_{0-t} = area under the concentration–time curve from time 0 to time of last measurable concentration; CL = clearance; $T_{1/2}$ = terminal elimination half-life; Vd = volume of distribution.

with plasma concentrations of AQUAVAN® Injection. The pharmacokinetics of $Propofol_{GPI}$ (compartments 4–6) were described by the nonlinear input from the AQUAVAN® Injection central compartment and linear elimination. Rate constants of one of the peripheral compartments decreased with plasma concentrations of $Propofol_{GPI}$. The parameter estimates are presented in table 5. The NONMEM representation of the model is presented in the appendix.

All of the model parameters were well estimated, with the relative SE within the range of 4.2–35.5% for the fixed effect parameters, 23.3–44.7% for the variances of the random effect parameters, and 10.9–20.8% for the variances of the error terms. Intersubject variability of pharmacokinetic parameters (coefficient of variation of the random effects) was in the range of 15.1–42.0%. Proportional residual error was estimated to be 10.9% for AQUAVAN® Injection and 21.1% for $Propofol_{GPI}$ plasma concentrations.

Weight was a significant covariate in the model influencing AQUAVAN® Injection volume of the central compartment, metabolism, and elimination of AQUAVAN® Injection. Weight and sex were not significant covariates for the $Propofol_{GPI}$ model, although the predicted $Propofol_{GPI}$ concentration depended on weight due to the weight-dependence of AQUAVAN® Injection pharmacokinetics.

Model Evaluation. Goodness-of-fit plots (figs. 5–7) indicated that the model provided an adequate description of the observed data. Figure 5 presents plots of observed concentrations *versus* population and individual predictions. The points are scattered around the diagonal (unity) line. Figures 6 and 7 present, respectively, population and individual predictions for the arterial concentration–time courses of $Propofol_{GPI}$ for each subject, grouped by dose. The points illustrate the observed data.

Absence of trends on the plots of interindividual random effects *versus* dose and weight demonstrated that the model adequately accounted for all dose and weight dependencies.

The bootstrap analysis supported the validity of the pharmacokinetic model. Distributions of all parameters were close to normal; all of the parameters were well estimated. Confidence intervals for the population pa-

Table 2. Mean (SD) Arterial Pharmacokinetic Parameters of $Propofol_{GPI}$ after Administration of AQUAVAN® Injection

Cohort No.	$Propofol_{GPI}$ Dose,* mg/kg	C_{max}, μg/ml	AUC_{0-t}, μg · h/ml	CL/F,† l · h^{-1} · kg^{-1}	Vd/F,† l/kg	$T_{1/2}$, h	T_{max},‡ min
1	2.69	0.615	0.480	5.86§	24.6§	2.84§	3
		(0.20)	(0.14)	(0.97)	(11.5)	(0.91)	(1.8–10.2)
2	5.38	1.55	1.15	4.37	20.5	3.40	4.2
		(0.49)	(0.18)	(0.86)	(8.5)	(1.7)	(1.2–7.2)
3	8.06	3.30	1.96	3.93	19.8	3.41	7.2
		(1.08)	(0.35)	(0.62)	(7.2)	(0.69)	(4.2–7.2)
4	10.75	4.87	2.81	3.51‖	15.8‖	3.09‖	7.2
		(0.89)	(0.31)	(0.30)	(4.2)	(0.75)	(4.2–10.2)
5	13.44	5.28	3.84	3.33‖	16.0‖	3.39‖	6
		(0.90)	(0.43)	(0.43)	(8.7)	(2.1)	(4.2–10.2)
6	16.13	8.24	5.37	2.85	19.4	4.89	6
		(2.1)	(1.24)	(0.76)	(5.3)	(1.7)	(1.2–10.2)

* Amount of $Propofol_{GPI}$ in the corresponding AQUAVAN® Injection dose. † Apparent value, based on amount of $Propofol_{GPI}$ in the corresponding AQUAVAN® Injection dose. ‡ Median (range). § n = 4. ‖ n = 5.

AUC_{0-t} = area under the concentration-time curve from time 0 to time of last measurable concentration; CL/F = apparent clearance; C_{max} = observed maximum plasma concentration; $T_{1/2}$ = terminal elimination half-life; T_{max} = time of C_{max}; Vd/F = apparent volume of distribution.

Copyright © by the American Society of Anesthesiologists. Unauthorized reproduction of this article is prohibited.

rameters computed from the bootstrap parameter distributions were similar to the confidence intervals obtained by NONMEM. The leverage analysis showed that all parameter estimates from the subject subsets were within the 95% confidence intervals. No subset of the subject population had undue influence on the parameter estimates. Regarding the prediction errors for the final model, it was found that bias (median PPE) for the population estimates was 0.2% for AQUAVAN® Injection and −2.1% for $Propofol_{GPI}$. For the individual estimates, median PPE was −0.2% for AQUAVAN® Injection and 0.2% for $Propofol_{GPI}$. Precision (median APPE) values were 15.9% and 4.7% for the population and 21.5% and 10.7% for individual estimates, for AQUAVAN® Injection and $Propofol_{GPI}$, respectively.

Model Prediction. The final model included several nonlinearities: (1) the rate of AQUAVAN® Injection metabolism (K_{MET}) and AQUAVAN® Injection distribution rate constant (K_{13}) increased linearly with plasma concentrations of AQUAVAN® Injection (C_1), and (2) the rate of $Propofol_{GPI}$ distribution (K_{45} and K_{54}) decreased with plasma concentrations of $Propofol_{GPI}$ (C_4). To assess the influence of each of these nonlinearities, these were excluded from the final model one by one, and the simplified models were compared with the full model. Table 6 shows the ratios of the predicted $Propofol_{GPI}$ C_{max} of the simplified models ($C_{max}^{simplified}$) to the final model (C_{max}^{final}) for the lowest and the highest dose groups. For AQUAVAN® Injection on itself, predictions for plasma concentrations were nearly identical for all of the models.

The final model indicated two routes of AQUAVAN® Injection elimination: the concentration-independent elimination and the concentration-dependent metabolism to $Propofol_{GPI}$. The model without the direct elimination term adequately described the pharmacokinetics of AQUAVAN® Injection, as well as $Propofol_{GPI}$ at the intermediate doses, but $Propofol_{GPI}$ was biased by approximately 30% at the lowest and the highest ends of the dose range.

Weight was identified as a statistically significant covariate. The model indicated that weight-dependent dosing is preferable to fixed dosing. Simulations based on the model showed that nearly equal exposure is obtained for subjects with different weights if the administered dose is proportional to weight in the power of 0.75.

Disposition of AQUAVAN® Injection and $Propofol_{GPI}$ in a typical 70-kg person according to the model is presented in table 7.

Discussion

Noncompartmental Pharmacokinetics

The arterial plasma concentrations from the parent drug AQUAVAN® Injection followed an apparent multiexponential decline after the end of the bolus dose. The rapid decline was followed by a slower terminal phase. The rapid distribution and elimination and small volumes of distributions are consistent with the previous phase I trial from Fechner *et al.* [9] during short-lasting continuous infusion of AQUAVAN® Injection. The dose escalation for AQUAVAN® Injection resulted in less-than-dose-proportional increases for both C_{max} and AUC. In contrast to the parent drug, $Propofol_{GPI}$ was characterized by a classic large Vd and CL. Its time to reach peak concentrations (hereby also including the time for the hydrolysis of AQUAVAN® Injection to $Propofol_{GPI}$) was rapid, with mean T_{max} values between 3 and 7.2 min. There was no apparent trend in increasing time to peak plasma concentrations (T_{max}) with increasing doses, although subjects in cohorts 1 and 2 showed some lower T_{max} values. With increasing dose, more-than-proportional increases in both C_{max} and AUC were found.

The pharmacokinetic parameters (CL, Vd, and $T_{1/2}$) of $Propofol_D$ are consistent with the original data for propo-

Table 3. Mean (SD) Arterial Pharmacokinetic Parameters of $Propofol_D$

Cohort No.	$Propofol_D$,* mg/kg	C_{max}, μg/ml	AUC_{0-t}, μg · h/ml	CL, l · h^{-1} · kg^{-1}	Vd, l/kg	$T_{1/2}$, h	T_{max},†‡ min
1	1.01	7.24	0.507	2.39§	9.34§	2.73§	1.8
		(3.9)	(0.303)	(0.12)	(1.8)	(0.66)	(1.2–1.8)
2	1.33	8.32	0.648	1.93#	12.3#	4.44#	1.2
		(3.1)	(0.18)	(0.29)	(5.3)	(1.73)	(1.2–1.8)
3	2.37	11.9	1.27	1.89#	14.2#	4.73#	1.8
		(5.1)	(0.40)	(0.53)	(10.7)	(2.81)	(1.8–4.2)
4	2.85	14.1	1.42	1.84#	12.6#	4.64#	4.2
		(3.7)	(0.31)	(0.16)	(5.48)	(1.63)	(1.8–4.2)
5	4.03	16.5	2.14	1.82	7.89	3.02	4.2
		(3.2)	(0.55)	(0.16)	(4.92)	(1.92)	(4.2–7.2)
6	5.10	16.3#	2.92#	1.79‖	8.45‖	3.22‖	4.2§
		(4.7)	(0.69)	(0.21)	(4.0)	(1.35)	(1.8–10.2)

* Mean $Propofol_D$ dose in subjects from the corresponding AQUAVAN® Injection dose group. † Median (range). ‡ Observed maximum plasma concentration (C_{max}) occurred at the first sampling time (1 min) for two lowest dosing groups because of rapid administration. § n = 2. ‖ n = 4. # n = 5.

AUC_{0-t} = area under the concentration–time curve from time 0 to time of last measurable concentration; CL = clearance; Vd = volume of distribution; $T_{1/2}$ = terminal elimination half-life; T_{max} = time of C_{max}.

Copyright © by the American Society of Anesthesiologists. Unauthorized reproduction of this article is prohibited.

Table 4. Mean (SD) Venous Pharmacokinetic Parameters for Formate after Administration of AQUAVAN® Injection or $Propofol_D$

Cohort No.	AQUAVAN® Injection C_{max}, μg/ml	$Propofol_D$ C_{max}, μg/ml
1	39.1	40.8
	(8.8)	(10.2)
2	42.4	41.3
	(9.5)	(5.0)
3	29.6	31.6
	(4.5)	(6.9)
4	42.4	40.9
	(11.4)	(7.0)
5	34.8	37.6
	(8.6)	(5.1)
6	30.8	28.3
	(4.9)	(3.0)

C_{max} = observed maximum plasma concentration.

fol bolus injection in a lipid emulsion as published by Kay *et al.*[13] and Cockshott.[14]

One of the aims of the study was to compare the noncompartmental pharmacokinetics from $Propofol_{GPI}$ and $Propofol_D$. One might argue that comparison between both drugs is useless because of the differences in administration rates. However, in this study, comparison is possible because the onset and peak levels of the pharmacodynamic effects were similar, as documented in the accompanying article.[6] Therefore, the onset and peaks of concentrations can be compared. It was expected that the disposition of $Propofol_{GPI}$ should be similar to the disposition of the known propofol lipid emulsion. However, peak plasma concentrations of $Propofol_D$ were still higher than those from $Propofol_{GPI}$, with the ratio of C_{max} values decreasing from 12 at the lowest dose to 2 at the highest dose, even though $Propofol_D$ was administered slower than AQUAVAN® Injection. Decline of plasma concentrations was slower for $Propofol_{GPI}$, and AUC values were higher in $Propofol_{GPI}$ than $Propofol_D$. Ratios of mean propofol AUC ($Propofol_{GPI}$ to $Propofol_D$) ranged between 1.5 and 2.1 for all dose groups (except the lowest dose group, with a ratio of 1.1), with no apparent relation to dose. In relation to this, apparent clearance (CL/F) and Vd/F were much higher in the $Propofol_{GPI}$ than in $Propofol_D$.

These differences in apparent CL and Vd might be explained by the following: (1) the formulation differences in distribution of lipid and nonlipid propofol, (2) incomplete metabolism of the AQUAVAN® Injection

Table 5. Parameters of the Final Population Pharmacokinetic Model

Parameter	Estimate	%RSE	95% Confidence Interval	Units
Fixed-effect parameters				
V_1	2.78	4.21%	2.55–3.01	l
K_{ELI}	0.0884	8.87%	0.0730–0.104	l/min
K_{12}	0.111	28.5%	0.0491–0.173	l/min
K_{21}	0.409	14.9%	0.290–0.528	l/min
A_{K13}	4.79×10^{-3}	14.9%	3.39×10^{-3} to 6.19×10^{-3}	l/min
B_{K13}	3.54	28.5%	1.56–5.52	l/μmol
K_{31}	0.0265	3.28%	0.0248–0.0282	l/min
A_{Kmet}	0.0155	35.5%	0.00472–0.0263	l/min
B_{Kmet}	2.92×10^{-5}	30.9%	1.15×10^{-5} to 4.69×10^{-5}	$l \cdot \mu mol^{-1} \cdot min^{-1}$
V_4	1.00	Fixed		l
K_{40}	1.19	22.5%	0.665–1.72	l/min
K_{45M}	2.23	24.6%	1.15–3.31	l/min
K_{54M}	0.0307	19.8%	0.0188–0.0426	l/min
K_{46}	22.2	33.8%	7.48–36.9	l/min
K_{64}	1.19	18.3%	0.763–1.62	l/min
PK_{50}	4.62	29.0%	1.99–7.25	μM
PW_{WT}	0.685	21.3%	0.399–0.971	
Interindividual variability				Variability
ω^2_{V1}	0.0236	28.1%	0.0106–0.0366	CV = 15.4%
ω^2_{KELI}	0.0227	23.3%	0.0123–0.0331	CV = 15.1%
ω^2_{K13}	0.0442	21.9%	0.0253–0.0631	CV = 21.0%
ω^2_{AKmet}	0.176	40.6%	0.0361–0.316	CV = 42.0%
ω^2_{K45}	0.148	44.7%	0.0184–0.278	CV = 38.5%
ω^2_{K46}	0.0823	29.3%	0.0351–0.130	CV = 28.7%
Residual (intraindividual) variability				
σ^2_1	0.0118	20.8%	0.00698–0.0166	CV = 10.9%
σ^2_2	0.0444	10.9%	0.0350–0.0538	CV = 21.1%

ω^2_{V1}, ω^2_{KELI}, ω^2_{K13}, ω^2_{AKmet}, ω^2_{K45}, ω^2_{K46} = variances of interindividual distributions for the respective parameters; σ^2_1, σ^2_2 = variances of the residual error for AQUAVAN® Injection and $Propofol_{GPI}$ concentrations, respectively; B_{K13}, B_{Kmet} = terms of rate constants proportional to concentration of AQUAVAN® Injection; CV = coefficient of variation; K_{45M}, K_{54M}, PK_{50} = Michaelis-Menten constants of propofol distribution; K_{ELI}, K_{12}, K_{21}, A_{K13}, K_{31}, A_{Kmet}, K_{40}, K_{46}, K_{64} = concentration-independent rate constants; PW_{WT} = parameter for weight in the covariate power model; %RSE = percent relative standard error; V_1, V_4 = central compartment volume for AQUAVAN® Injection and $Propofol_{GPI}$, respectively.

Copyright © by the American Society of Anesthesiologists. Unauthorized reproduction of this article is prohibited.

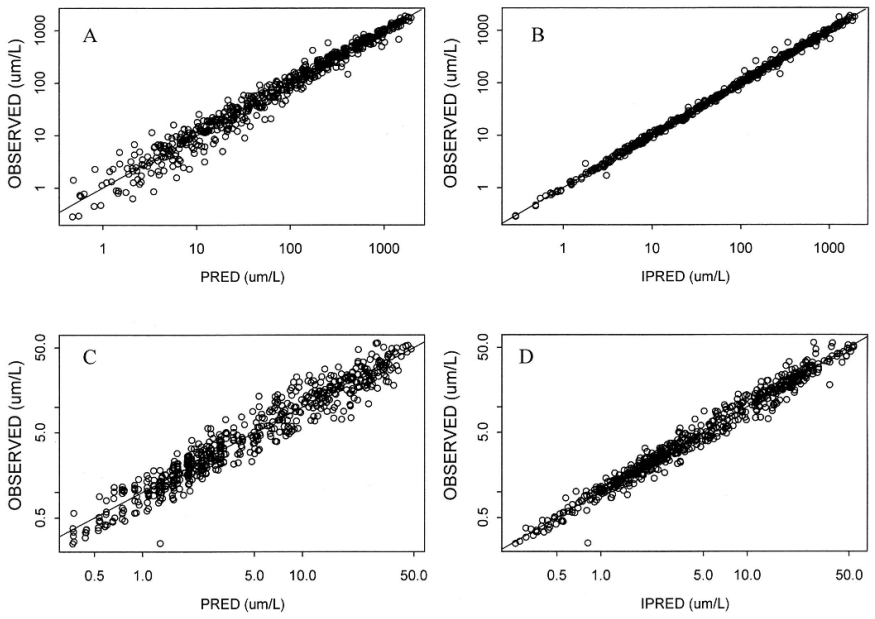


Fig. 5. Goodness-of-fit plots for the final pharmacokinetic arterial population model: observed *versus* population (PRED) or individual (IPRED) predicted concentrations for AQUAVAN® Injection (*A* and *B*) and Propofol$_{GPI}$ (*C* and *D*). Figures in the chart represent the administered dose.

prodrug (fraction of the metabolized drug F < 1), or (3) metabolism of a fraction of the prodrug and further metabolism of Propofol$_{GPI}$ in the same tissue without Propofol$_{GPI}$ appearing in circulation. Within this study, these hypotheses are indistinguishable. As found by Dutta and Ebling,[15,16] Vd in rats was much higher for a lipid-free propofol than for propofol lipid emulsion (producing half the C_{max} of propofol lipid emulsion at equipotent doses), and this was caused by a higher uptake of lipid-free propofol in the lungs. However, because they did not use a prodrug, this finding was completely the result of formulation differences. Alternatively, because

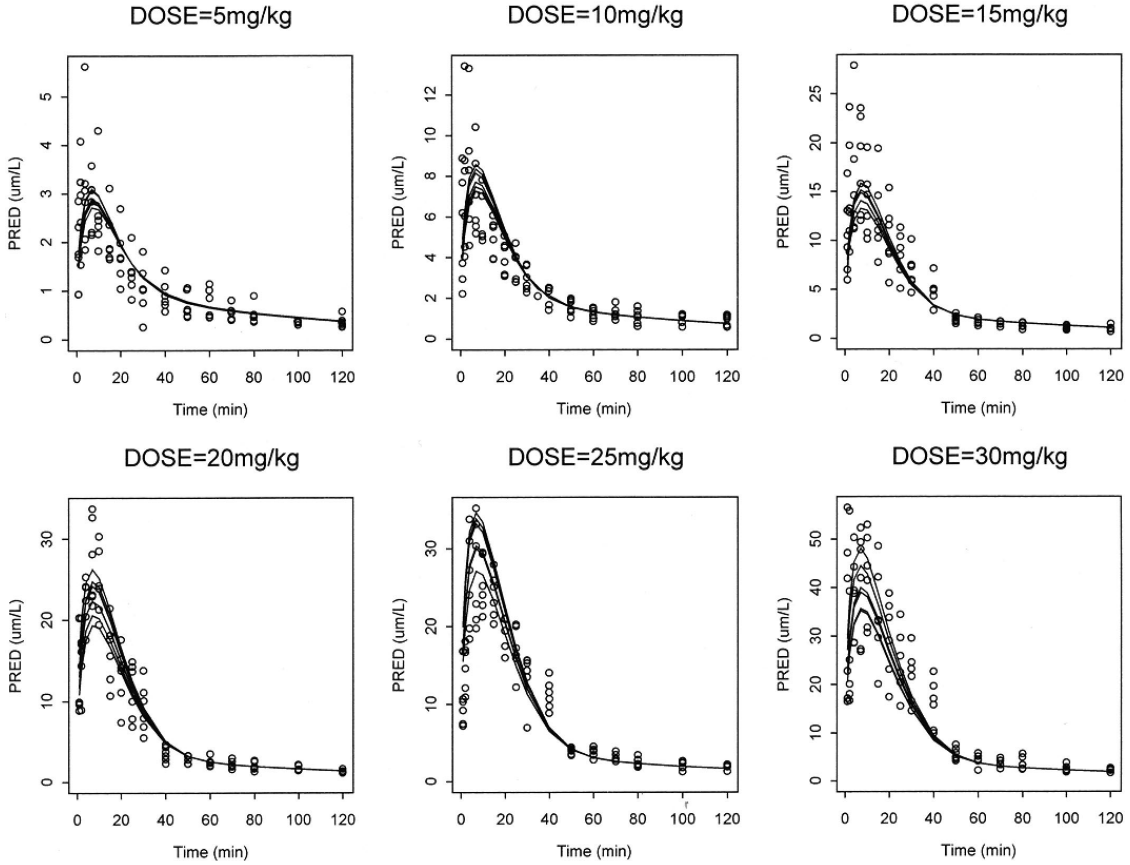


Fig. 6. Population predictions (PRED) of arterial Propofol$_{GPI}$ concentrations (*lines*) from the final population pharmacokinetic model and the observed data (*points*).

Copyright © by the American Society of Anesthesiologists. Unauthorized reproduction of this article is prohibited.

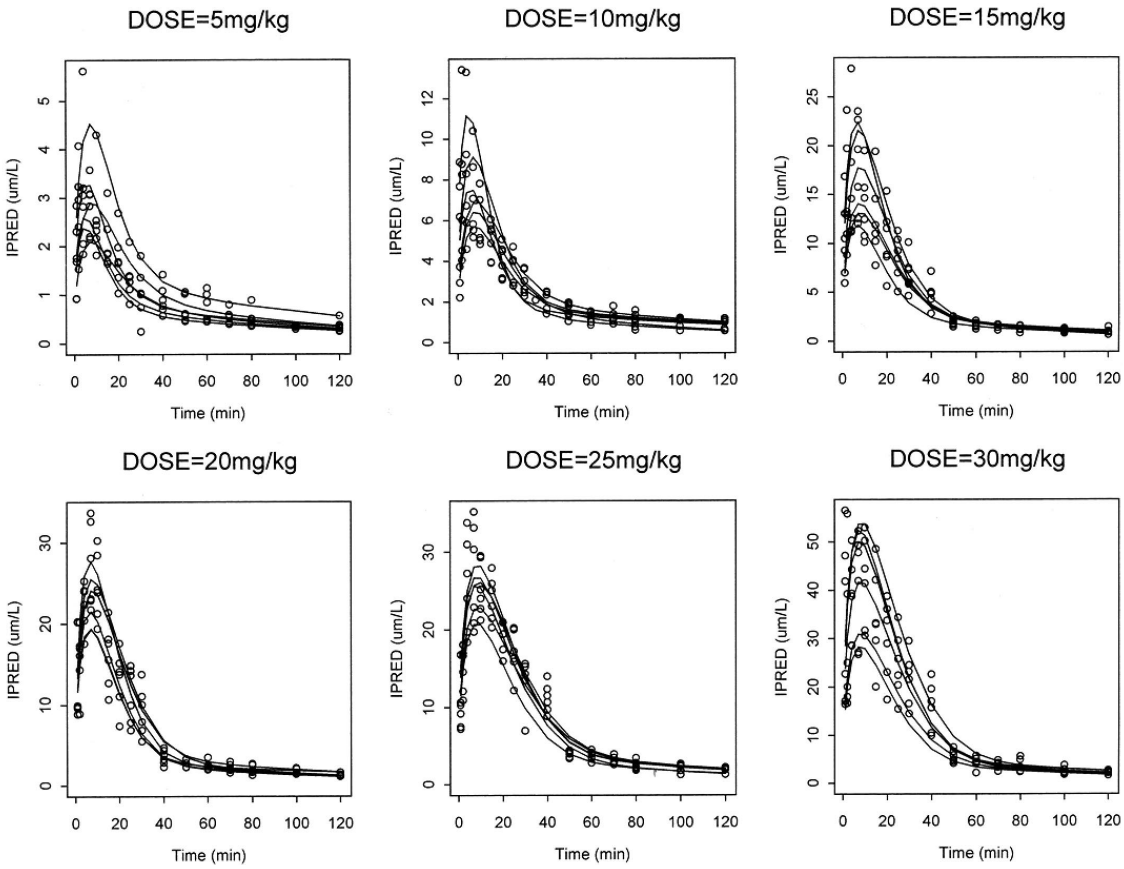


Fig. 7. Individual predictions (IPRED) of arterial Propofol$_{GPI}$ concentrations (*lines*) from the final population pharmacokinetic model and the observed data (*points*).

AQUAVAN® Injection is a prodrug, the higher apparent Vd and CL could be due to the incomplete liberation of propofol from the prodrug, as was hypothesized previously by Fechner *et al.*.[9] It is impossible to estimate F without injecting and dosing the active metabolite on itself, which was not done in this study. Because no hepatic P450 metabolism of the prodrug is shown in an *in vitro* metabolic stability study (data on file and personal communication, E. G, April 2004) and no AQUAVAN® Injection is excreted in the urine, the "lipid/nonlipid formulation" or "metabolism in the tissue" reasoning are more likely than "incomplete metabolism."

When comparing the propofol C_{max} at "equipotent" doses of both drugs, we observe that the C_{max} for Propofol$_{GPI}$ is much lower than for Propofol$_D$, even though Propofol$_D$ was given much slower than the bolus of AQUAVAN® Injection, whereas the propofol dose is higher for AQUAVAN® Injection (adjusted for difference in molecular weight, table 2) than for Propofol$_D$. This is in accord with previous work in rats from Dutta and Ebling,[16,17] where dose of lipid-free propofol was twice the equipotent dose of lipid emulsion, whereas peak propofol plasma concentration from the lipid-free formulation was half of that from the lipid emulsion at equipotent dose.

Formate concentrations after administration of AQUAVAN® Injection did not increase from their predose concentrations in any of the dosing groups and were not different from the endogenous concentrations in the Propofol$_D$ dosing group.

Compartmental Pharmacokinetics

Compartmental modeling showed that the combined pharmacokinetic behavior of AQUAVAN® Injection and its liberated Propofol$_{GPI}$ was best described by a nonlinear, six-compartment model composed of two three-compartment models connected to each other by hydrolysis of AQUAVAN® Injection to Propofol$_{GPI}$. As shown in figure 2, nonlinearities were found in both metabolism and distribution of AQUAVAN® Injection and Propofol$_{GPI}$. The contributions of these nonlinearities were tested by comparing the full nonlinear model with a partially linear or linear model. Of these nonlinearities, only the nonlinearity of metabolism is important to describe the pharmacokinetics of AQUAVAN® Injection. Not accounting for the nonlinearity of metabolism leads to an overestimation of the C_{max} of Propofol$_{GPI}$ at low doses and underestimation at high doses of approximately 43% and 36%, respectively. At the same time, the linear model for distribution of AQUAVAN® Injection and Propofol$_{GPI}$ resulted in an underestimation of

Copyright © by the American Society of Anesthesiologists. Unauthorized reproduction of this article is prohibited.

Table 6. Ratios of Predicted Maximum Plasma Concentrations for the AQUAVAN® Injection Simplified Models to That of the Final Model

Model Description	$C_{max}^{simplified}/C_{max}^{final}$ Dose = 5 mg/kg	$C_{max}^{simplified}/C_{max}^{final}$ Dose = 30 mg/kg
Final population model	1.00	1.00
Linear AQUAVAN® Injection metabolism	1.43	0.64
Linear distribution of AQUAVAN® Injection and $Propofol_{GPI}$	0.95	0.90
Linear model: linear metabolism and distribution of AQUAVAN® Injection and $Propofol_{GPI}$	1.62	0.63

C_{max} = maximum plasma concentration.

the C_{max} of $Propofol_{GPI}$ by only 5–10%. Although AQUAVAN® Injection and $Propofol_{GPI}$ have nearly linear distribution and elimination, metabolism of AQUAVAN® Injection to $Propofol_{GPI}$ is nonlinear, thus overall leading to a nonlinear relation between AQUAVAN® Injection dose and $Propofol_{GPI}$ concentration–time profile.

The model indicated two routes of AQUAVAN® Injection elimination: the concentration-independent direct elimination and the concentration-proportional metabolism to $Propofol_{GPI}$. If the metabolism were linear, these two routes could not be distinguished without separately injecting $Propofol_{GPI}$ as explained above in the noncompartmental section. Because metabolism of AQUAVAN® Injection seemed to be nonlinear, the model was able to estimate parameters of the two routes of AQUAVAN® Injection elimination. The direct elimination phenomenon is consistent with any of the three hypotheses of high $Propofol_{GPI}$ clearance discussed in the noncompartmental modeling section. These hypotheses cannot be distinguished within the model. As shown in the model prediction section, blocking the direct elimination route results in a $Propofol_{GPI}$ C_{max} bias of 30% at low and high dosages.

Table 7. AQUAVAN® Injection and $Propofol_{GPI}$ Pharmacokinetic Parameters for a Typical 70-kg Subject

AQUAVAN® Injection						
Cohort number	5	10	15	20	25	30
Percent metabolized to propofol	18	21	24	26	28	30
Time to 50% elimination, min	8	8	8	7	7	7
Time to 80% elimination, min	21	21	22	22	22	22
Time to 90% elimination, min	33	34	36	37	38	39
Percent eliminated by 120 min	99	99	99	99	99	99
$Propofol_{GPI}$						
% of C_{max} at 2 min	73	73	73	74	75	76
% of C_{max} at 3 min	84	84	84	85	86	87
% of C_{max} at 5 min	96	96	96	96	97	97
T_{max}	7.5	7.5	7.5	7.5	7.5	7
Elimination time to 90% C_{max}, min	13	13	13	13	13	13
Elimination time to 80% C_{max}, min	16	16	16	16	16	16
Elimination time to 50% C_{max}, min	27	25	25	25	25	25
Elimination time to 20% C_{max}, min	72	49	43	41	41	41

C_{max} = maximum plasma concentration; T_{max} = time when C_{max} occurred.

The nonlinearity found in the model indicates that the rate of metabolism is higher at higher plasma concentrations of AQUAVAN® Injection. Therefore, during bolus administration of AQUAVAN® Injection, plasma concentrations of $Propofol_{GPI}$ increase faster than expected from the hydrolysis half-life of 7.2 ± 1.1 min reported by Fechner *et al.* [9] based on 10-min infusion data. Although peak concentrations of $Propofol_{GPI}$ are reached at approximately 7.5 min, approximately 75% of it is already reached by 2 min after the bolus administration, as shown in table 7. Saturation of AQUAVAN® Injection protein binding at high plasma concentrations may be responsible for this nonlinearity. Because only the unbound AQUAVAN® Injection is hydrolyzed to $Propofol_{GPI}$, an increased unbound fraction would lead to a higher C_{max} of $Propofol_{GPI}$.

The pharmacokinetic model showed that dosing proportionally to weight would overdose heavier subjects and underdose lighter ones, suggesting a less-than-weight-proportional adjustment of dose to ensure equal exposure. This is consistent with many reports in the propofol literature indicating that lean body mass is a better predictor of propofol exposure than is weight.[18–20] Our model is based on the young healthy volunteers' data with a narrow range of weights (54–84 kg); therefore, this result should be interpreted only qualitatively when extrapolating to a broader patient population.

In classic propofol literature, known compartmental models are presented as being linear, although a large bias on the initial concentration is reported due to possible model misspecifications.[18] The model of AQUAVAN® Injection and $Propofol_{GPI}$ is presented as nonlinear, although nonlinearity in distribution accounts for only 5–10% of peak concentrations of $Propofol_{GPI}$. As a result, the linearity of $Propofol_{GPI}$ behavior is similar to that of the classic lipid emulsion formulation of propofol.

One could question why only the AQUAVAN® Injection and $Propofol_{GPI}$ concentrations obtained in the first 125 min were included in the model development. It must be realized that this is a bolus study without any continuous infusion. The developed model is complicated and nonlinear. For it to describe long tails of low concentrations (beyond 125 min), the complexity of the model should be further increased. Otherwise, adding additional data would compromise the description of the concentration–time course in the first 2 h. Also, it is not practically feasible (computer time) to develop the model with the same high resolution power (near the peaks) using all the data (until 480 min), let alone increasing number of compartments. Our goal was to develop a model that attempted to describe the very wide range of bolus doses and describe the data with high resolution, with emphasis on good description of early peak concentration–time course. In the future,

Copyright © by the American Society of Anesthesiologists. Unauthorized reproduction of this article is prohibited.

when therapeutic doses are evaluated, the models will be less nonlinear, and it will be feasible to model long periods of time.

In conclusion, when exploring the noncompartmental pharmacokinetics of AQUAVAN® Injection, $Propofol_{GPI}$, and formate and when comparing $Propofol_{GPI}$ with $Propofol_D$, the dose-dependent exposure to $Propofol_{GPI}$ increased at increasing doses of AQUAVAN® Injection. C_{max} was lower for $Propofol_{GPI}$ than for $Propofol_D$ at "equipotent" doses as determined by equal Bispectral Index peak values. After the administration of AQUAVAN® Injection, concentrations of formate were not higher than their predose concentrations in any of the dosing groups and were not different from the endogenous concentrations in the $Propofol_D$ dosing group. AQUAVAN® Injection is not excreted in the urine. In addition, when modeling the data from the AQUAVAN® Injection bolus using compartmental modeling, the pharmacokinetic behavior of AQUAVAN® Injection and its liberated $Propofol_{GPI}$ was best described by a nonlinear, six-compartment model, composed of two three-compartment models connected to each other by hydrolysis of AQUAVAN® Injection to $Propofol_{GPI}$. It can be stated that pharmacokinetic differences in propofol formulations are clinically important because they lead to different time course of the drug effect resulting in a different clinical behavior.

References

1. Smith I, White PF, Nathanson M: Propofol: An update on its clinical use. ANESTHESIOLOGY 1994; 81:1005–43
2. Picard P, Tramer MR: Prevention of pain on injection with propofol: A quantitative systematic review. Anesth Analg 2000; 90:963–9
3. Fulton B, Sorkin EM: Propofol: An overview of its pharmacology and a review of its clinical efficacy in intensive care sedation. Drugs 1995; 50:636–57
4. Barrientos-Vega R, Mar Sanchez-Soria M, Morales-Garcia C, Robas-Gomez A, Cuena-Boy R, Ayensa-Rincon A: Prolonged sedation of critically ill patients with midazolam or propofol: Impact on weaning and costs. Crit Care Med 1997; 25:33–40
5. Schywalsky M, Ihmsen H, Tzabazis A, Fechner J, Burak E, Vornov J, Schwilden H: Pharmacokinetics and pharmacodynamics of the new propofol prodrug GPI 15715 in rats. Eur J Anaesthesiol 2003; 20:182–90
6. Struys MMRF, Vanluchene ALG, Gibiansky E, Gibiansky L, Vornov J, Mortier EP, Van Bortel L: AQUAVAN® injection, a water-soluble prodrug of propofol, as a bolus injection: A phase I dose-escalation comparison with DIPRIVAN® injection: II. Pharmacodynamics and safety. ANESTHESIOLOGY 2005; 103: 730–743
7. Kazama T, Ikeda K, Morita K, Kikura M, Ikeda T, Kurita T, Sato S: Investigation of effective anesthesia induction doses using a wide range of infusion rates with undiluted and diluted propofol. ANESTHESIOLOGY 2000; 92:1017–28
8. Plummer GF: Improved method for the determination of propofol in blood by high- performance liquid chromatography with fluorescence detection. J Chromatogr 1987; 421:171–6
9. Fechner J, Ihmsen H, Hatterscheid D, Schiessl C, Vornov JJ, Burak E, Schwilden H, Schuttler J: Pharmacokinetics and clinical pharmacodynamics of the new propofol prodrug GPI 15715 in volunteers. ANESTHESIOLOGY 2003; 99: 303–13
10. Hanzlik RP, Fowler SC, Eells JT: Absorption and elimination of formate following oral administration of calcium formate in female human subjects. Drug Metab Dispos 2005; 33:282–6
11. Yamaoka K, Nakagawa T, Uno T: Statistical moments in pharmacokinetics. J Pharmacokinet Biopharm 1978; 6:547–58
12. Beal S, Sheiner L: NONMEM User's Guides. San Francisco, NONMEM Project Group, University of California, 1992
13. Kay NH, Uppington J, Sear JW, Douglas EJ, Cockshott ID: Pharmacokinetics of propofol ("Diprivan") as an induction agent. Postgrad Med J 1985; 61 (suppl 3):55–7
14. Cockshott ID: Propofol ("Diprivan") pharmacokinetics and metabolism: An overview. Postgrad Med J 1985; 61 (suppl 3):45–50
15. Dutta S, Ebling WF: Formulation-dependent brain and lung distribution kinetics of propofol in rats. ANESTHESIOLOGY 1998; 89:678–85
16. Dutta S, Ebling WF: Formulation-dependent pharmacokinetics and pharmacodynamics of propofol in rats. J Pharm Pharmacol 1998; 50:37–42
17. Dutta S, Ebling WF: Emulsion formulation reduces propofol's dose requirements and enhances safety. ANESTHESIOLOGY 1997; 87:1394–405
18. 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
19. Barr J, Egan TD, Sandoval NF, Zomorodi K, Cohane C, Gambus PL, Shafer SL: Propofol dosing regimens for ICU sedation based upon an integrated pharmacokinetic–pharmacodynamic model. ANESTHESIOLOGY 2001; 95:324–33
20. Kazama T, Morita K, Ikeda T, Kurita T, Sato S: Comparison of predicted induction dose with predetermined physiologic characteristics of patients and with pharmacokinetic models incorporating those characteristics as covariates. ANESTHESIOLOGY 2003; 98:299–305

Appendix: NONMEM Representation of the Population Pharmacokinetic Model

$PK

; AQUAVAN model

$V_1 = \theta_1(WT/70)^{\theta 16}\exp(\eta_1)$, $K_{ELI} = \theta_2(WT/70)^{\theta 16}\exp(\eta_2)/10$,

$K_{12} = \theta_3$, $K_{21} = \theta_4$,

$A_{K13} = \theta_5\exp(\eta_3)/10$, $B_{K13} = \theta_{17}$, $K_{31} = \theta_6/10$,

$A_{Kmet} = \theta_7\exp(\eta_4)/(WT/70)^{\theta}{}_{16}/10$, $B_{Kmet} = \theta_8/10000$,

; Propofol model

$V_4 = \theta_9$, $K_{40} = \theta_{10}$, $K_{45M} = \theta_{11}\exp(\eta_5)$,

$K_{54M} = \theta_{12}/10$, $K_{46} = \theta_{13}\exp(\eta_6)$, $K_{64} = \theta_{14}$,

$PK_{50} = \theta_{15}$

$DES

$C_1 = A(1)/V_1$

$K_{MET} = A_{Kmet} + B_{Kmet}{}^*C_1$

$K_{13} = A_{K13}\ (1 + B_{K13}{}^*C_1/1000)$

$C_4 = A(4)/V_4$

$K_{45} = K_{45M}\ PK_{50}/(C_4 + PK_{50})$

$K_{54} = K_{54M}\ PK_{50}/(C_4 + PK_{50})$

$DADT(1) = -(K_{ELI} + K_{MET} + K_{12} + K_{13})^*A(1) + K_{21}{}^*A(2) + K_{31}{}^*A(3)$

$DADT(2) = K_{12}{}^*A(1) - K_{21}{}^*A(2)$

$DADT(3) = K_{13}{}^*A(1) - K_{31}{}^*A(3)$

$DADT(4) = -(K_{45} + K_{46} + K_{40})^*A(4) + K_{54}{}^*A(5) + K_{64}{}^*A(6) + K_{MET}{}^*A(1)$

$DADT(5) = K_{45}{}^*A(4) - K_{54}{}^*A(5)$

$DADT(6) = K_{46}{}^*A(4) - K_{64}{}^*A(6)$

$ERROR

IF (AQUAVAN) $Y = \log(C_1) + \varepsilon_1$

IF (Propofol) $Y = \log(C_4) + \varepsilon_2$

Copyright © by the American Society of Anesthesiologists. Unauthorized reproduction of this article is prohibited.