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AQUAVAN® Injection, a Water-soluble Prodrug of Propofol, as a Bolus Injection: A Phase I Dose-escalation Comparison with DIPRIVAN® (Part 2)

Pharmacodynamics and Safety

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Background: **AQUAVAN® Injection (AQ) (GPI 15715; Guilford Pharmaceuticals Inc., Baltimore, MD) is a water-soluble prodrug of propofol. The authors explored the pharmacodynamics and safety of AQ and compared it with propofol lipid emulsion ($Propofol_D$).**

Methods: **After institutional review board approval, 36 volunteers with American Society of Anesthesiologists physical status of I were randomly allocated into six cohorts (male/female: 3/3 per cohort) and given a single bolus of AQ (5, 10, 15, 20, 25, or 30 mg/kg). A Bispectral Index® monitor (Aspect Medical Systems Inc., Newton, MA) measured the hypnotic effect. The lowest Bispectral Index level (BIS_{peak}) was recorded. One week later, $Propofol_D$ was given to the same subjects at 50 mg/min to reach a similar BIS_{peak}. Heart rate, oxygen saturation measured by pulse oximetry, blood pressure, and side effects were monitored. Incidence and duration of apnea and loss (LOC_{verbal}) and return of response to verbal command were measured. A population compartmental pharmacokinetic–pharmacodynamic model was developed for AQ using NONMEM and evaluated using simulations, leverage, and bootstrap analyses.**

Results: **In the higher dosages (cohorts 4–6), all subjects achieved LOC_{verbal}. Similar times until LOC_{verbal} were seen for AQ and $Propofol_D$. A dose-related increase in duration of LOC_{verbal} was longer for AQ than for $Propofol_D$. AQ BIS_{peak} occurred later than with $Propofol_D$. Pain on injection was only present with $Propofol_D$ (12 of 36). With AQ, transient paresthesias and pruritus were seen. Hemodynamic profiles were similar for both drugs, except for an initial tachycardia after AQ administration. Dose-dependent apnea was more pronounced with $Propofol_D$ than with AQ. The AQ combined pharmacokinetic–pharmacodynamic profile was best described by a nonlinear, six-compartment pharmacokinetic model and an effect site compartment. A dependency of the k_{e0} value on the $Propofol_{GPI}$ plasma concentration was noted.**

Conclusion: **Bolus administration of AQ achieves LOC_{verbal} at a similar time as an equipotent amount of $Propofol_D$ but shows a longer time to BIS_{peak} and prolonged pharmacodynamics. For both drugs, excellent drug safety was achieved, although there was a tendency of fewer and shorter duration of apneas for AQ.**

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AQUAVAN® Injection (GPI 15715; Guilford Pharmaceuticals Inc., 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-stable phosphono-O-methyl prodrug. By undergoing hydrolysis, propofol (hereafter called $Propofol_{GPI}$) is liberated as an active metabolite together with formaldehyde and phosphate. Formaldehyde is rapidly converted to formate. Although formaldehyde and formate are also endogenously produced by normal cellular metabolism resulting in detectable serum concentrations of formate, toxic concentrations might cause acidosis, ketonemia and acetonuria, respiratory failure, and ocular disturbance leading to blindness.[1]

In the accompanying pharmacokinetic article,[2] we explored the noncompartmental pharmacokinetics of AQUAVAN® Injection, $Propofol_{GPI}$, and formate after bolus administration of AQUAVAN® Injection and compared them with the noncompartmental pharmacokinetics of lipid emulsion propofol (DIPRIVAN®; AstraZeneca, London, United Kingdom; hereafter called $Propofol_D$) administered as a fast infusion. In addition, compartmental modeling was conducted for AQUAVAN® Injection. We found that the exposure to $Propofol_{GPI}$ increased faster than proportionally with increasing dosages of AQUAVAN® Injection. Maximum plasma concentrations were lower for $Propofol_{GPI}$ than for $Propofol_D$ at equipotent dosages. In addition, modeling the data from bolus administration of AQUAVAN® Injection showed that the combined pharmacokinetic behavior of the prodrug 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 $Propofol_{GPI}$.

The prodrug approach should lead to rapid intravascular liberation of the active drug. It might be hypothesized that AQUAVAN® Injection, presumably because of a more gradual increase in propofol blood concentration, might be associated with less cardiorespiratory changes than propofol emulsion.

When administering AQUAVAN® Injection as a constant rate infusion in healthy volunteers over 10 min, Fechner *et al.*[3] revealed that, compared with $Propofol_D$, the potency seemed to be higher with respect to plasma concentration but was apparently less with respect to dose. Using a preliminary pharmacokinetic model from

this study,[3] Fechner *et al.*[4] used a target-controlled infusion with various levels (slowly increased and decreased) of target propofol concentrations to compare the pharmacokinetics and pharmacodynamics from AQUAVAN® Injection with those from $Propofol_D$. They concluded that $Propofol_{GPI}$ showed different pharmacokinetics and pharmacodynamics, particularly a higher potency with respect to concentration. These differences may indicate an influence of the formulation. Also, they did not find a hysteresis between plasma concentration and effect for $Propofol_{GPI}$. However, Fechner *et al.* did not study the behavior of AQUAVAN® Injection when injected as a bolus. Also, a more in-depth exploration of the pharmacokinetic–pharmacodynamic behavior at higher dosages or administration rates is required.

After having explored the pharmacokinetics of AQUAVAN® Injection,[2] the aim of this study was to evaluate the pharmacodynamics, safety, and tolerability of AQUAVAN® Injection up to a dose producing maximal hypnotic effect as defined by electroencephalogram-derived assessment (burst suppression ratio and Bispectral Index [BIS]) and to compare the dynamic properties of $Propofol_{GPI}$ to those of $Propofol_D$. Because no combined pharmacokinetic–pharmacodynamic model exists for AQAUVAN® Injection, a predictive population pharmacokinetic–pharmacodynamic model was developed.

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 men and 18 women) aged between 18 and 45 yr were included. Inclusion and exclusion criteria are described in the accompanying article.[2]

As stated in the accompanying article,[2] the dose escalation protocol was based on the AQUAVAN® Injection dose. Three subjects of each sex were evaluated at each dose level of AQUAVAN® Injection, starting at 5 mg/kg and with increments of 5 mg/kg for each next dose level. Dose escalation was stopped after the maximal electroencephalographic effect criterion was obtained, defined as an electroencephalographic burst suppression ratio higher than 10% as shown on the BIS® monitor (Aspect Medical Systems Inc., Newton, MA) (as explained in the Materials and Methods section). More details on the calculations of burst suppression ratio can be found elsewhere.[5] After the completion of each dose group, assessment of the safety and tolerability profile was made, including a review of adverse events, vital sign measurements, clinical laboratory findings, and physical and neurologic assessments. If mean arterial pressure decreased below 40 in any subject for more than 5 min, the escalation would have been stopped. The dosing paradigm was completed with six AQUAVAN® Injection dose levels (5, 10, 15, 20, 25, and 30 mg/kg) for both sexes.

Table 1. Observer's Assessment of Alertness/Sedation Scale Score

Score	Responsiveness
5	Responds readily to name spoken in normal tone
4	Lethargic response to name spoken in normal tone
3	Responds only after name is called loudly and/or repeatedly
2	Responds only after mild prodding or shaking
1	Responds only after painful trapezius squeeze
0	No response after painful trapezius squeeze

A 20-gauge arterial catheter was inserted in the arteria radialis of the dominant arm for frequent arterial blood sampling as described in the accompanying article.[2] Baseline measures were taken before drug administration. During 122 min after drug administration, heart rate, oxygen saturation, respiration ratio, capnography, and body temperature were continuously monitored using a S5-cardiorespiratory monitor (Datex-Ohmeda, Helsinki, Finland). Noninvasive blood pressure was automatically taken every minute at the contralateral arm to the arterial line. All volunteers received an oxygen mask with 100% oxygen during the study. Arterial laboratory tests for obtaining information on blood gases, ionized calcium, electrolytes, triglycerides, total lipid, total cholesterol, high-density lipoprotein, and low-density lipoprotein were taken at 10, 60, 120, and 240 min after drug administration. For safety, five 12-lead electrocardiograms were taken during the study.

Arterial and venous sampling was performed as described in the accompanying pharmacokinetic article.[2]

To measure the hypnotic pharmacodynamic effects of the study drugs, a computerized univariate electroencephalogram-derived measure, the BIS, was used.

The BIS (version 4.0) was derived from the frontal electroencephalogram and calculated by the A-2000 monitor (Aspect Medical Systems Inc.) using the four BIS® Sensor electrodes. Electrode impedance was less than 5 kΩ. The smoothening time of the BIS® monitor was set at 15 s. BIS values range from 100 to 0, with lower values denoting more drug effect.[6] Beside BIS, the A-2000 monitor displays also the burst suppression ratio of the electroencephalogram. As said, a burst suppression ratio greater than 10% was used as an endpoint of the dose-escalation protocol. In addition to the BIS measures, loss and return of response to verbal command (LOC_{verbal} and ROC_{verbal}) were clinically assessed every minute using the modified Observer's Assessment of Alertness/Sedation scale, as explained in table 1. LOC_{verbal} and ROC_{verbal} were defined as the transition between Observer's Assessment of Alertness/Sedation levels 3 and 2 (or *vice versa*). Duration of unconsciousness was defined as the period between LOC_{verbal} and ROC_{verbal}.

All data were continuously recorded using data-man-

agement software (RUGLOOP Monitor-Only; Demed Engineering, Temse, Belgium). In addition, the data were also recorded manually at predefined time points in Case Report Forms as required by Food and Drug Administration regulations. During the study period, all adverse events were logged. An adverse event was defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of one of the investigational drugs, whether considered related to the treatment or not.

All volunteers stayed monitored (electrocardiogram, saturation, blood pressure) for 2 h after drug administration and resided in the clinic overnight (until 24 h after drug administration) as a safety precaution. After both treatment phases, subjects were asked to return to the clinic approximately 3 days postdose for a follow-up safety evaluation containing a physical/neurologic examination, visual assessment by an ophthalmologist, clinical laboratory tests, and urinalysis.

Pharmacodynamics and Safety

The hypnotic effect of both drugs was evaluated using BIS. Besides overall trends, the lowest BIS value (BIS_{peak}) and the time required to obtain BIS_{peak} ($T_{BIS,\ peak}$) were analyzed and compared between groups. Changes in heart rate after the drug injection were analyzed. The incidence and magnitude of increase in heart rate from baseline and the incidence of tachycardia (heart rate $>$ 90 beats/min) were calculated. Incidence and magnitude of bradycardia (heart rate $<$ 50 beats/min) were also investigated. Hemodynamic changes were assessed by investigating the changes in mean arterial blood pressure (MAP) after drug injection. The increase and decrease in MAP, defined as the highest and lowest MAP ($MAP_{highest}$ and MAP_{lowest}) and the time points when $MAP_{highest}$ and MAP_{lowest} occurred ($T_{MAP,\ highest}$ and $T_{MAP,\ lowest}$) were calculated. The incidence and duration of apnea (defined as no capnography for more than 10 s) were calculated for each subject.

Safety was evaluated based on adverse events, vital signs, and clinical laboratory test results on urinalysis, venous blood samples (hematology, serum chemistry, and electrolytes), and arterial blood samples (blood gases, calcium, phosphorus, and electrolytes). If a laboratory phosphorous concentration at or above 12.4 mg/dl was observed after AQUAVAN® Injection administration in any subject, the study was to be concluded.

Statistical Analysis for the Pharmacodynamic and Safety Data

The pharmacodynamic and safety data were analyzed using an unpaired or a paired *t* test or the Mann–Whitney or Wilcoxon matched pairs test, depending on the data (paired or unpaired) and their distribution. A Bonferroni correction was used if required, to correct for multiple testing.

A Population Pharmacokinetic–Pharmacodynamic Model for Propofol Originated from AQUAVAN® Injection ($Propofol_{GPI}$)

Two approaches were used in the development of the population pharmacokinetic–pharmacodynamic model. First, a sequential pharmacokinetic–pharmacodynamic model was developed and validated; then, a simultaneous pharmacokinetic–pharmacodynamic model was built. For the sequential model, estimates of individual arterial pharmacokinetic parameters (transfer rate constants and volumes of AQUAVAN® Injection and $Propofol_{GPI}$ central compartments) from the established earlier population pharmacokinetic model[2] were used to compute individual predictions of $Propofol_{GPI}$ plasma concentrations for each subject. The predicted propofol concentration was an independent variable; the observed BIS (recorded at the specific time points as reported in the Case Report Forms) was a pharmacodynamic response variable in the pharmacokinetic–pharmacodynamic model. For the simultaneous pharmacokinetic–pharmacodynamic model, the observed arterial plasma concentrations of AQUAVAN® Injection and $Propofol_{GPI}$ were dependent variables together with BIS, and all pharmacokinetic parameters and their distributions were obtained together with the parameters of the pharmacodynamic model. The sequential model is easier to develop; it also allows the more precise estimation of pharmacokinetic parameters, while it may inflate the variability of pharmacodynamic parameters (the estimated concentrations are used in the pharmacodynamic model as if they are observed, thus transferring the burden of the difference between the observed and predicted concentrations to be picked up by the variability in pharmacodynamic parameters).

Model Description and Development. The pharmacodynamic effect (BIS) was described by a sigmoid E_{max} model (Hill model) of propofol concentration C_E in an effect site compartment: $BIS = BIS_0 - E_{max} \times C_E^{\gamma}/(EC_{50}^{\gamma} + C_E^{\gamma})$, where BIS_0 is the baseline BIS value, E_{max} is the maximum decrease of BIS, EC_{50} is the effect site concentration that corresponds to half of the maximum effect, and γ is the Hill coefficient that describes the steepness of the concentration–effect relation. The effect site compartment accounted for the delay (hysteresis) between plasma $Propofol_{GPI}$ concentrations and the effect and was linked to the central (plasma) $Propofol_{GPI}$ compartment by the first-order process with the equilibration rate constant k_{e0}.

Pharmacodynamic parameters were assumed to be log-normally distributed in the population and were described by the exponential error model: $Par_j = Par_0 \times \exp(\eta_{Par\ j})$, where for each parameter of the model (E_{max}, EC_{50}, γ, or k_{e0}), Par_j and Par_0 are the individual (in the *j*th subject) and population (in the typical subject) values of the parameter, and $\eta_{Par\ j}$ is the individual value for the *j*th

Table 2. Demographics, AQUAVAN® Injection, and Propofol$_D$ Dose

	Cohort 1 (n = 6)	Cohort 2 (n = 6)	Cohort 3 (n = 6)	Cohort 4 (n = 6)	Cohort 5 (n = 6)	Cohort 6 (n = 6)	Total (n = 36)
Age, yr	21.3 ± 1.2	22.7 ± 1.6	24.2 ± 4.3	24.7 ± 5.2	27.7 ± 8.4	25.2 ± 8.5	24.3 ± 5.6
Weight, kg	71.2 ± 8.4	70.7 ± 7.8	68.2 ± 7.9	70.0 ± 11.3	67.4 ± 8.2	64.8 ± 10.5	68.7 ± 8.7
Height, cm	176 ± 9	177 ± 9	172 ± 9	170 ± 12	174 ± 6	173 ± 9	174 ± 9
Dose, mg/kg							
AQ	5	10	15	20	25	30	NR
DI	1.01 ± 0.2	1.33 ± 0.4	2.37 ± 0.3	2.85 ± 0.4	4.03 ± 1.2	5.10 ± 0.9	NR

For "total" study results, only non–cohort-dependent parameters were included. Data are presented as mean ± SD.
AQ = AQUAVAN® Injection; DI = Propofol$_D$; NR = not relevant.

subject that describes the difference between Par_j and Par_0. For each parameter, the interindividual random variable η_{Par} is assumed to be normally distributed with mean 0 and variance ω^2_{Par}. An intraindividual residual variability was described by an additive error model. The first-order estimation method of NONMEM[7] was used for model development; the first-order conditional estimation method was used to obtain the parameters of the final model. The aim of model development was to modify the form of the relation (if needed) to assure independence of individual parameters on dose and to minimize the number of random effects. Diagnostic goodness-of-fit plots, graphical analysis of random effect distributions, and the likelihood ratio test of the objective function values of competing models were used for model selection. Although not intended, the independence of individual parameters on body weight was also tested.

Model Evaluation. The predictive performance of the sequential population pharmacokinetic–pharmacodynamic model was evaluated through the leverage analysis and bootstrap simulations similarly to evaluation of the population pharmacokinetic model.[2] The simultaneous pharmacokinetic–pharmacodynamic model was evaluated by comparison of the parameter estimates and predictions with the pharmacokinetic and sequential pharmacokinetic–pharmacodynamic models. In addition, a posterior predictive check was performed by simulation of 500 trials identical to the original one (in design, doses, number of subjects, and their weights) and comparison of obtained medians and 90% confidence intervals of the predicted data (AQUAVAN® Injection and Propofol$_{GPI}$ plasma concentrations and BIS) for each of 36 subjects to the observed values. Comparison of the observed values with 10th, 25th, 50th, 75th, and 90th percentiles of predicted minimum BIS values was also performed.

Model Predictions. The shape and variability of the relation between BIS and Propofol$_{GPI}$ effect site concentrations, dependence of k_{e0} on Propofol$_{GPI}$ plasma concentration, and relation between lowest BIS values (BIS_{peak}) and BIS at maximum plasma Propofol$_{GPI}$ concentration ($C_{max,\ PropofolGPI}$) was explored.

Results

All 36 volunteers were included in the analysis. Demographics were similar among the six cohorts, as seen in table 2. For each cohort, table 2 shows the dose of Propofol$_D$ required to achieve an approximately similar BIS_{peak} level as after bolus administration of AQUAVAN® Injection.

Comparison of the Cerebral Effect of Propofol$_{GPI}$ versus Propofol$_D$

All individual BIS trends are plotted in figure 1 for each cohort and for both treatments. A dose-dependent decrease is observed throughout the figures. This is also seen in table 3, which shows the lowest BIS values (BIS_{peak}) obtained for each cohort. Overall, similar BIS_{peak} levels were achieved for both drugs, although some small differences were observed in two cohorts. Time to obtain BIS_{peak} tended to be shorter for Propofol$_D$ than for Propofol$_{GPI}$. No dose dependency was revealed in $T_{BIS,\ peak}$ (table 3). A burst suppression ratio higher than 10% was only observed in cohorts 5 and 6, as seen in table 3.

LOC_{verbal} was not observed in cohorts 1 and 2. As shown in table 3, similar times until LOC_{verbal} were seen for both drugs, and BIS values at LOC_{verbal} were also similar. Duration of unconsciousness increased with dose, and it was longer for AQUAVAN® Injection.

Comparison of Propofol$_{GPI}$ versus Propofol$_D$ on Hemodynamics, Respiration, and Safety

The changes in heart rate after the drug injections were studied. No episodes of bradycardia were observed for either drug. Increase in heart rate from baseline was seen in nearly all volunteers as described in table 4. The magnitude of increase was more pronounced for AQUAVAN® Injection resulting in a high incidence of short-lasting tachycardia episodes after the bolus. Changes in MAP are shown in table 5. Overall, hemodynamics were stable and comparable between groups. No hypotension (MAP lower than 40 mmHg) was observed. For AQUAVAN® Injection, a small initial increase ($MAP_{highest}$) above $MAP_{baseline}$ was seen in most subjects (30 of 36). Thereafter, blood pressure decreased below $MAP_{baseline}$ for all subjects. For Propofol$_D$, 21 of 36 volunteers showed a biphasic profile in MAP (a small initial

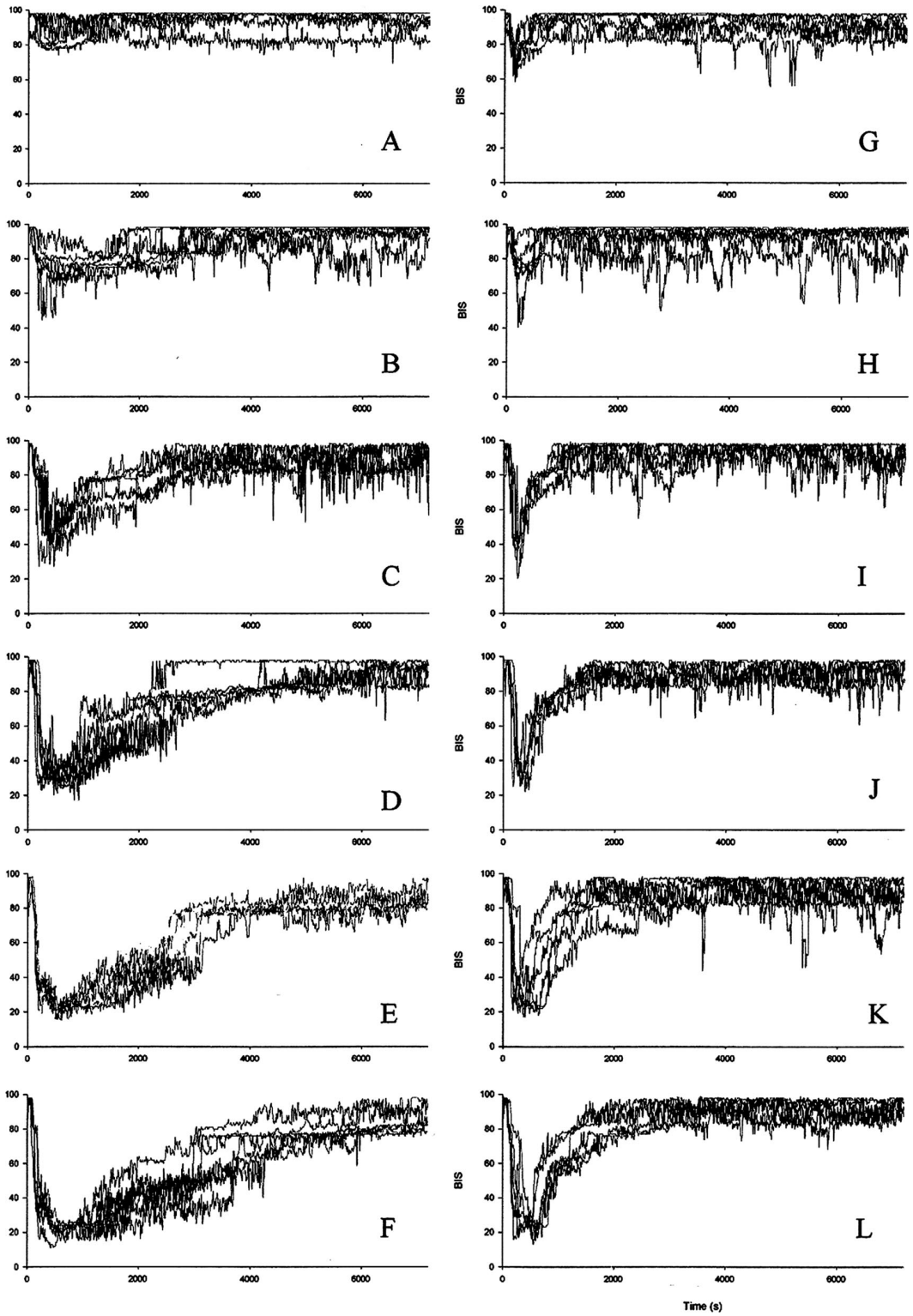

Fig. 1. All individual Bispectral Index trends for each cohort (n = 6) and for both treatment groups. *A–F* show the AQUAVAN® Injection dosages, 5, 10, 15, 20, 25, and 30 mg/kg, respectively. *G–L* show the equipotent Propofol$_D$ dosages that correspond respectively to *A–F*.

increase followed by a decrease in MAP compared with baseline), whereas 15 of 36 volunteers showed only a decrease. As shown in table 6, the time until lowest MAP was longer for AQUAVAN® Injection.

Duration and incidence of apnea are shown in table 6 for both drugs.

Formate concentration–time profiles were flat across all dose groups, regardless of the treatment arm. There

Table 3. AQUAVAN® Injection and Propofol$_D$ Pharmacodynamic Parameters

	Cohort 1 (n = 6)	Cohort 2 (n = 6)	Cohort 3 (n = 6)	Cohort 4 (n = 6)	Cohort 5 (n = 6)	Cohort 6 (n = 6)	Total (n = 36)
BSR > 10, n							
AQ	0/6	0/6	0/6	0/6	3/6	5/6	NR
DI	0/6	0/6	0/6	0/6	5/6	5/6	NR
BIS_{peak}							
AQ	80 ± 3	69 ± 12	42 ± 9*	26 ± 5	19 ± 4*	17 ± 4	42 ± 26
DI	74 ± 6	69 ± 13	30 ± 8*	29 ± 4	23 ± 5*	19 ± 4	40 ± 24
$T_{BIS,\ peak}$, s							
AQ	490 ± 45*	830 ± 362	493 ± 97*	640 ± 123*	560 ± 81	708 ± 280	623 ± 225†
DI	210 ± 32*	460 ± 603	241 ± 41*	300 ± 84*	460 ± 172	495 ± 122	364 ± 273†
LOC_{verbal}, n							
AQ	0/6	0/6	5/6	6/6	6/6	6/6	23/36
DI	0/6	0/6	6/6	6/6	6/6	6/6	24/36
BIS at LOC_{verbal}							
AQ	—	—	60 ± 11	73 ± 19	63 ± 23	70 ± 16	67 ± 18
DI	—	—	70 ± 13	58 ± 22	65 ± 12	66 ± 7	65 ± 15
T_{LOC}, s							
AQ	—	—	303 ± 105	157 ± 69	161 ± 39	142 ± 50	NR
DI	—	—	178 ± 59	183 ± 62	207 ± 83	185 ± 62	NR
$LOC_{duration}$, s							
AQ	0 ± 0	0 ± 0	700 ± 640	1,507 ± 914*	2,703 ± 267*	3,335 ± 786*	NR
DI	0 ± 0	0 ± 0	288 ± 151	415 ± 94*	748 ± 244*	965 ± 326*	NR

For "total" study results, only non–cohort-dependent parameters were included. Data are presented as mean ± SD.

* $P < 0.05$ between AQ and DI treatment within same cohort. † $P < 0.05$ between AQ and DI treatment (pooled data).

AQ = AQUAVAN® Injection; BIS_{peak} = lowest Bispectral Index value obtained after administration of AQ or DI; BSR = burst suppression ratio; DI = Propofol$_D$; $LOC_{duration}$ = duration of unconsciousness; LOC_{verbal} = loss of response to verbal command; NR = not relevant; $T_{BIS,\ peak}$ = time until lowest Bispectral Index value; T_{LOC} = time until LOC_{verbal}.

was no increase in formate concentrations from baseline in any dose or drug.

All 36 subjects reported adverse events. Reporting of adverse events did not increase with dose. Therefore, adverse events are listed in table 7 without breaking up into cohorts. No serious adverse events were noticed. As seen in table 7, the total number of side effects was higher in the AQUAVAN® Injection group. Safety clinical laboratory test results on urinalysis and venous blood samples (hematology, serum chemistry, and electrolytes) were within normal fluctuations as expected in the healthy population. No clinically meaningful changes from screening to baseline, checkout, or follow-up were observed. For the arterial blood samples, changes in blood gases reflect ventilation; they were similar between the two treatments. No clinically relevant changes were noted in electrolytes: sodium, potassium, or chloride. Ionized calcium concentrations were equal between the two drugs and without clinically relevant increases. Inorganic phosphate values increased somewhat in the highest AQUAVAN® Injection dosages within the first hour after the bolus injection but re-

Table 4. Heart Rate Changes after Drug Injection within Each AQUAVAN® Injection Cohort and Corresponding Propofol$_D$ Cohort and for the Total Study Population

	Cohort 1 (n = 6)	Cohort 2 (n = 6)	Cohort 3 (n = 6)	Cohort 4 (n = 6)	Cohort 5 (n = 6)	Cohort 6 (n = 6)	Total (n = 36)
$HR_{baseline}$							
AQ	86 ± 13	83 ± 14	73 ± 9	61 ± 5	84 ± 22	77 ± 12	78 ± 15
DI	73 ± 6	83 ± 17	76 ± 16	71 ± 10	72 ± 18	79 ± 16	76 ± 14
Subjects with increased HR from baseline, n							
AQ	3/6	5/6	6/6	6/6	6/6	6/6	32/36
DI	4/6	5/6	6/6	6/6	5/6	6/6	32/36
Δ HR							
AQ	30 ± 17*	25 ± 14*	29 ± 14*	41 ± 14*	28 ± 12	29 ± 19	31 ± 15†
DI	12 ± 8*	11 ± 8*	14 ± 8*	12 ± 10*	19 ± 10	17 ± 5	14 ± 8†
Subjects with $HR_{> 90}$, n							
AQ	4/6	5/6	6/6	5/6	6/6	6/6	33/36†
DI	1/6	3/6	3/6	1/6	2/6	3/6	13/36†

Data are presented as mean ± SD (beats/min).

* $P < 0.05$ between AQ and DI treatment within same cohort. † $P < 0.05$ between AQ and DI treatment (pooled data).

AQ = AQUAVAN® Injection; DI = Propofol$_D$; Δ HR = difference between $HR_{baseline}$ and highest heart rate after drug injection; $HR_{baseline}$ = heart rate before drug injection; $HR_{> 90}$ = tachycardia defined as an incidence of heart rate higher than 90 beats/min.

Table 5. Mean Arterial Blood Pressure before and after Drug Injection for Each AQUAVAN® Injection Cohort and Corresponding Propofol$_D$ Cohort

	Cohort 1 (n = 6)	Cohort 2 (n = 6)	Cohort 3 (n = 6)	Cohort 4 (n = 6)	Cohort 5 (n = 6)	Cohort 6 (n = 6)	Total (n = 36)
$MAP_{baseline}$, mmHg							
AQ	96 ± 5	99 ± 11	88 ± 10	95 ± 11	94 ± 15	88 ± 5	94 ± 10†‡
DI	90 ± 8	99 ± 13	84 ± 6	93 ± 6	92 ± 7	92 ± 6	92 ± 9†
$MAP_{highest}$, mmHg‖							
AQ	106 ± 7	107 ± 12	105 ± 15	111 ± 14	104 ± 15	99 ± 8	105 ± 12‡
DI	93 ± 8	98 ± 16	94 ± 10	109 ± 0	101 ± 13	91 ± 6	96 ± 11
$T_{MAP,\ highest}$, min‖#							
AQ	1 (1–2)	1 (1–3)	1 (1–2)	2 (1–3)	2 (1–2)	2 (1–3)	2 (1–3)
DI	1.5 (1–8)	1 (1–1)	1 (1–1)	1.5 (1–3)	2 (1–2)	1.5 (1–3)	1 (1–8)
MAP_{lowest}, mmHg							
AQ	79 ± 8	83 ± 10	72 ± 5	70 ± 11	65 ± 6	60 ± 4	72 ± 11†
DI	75 ± 6	83 ± 10	71 ± 4	76 ± 5	70 ± 8	68 ± 2	74 ± 8†
$T_{MAP,\ lowest}$, min‖#							
AQ	13.5 (7–19)	11.5 (1–29)	9.5 (55–21.5)	24 (13–29)	21 (7–27)	30 (11–36.6)	19 (1–36.6)*
DI	5.5 (2–26)	13.5 (2–20)	6.5 (4–8)	7 (2–25)	7 (5–10)	6 (6–20)	7 (2–26)*

* $P < 0.05$ between both drug treatments. † $P < 0.05$ between $MAP_{baseline}$ and MAP_{lowest}. ‡ $P < 0.05$ between $MAP_{baseline}$ and $MAP_{highest}$. ‖ Mean arterial blood pressure increase above baseline due to "waking up" after a period of unconsciousness was not taken into account. # Median (min–max).

AQ = AQUAVAN® Injection; DI = Propofol$_D$; $MAP_{baseline}$ = mean arterial blood pressure before drug injection; $MAP_{highest}$ = highest mean arterial blood pressure above $MAP_{baseline}$ reached after drug injection; MAP_{lowest} = lowest mean arterial blood pressure below $MAP_{baseline}$ reached after drug injection; $T_{MAP,\ highest}$ = time required to reach $MAP_{highest}$; $T_{MAP,\ lowest}$ = time required to reach MAP_{lowest}.

turned to normal ranges without reaching toxicity concentrations. Cholesterol, high-density lipoprotein, and low-density lipoprotein values in arterial samples did not fluctuate significantly across the treatment groups or over time. For Propofol$_D$, triglyceride concentrations increased significantly at higher dosages at 10 min after drug administration but returned thereafter to normal concentrations. No increases in triglyceride concentrations were seen after administration of AQUAVAN® Injection.

A Population Pharmacokinetic–Pharmacodynamic Model for Propofol Originated from AQUAVAN® Injection (Propofol$_{GPI}$)

In the sequential pharmacokinetic–pharmacodynamic model, individual predictions of arterial Propofol$_{GPI}$ concentrations (shown as lines in fig. 2) from the population pharmacokinetic model were used as the independent variable, and BIS data were used as the dependent variable. The arterial population pharmacokinetic–pharmacodynamic model (fig. 3) described the change of BIS from baseline as the Hill function of Propofol$_{GPI}$ concentration in the effect compartment, where the effect compartment rate k_{e0} increased proportionally with the arterial Propofol$_{GPI}$ plasma concentration. The parameter estimates are detailed in table 8. The fixed effect parameters (K_{E00}, E_{MAX}, EC_{50}, and γ) and the variance of the error term (σ^2) were well estimated, with the relative SE within the range 2.8–15.7%. Variances of the random effect parameters (ω^2_{KE00}, ω^2_{EC50}, and ω^2_{γ}) had relative standard errors within the range 24.0–34.7%. Interindividual variability of the parameters (coefficient of variation of the random effects) was in the range 28.4–70.6%. The SD of the additive residual error was estimated as 4.93 units (of BIS).

Figure 4 shows the mean observed Propofol$_{GPI}$ concentrations *versus* mean BIS values at each time point for each AQUAVAN® Injection cohort, hereby denoting the hysteresis. After modeling, figure 5 depicts the mean predicted Propofol$_{GPI}$ effect site concentration *versus* mean BIS values at each time point for each AQUAVAN® Injection cohort, hereby denoting the quality of the hysteresis collapse.

Graphical exploration of goodness of fit demonstrated the adequacy of the model, as shown in figure 6 of population observed and predicted BIS values by dose group. The leverage analysis showed that all of the parameter estimates from 20 subsets were within the 95%

Table 6. Incidence and Duration of Apnea for Each AQUAVAN® Injection Cohort and Each Corresponding Propofol$_D$ Cohort

	Cohort 1 (n = 6)	Cohort 2 (n = 6)	Cohort 3 (n = 6)	Cohort 4 (n = 6)	Cohort 5 (n = 6)	Cohort 6 (n = 6)	Total (n = 36)
Subjects with apnea, n							
AQ	0/6	0/6	2/6	4/6	3/6	5/6	14/36
DI	1/6	0/6	2/6	5/6	4/6	6/6	18/36
Duration of apnea, s							
AQ	0 ± 0	0 ± 0	29 ± 18	63 ± 24	51 ± 38	144 ± 89	85 ± 71
DI	20 ± 0	0 ± 0	40 ± 10	78 ± 43	142 ± 85	235 ± 155	137 ± 123

AQ = AQUAVAN® Injection; DI = Propofol$_D$.

Table 7. Treatment-emergent Adverse Events for Both Treatment Groups (All Six Cohorts Combined)

Adverse Events	AQUAVAN® Injection, n	$Propofol_D$, n
Atrioventricular block	1/36	0/36
Abdominal distention	1/36	0/36
Abdominal pain NOS	2/36	2/36
Diarrhea NOS	1/36	1/36
Chest pressure sensation	3/36	0/36
Fatigue	3/36	4/36
Injection site pain	0/36*	12/36*
Injection site paresthesia	0/36	2/36
Thirst	1/36	0/36
Weakness	1/36	0/36
Nasopharyngitis	3/36	1/36
Decreased appetite NOS	1/36	0/36
Arthralgia	1/36	1/36
Joint stiffness	2/36	0/36
Pain in limb	10/36	7/36
Peripheral swelling	2/36	4/36
Sensation of heaviness	1/36	0/36
Dizziness	1/36	1/36
Headache NOS	6/36	1/36
Hyperesthesia	2/36	2/36
Hypoesthesia	2/36	0/36
Muscle contractions involuntary	5/36	1/36
Paresthesia	36/36*	3/36*
Psychic excitability	1/36	0/36
Skin erythema	1/36	3/36
Pruritus NOS	3/36	2/36
Rash NOS	1/36	0/36
Hematoma NOS	3/36	0/36
Petechiae	1/36	0/36
Lymphadenopathy	0/36	0/36

* $P < 0.05$ between groups.

NOS = not specified.

confidence intervals. No subset of the subject population had an undue influence on the parameter estimates. The bootstrap analysis confirmed the overall stability of the model and the absence of the local minima. The bootstrap parameter estimates and confidence intervals were similar to ones obtained by NONMEM.

The simultaneous pharmacokinetic–pharmacodynamic model confirmed the results of the sequential modeling. The parameter estimates and their confidence intervals were similar to the ones estimated by the sequential models; the model predictions were also similar. Figures 7 and 8 show the results of the posterior predictive check that was performed by simulation of 500 trials identical (in design, doses, number of subjects, and their weights) to the original one. The observed data (BIS values over time, points) were then compared to medians (dashed lines) and 90% confidence intervals (solid lines) of the predicted data for each of 36 subjects (fig. 7). Figure 8 compares the observed minimum BIS for each subject with the predicted 10th, 25th, 50th, 75th, and 90th percentiles of this value.

The shape and variability of the pharmacokinetic–pharmacodynamic relation is illustrated in figure 9. For the illustration, it is assumed that the baseline value of BIS is equal to 100. Half of the propofol effect is reached at the effect compartment concentration equal to $EC_{50} = 2.09$ μg/ml (the circle). Triangles correspond to the minimum BIS values after bolus doses listed on the plot.

An unusual feature of the model is the dependence of k_{e0} on $Propofol_{GPI}$ plasma concentration. To observe this dependency, figure 10 illustrates dependence of the delay between the time to reach maximum $Propofol_{GPI}$ plasma concentration ($T_{Cmax,\ PropofolGPI}$) and the time to reach maximum BIS effect ($T_{BIS,\ peak}$) *versus* the dose of AQUAVAN® Injection. Figures 10A and B show individual ratios between the time to reach the maximum

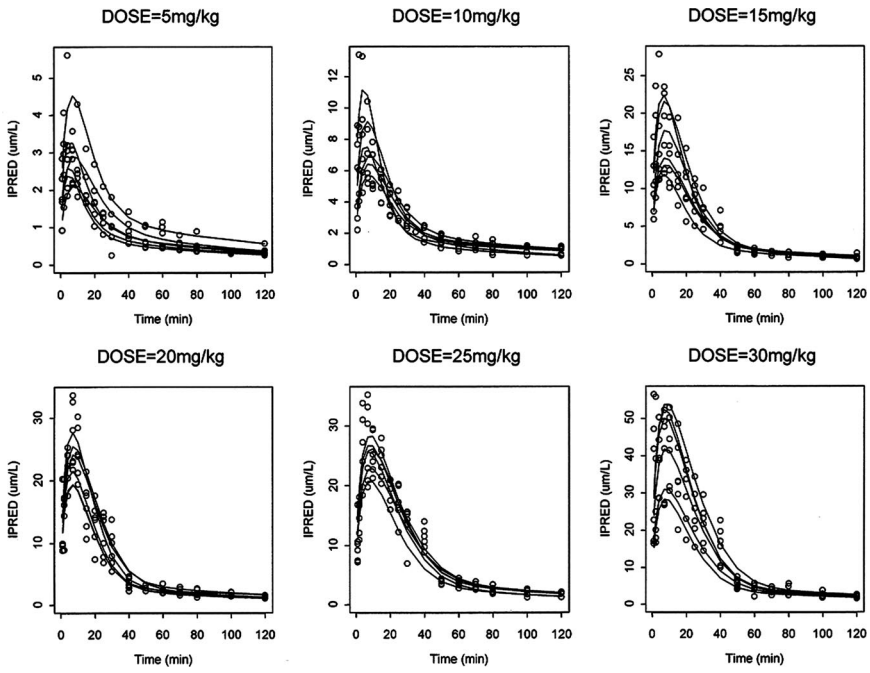

Fig. 2. Arterial $Propofol_{GPI}$ concentrations: individual predictions (IPRED) from the population pharmacokinetic model (*lines*) and the observed data (*points*).

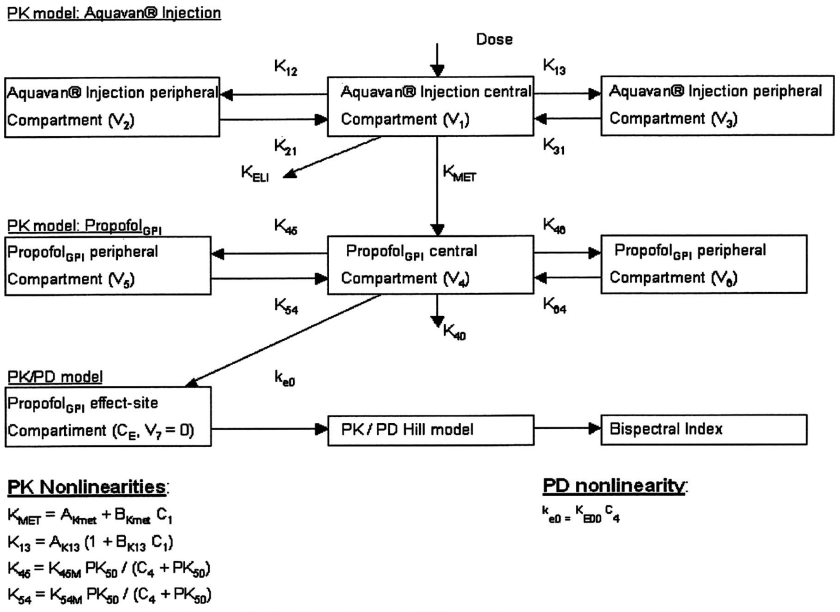

Fig. 3. The population pharmacokinetic–pharmacodynamic (PK/PD) model.

Propofol$_{GPI}$ plasma concentration ($T_{Cmax,\ PropofolGPI}$) and the time to reach maximum BIS effect ($T_{BIS,\ peak}$) for the observed data and for the model predictions, respectively. Figures 10C and D show individual differences for $T_{BIS,\ peak} - T_{Cmax,\ PropofolGPI}$ for the observed data and the model prediction, respectively. Each point corresponds to the data for one volunteer, the dotted line connects medians of the cohorts, and the solid line is a smooth regression. One can see that the delay is larger for smaller doses and that the model describes the general trend. The dependence of k_{e0} on Propofol$_{GPI}$ plasma concentration is illustrated in table 9, where k_{e0} is computed at the maximum Propofol$_{GPI}$ plasma concentration at each dose level. The k_{e0} increases substantially with increasing propofol concentrations, reaching a value of 1.2 min^{-1} (*i.e.*, equilibration $t_{1/2}$ = 0.58 min) at the highest concentration.

Table 10 shows BIS at $T_{Cmax,\ PropofolGPI}$ *versus* the lowest BIS as predicted by the population pharmacokinetic–pharmacodynamic model. For the illustration, it is assumed that the baseline value of BIS is equal to 100.

Discussion

AQUAVAN® Injection is a prodrug. The prodrug approach was originally successfully applied to phenytoin to create fosphenytoin.[8,9] Intravenous administration of AQUAVAN® Injection should theoretically result in a rapid intravascular liberation of the active metabolite, propofol, thereby avoiding the disadvantages of the lipid emulsion formulation. After having explored the pharmacokinetics of AQUAVAN® Injection,[2] the aim of this study was to evaluate the pharmacodynamics, safety, and tolera-

Table 8. Parameters of the PK/PD Model of AQUAVAN® Injection

Parameter	Estimate	%RSE	95% Confidence Interval	Units
Fixed-effect parameters				
K_{E00}*	0.0279	15.7%	0.0193–0.0365	$l \cdot \mu mol^{-1} \cdot min^{-1}$
E_{MAX}	80.6	2.78%	76.2–85.0	
EC_{50}	11.7	8.63%	9.72–13.7	μM
γ	1.63	6.69%	1.42–1.84	
Interindividual variability				Variability†
ω^2_{KE00}	0.498	33.1%	0.175–0.821	CV = 70.6%
ω^2_{EC50}	0.126	34.7%	0.0403–0.212	CV = 35.5%
ω^2_{γ}	0.0808	24.0%	0.00428–0.119	CV = 28.4%
Residual (intraindividual) variability				
σ^2	24.3	10.0%	19.5–26.4	SD = 4.93

* Parameter that describes k_{e0} as $k_{e0} = K_{E00} \times Cp$, where Cp is Propofol$_{GPI}$ plasma concentration. † Coefficient of variation (CV) for log-normally distributed random variables; SD for normally distributed random variables.

PK/PD = pharmacokinetic–pharmacodynamic; %RSE = percent relative standard error.

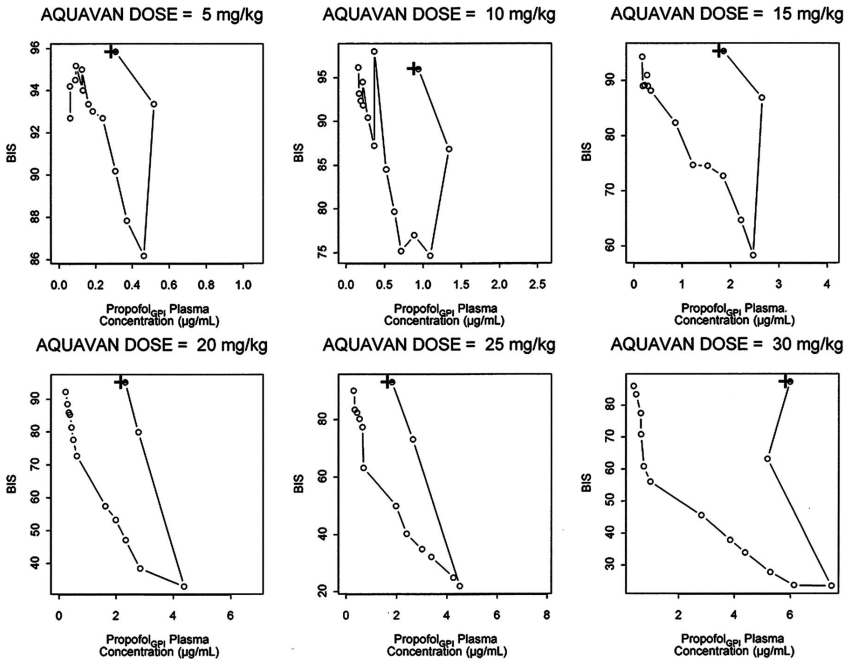

Fig. 4. Mean observed Propofol$_{GPI}$ plasma concentrations *versus* mean observed Bispectral Index (BIS) values at each time point for each AQUAVAN® Injection cohort. The starting point is shown as a *plus sign*.

bility of AQUAVAN® Injection up to a dose producing maximal hypnotic effect as defined by electroencephalogram-derived assessment (burst suppression and BIS) and to compare the dynamic properties of Propofol$_{GPI}$ to that of Propofol$_D$. In addition, a predictive population pharmacokinetic–pharmacodynamic model for AQUAVAN® Injection and Propofol$_{GPI}$ was developed.

Each bolus AQUAVAN® Injection dose was compared with an equipotent dose of Propofol$_D$ as measured by a cerebral measure of anesthetic drug effect (BIS). Because of a hysteresis between Propofol$_D$ plasma concentration and drug effect, it is impossible to titrate toward an equipotent dose when injecting the drug as fast as possible. To avoid overshoot at the clinical pharmacodynamic effect, a recommended infusion rate was used for Propofol$_D$.[10] One might ask why both drugs were not given at equimolar doses. We realized that larger molar doses of AQUAVAN® Injection were to be given compared with Propofol$_D$ to achieve comparable depth of anesthetic effect. Therefore, it seemed that a Propofol$_D$ comparator, dosed to effect with a rapid safe infusion, would give the best comparison on a patient-to-patient basis.

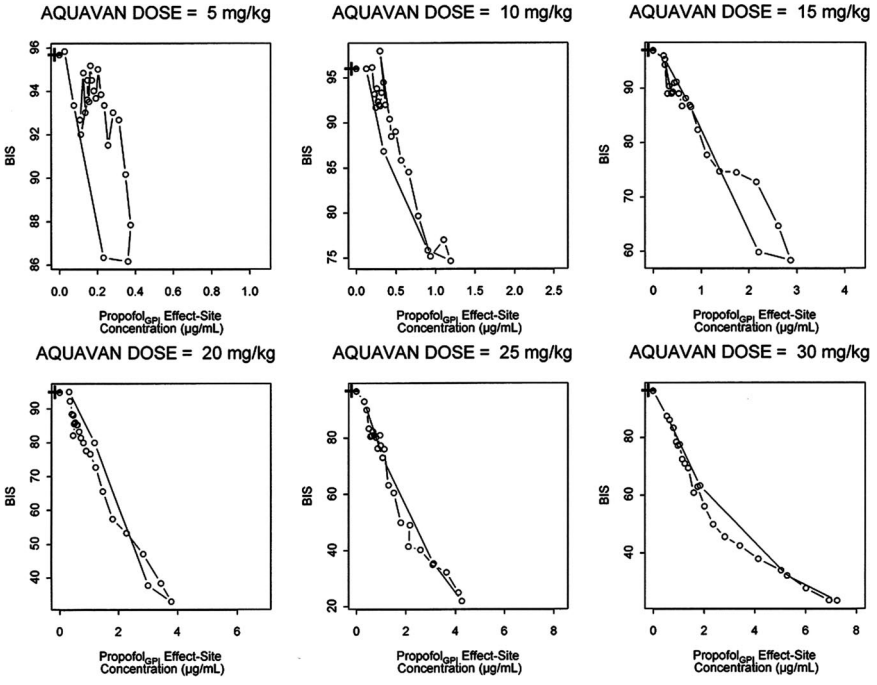

Fig. 5. Mean predicted Propofol$_{GPI}$ effect site concentration *versus* mean Bispectral Index (BIS) values at each time point for each AQUAVAN® Injection cohort. The starting point is shown as a *plus sign*.

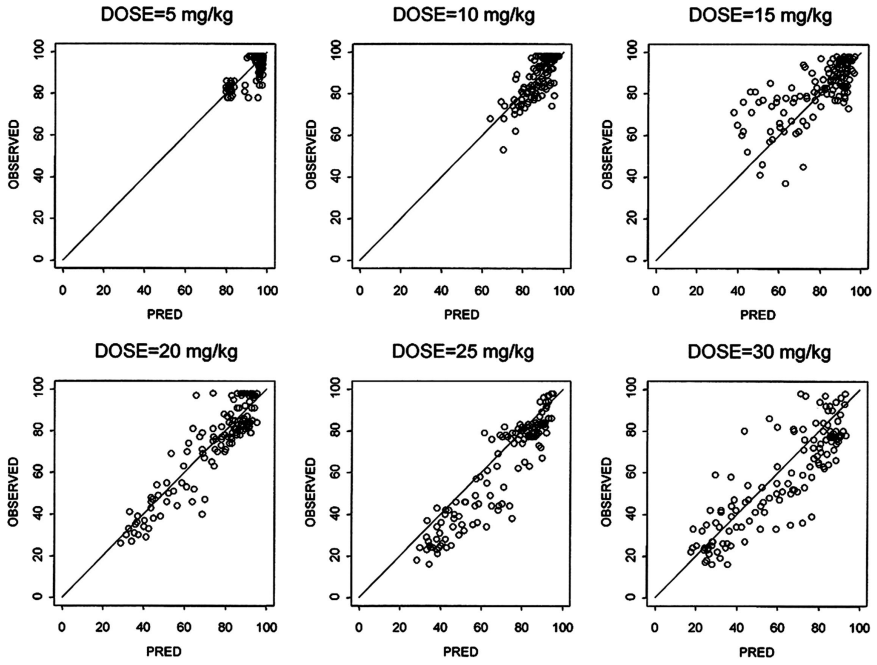

Fig. 6. Goodness-of-fit for each AQUAVAN® Injection cohort: observed Bispectral Index values (OBSERVED) *versus* population predictions (PRED) by the pharmacokinetic–pharmacodynamic model. *Unit line* provided for reference.

Comparison of the Cerebral Effect of Propofol$_{GPI}$ versus Propofol$_{D}$

The major clinical pharmacodynamic aim of this study was to compare the cerebral anesthetic–hypnotic effect of both drugs. The BIS was used as the cerebral measure of anesthetic drug effect, and the burst suppression ratio was used as the measure of maximal drug effect.[11] BIS has been validated as an accurate technique to measure the drug effect of Propofol$_{D}$.[6] As indicated by the absence of burst suppression, no subjects met the maximal effect criteria when given AQUAVAN® Injection dosages up to 20 mg/kg. Only patients receiving 25 and 30 mg/kg met the burst suppression criteria for maximal drug effect. As seen in table 3, both drugs achieved an equal overall drug effect as measured by the BIS$_{peak}$. A dose-dependent, monotonic decrease in BIS$_{peak}$ was observed in both drugs. Although different methods of administering the drugs were used, time to obtain BIS$_{peak}$ ($T_{BIS,\ peak}$) was still faster for Propofol$_{D}$. LOC$_{verbal}$ was not reached in cohorts 1 and 2. When LOC$_{verbal}$ was reached, equal times until LOC$_{verbal}$ were obtained between the drugs. This unexpected finding might be related to the slower administration of Propofol$_{D}$. However, because BIS at LOC$_{verbal}$ and time until LOC$_{verbal}$ were similar for both

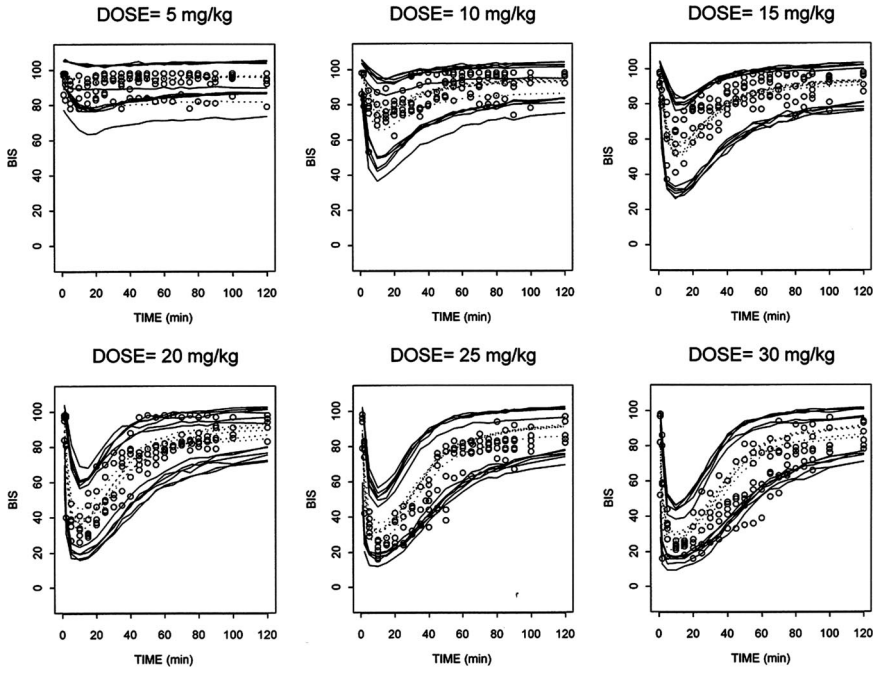

Fig. 7. The posterior predictive check results for Bispectral Index (BIS): comparison of the observed BIS (*points*) with medians (*dashed lines*) and 90% confidence intervals (*solid lines*) of the predicted BIS for each of 36 subjects obtained by simulation of 500 trials with the same design, subjects, and dosing as in the original trial.

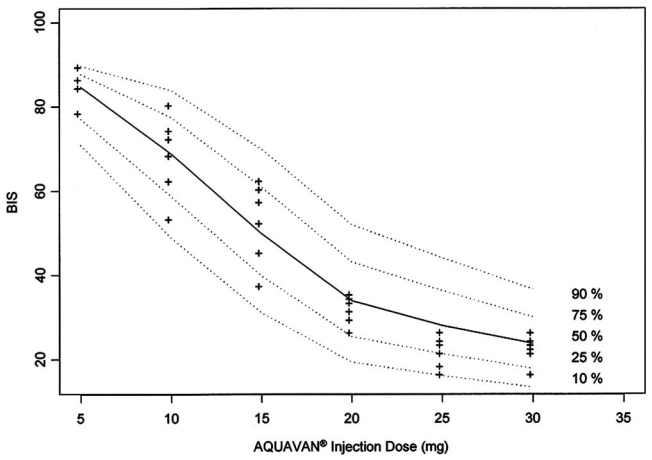

Fig. 8. Minimum Bispectral Index (BIS) values (over time) (BIS_{peak}) *versus* AQUAVAN® Injection dose: Observed individual BIS_{peak} (*crosses*) and model predicted 10th, 25th, 50th, 75th, and 90th percentiles of BIS.

drugs, whereas $T_{BIS,\ peak}$ was different, the time course of drug effect must be different between drugs after LOC_{verbal}. This can be proven by observing the different shapes of the BIS curves in figure 1 (shallow decrease of BIS after LOC_{verbal} for $Propofol_{GPI}$ in contrast to the sharp peak for $Propofol_D$). These finding are in accord with other reports. Banaszczyk *et al.*[12] studied propofol phosphate, a water-soluble propofol prodrug, in various animals and found that the onset of sedation ranged from a minute to several minutes and was much slower than lipid emulsion propofol.

No dose dependency on time until LOC_{verbal} was seen in cohorts 3–6 for either drug. The duration of unconsciousness was significantly longer for AQUAVAN® Injection. The longer duration of unconsciousness may be the consequence of the slower decrease of $Propofol_{GPI}$ concentration after AQUAVAN® Injection as already described in the accompanying article discussing the pharmacokinetics.[2]

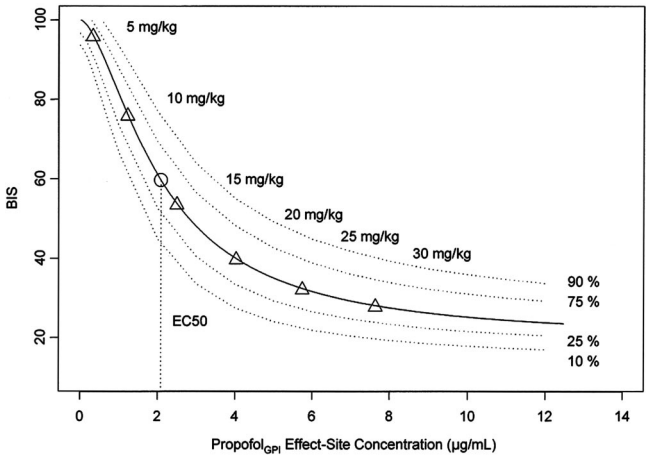

Fig. 9. Bispectral Index (BIS) *versus* $Propofol_{GPI}$ effect site concentration: median (*solid line*) and 10th, 25th, 75th and 90th percentiles (*dashed lines*). *Circle* marks EC_{50} concentration; *triangles* mark minimum BIS levels reached at different AQUAVAN® Injection bolus doses.

Comparison of $Propofol_{GPI}$ versus $Propofol_D$ on Hemodynamics, Respiration, and Safety

Hemodynamics were studied for both drugs. A more pronounced increase in heart rate was found in the AQUAVAN® Injection group compared with $Propofol_D$. In a previous phase I study,[3] a short-lasting tachycardia was also observed in most of the AQUAVAN® Injection subjects. We saw that the tachycardia occurred in the first minute after drug administration. Possible hypotheses for this tachycardia might be (1) a stress response after the transient paresthesias and pruritus experience in a still-awake patient or (2) an underlying physiologic mechanism resulting in heart rate increase. The origin of this tachycardia must be revealed in further studies.

Mean arterial blood pressure showed a biphasic profile for AQUAVAN® Injection in most of the patients. Initially, an overall significant increase (around 10–15 mmHg) was seen in the first 1–2 min, consistent with the increase in heart rate and onset of transient paresthesias and pruritus sensation. Thereafter, a smooth decrease of around 20–25% from baseline was observed. The delay of maximum MAP decrease, which occurred significantly later than the time to maximum hypnotic effect, is in accord with the results of Kazama *et al.*[13] for lipid emulsion propofol. For $Propofol_D$, no significant increase in MAP occurred. A decrease in MAP around 20% was recorded, which is similar to other studies investigating the cardiovascular depression of lipid emulsion propofol.[14,15] Because of the conversion process that leads to less rapid increase of propofol plasma concentrations after bolus administration of AQUAVAN® Injection, one might expect a reduced cardiovascular depression compared with $Propofol_D$.[3] In our study, no difference between the magnitude of cardiovascular depression was revealed, but the time of onset was longer (and smoother) for AQUAVAN® Injection. Of course, a faster administered bolus of $Propofol_D$ might have induced a larger cardiovascular depression. This faster injection rate was not applied in this study because it is recommended to inject $Propofol_D$ slowly.[16] Respiratory depression was seen in both drugs. A dose-dependent increase in both incidence and duration of apnea is revealed in both groups. However, there were no apneas in low AQUAVAN® Injection dosages (< 15 mg/kg), whereas $Propofol_D$ had apnea in the lowest dose. Also, a consistent trend of more apneas with longer duration is observed for $Propofol_D$ compared with AQUAVAN® Injection.

Various laboratory tests and vital signs were measured and compared between groups. All safety measures were within safety limits, making both drugs safe (when administered as in this study). Special attention was paid to ionized calcium, inorganic phosphate, and triglyceride

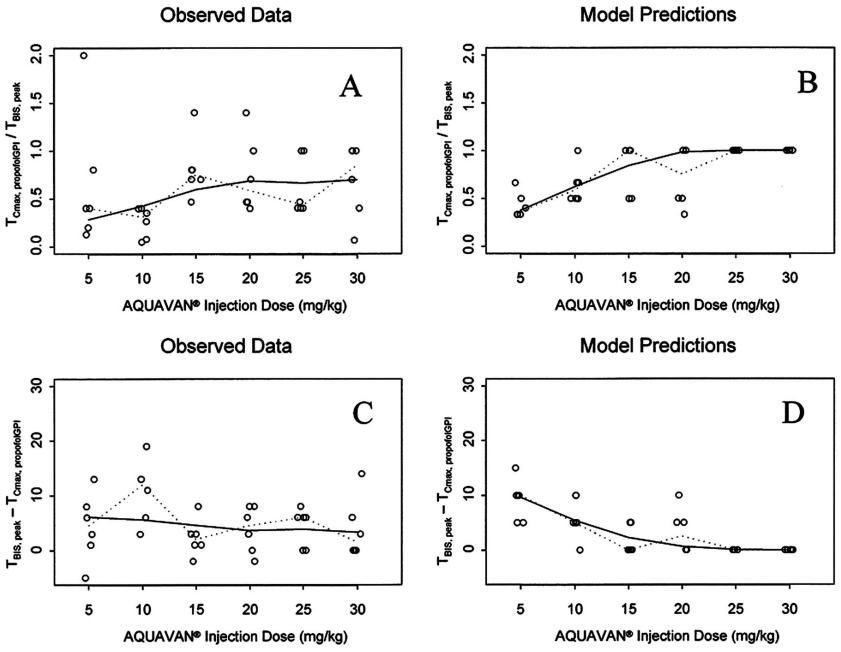

Fig. 10. Dependency of the delay between the time to reach maximum $Propofol_{GPI}$ plasma concentration ($T_{Cmax,\ PropofolGPI}$) and the time to reach maximum Bispectral Index effect ($T_{BIS,\ peak}$) *versus* the dose of AQUAVAN® Injection. *A* and *B* show individual ratios between $T_{Cmax,\ PropofolGPI}$ and $T_{BIS,\ peak}$ for the observed data and for the model predictions, respectively. *C* and *D* show individual differences for $T_{BIS,\ peak} - T_{Cmax,\ PropofolGPI}$ for the observed data and the model prediction, respectively. Each *point* corresponds to the data for one volunteer, the *dotted line* connects medians of the cohorts, and the *solid line* shows the smooth regression (= lowess regression).

concentrations as shown in table 6, because these values are related to the metabolism of AQUAVAN® Injection and lipid load of $Propofol_D$ lipid emulsion. No changes in ionized calcium were seen within and between dosages and drugs. Although increases in inorganic phosphate were seen in the highest AQUAVAN® Injection dosages, these concentrations never reached a toxic concentration as defined in the study protocol. Mean triglyceride values were notably higher 10 min postdose among subjects who received higher doses of $Propofol_D$ (cohorts 3–6). No increase in triglyceride concentrations were noticed after AQUAVAN® Injection administration. The occurrence of hyperlipidemia might be harmful during long-term administration of lipid emulsions of propofol.[17,18]

Across all dose levels of AQUAVAN® Injection, the most frequently reported events were nervous system disorders, which manifested primarily as paresthesia and pruritus. Injection site pain was the most frequently reported event after $Propofol_D$ administration. No pain on injection was reported in the AQUAVAN® Injection group. Most of the side effects were classified as minor and did not compromise the overall stability of the patients.

A Population Pharmacokinetic–Pharmacodynamic Model for Propofol Originated from AQUAVAN® Injection ($Propofol_{GPI}$)

The population pharmacokinetic–pharmacodynamic model of BIS was appropriately described by a Hill E_{max} model based on concentrations in the effect site compartment. Both sequential and simultaneous models described the data accurately based on graphical exploration, leverage and bootstrap analysis, and posterior predictive simulations of 500 trials.

Effect site $Propofol_{GPI}$ concentrations were described by the first-order process, represented by the k_{e0} rate

Table 9. Effect Compartment Rate Constant k_{e0} at Predicted $C_{max,\ PropofolGPI}$

	Cohort 1 (n = 6)	Cohort 2 (n = 6)	Cohort 3 (n = 6)	Cohort 4 (n = 6)	Cohort 5 (n = 6)	Cohort 6 (n = 6)
C_{max}, μg/ml	0.52	1.41	2.63	4.11	5.80	7.67
k_{e0}, min^{-1}	0.08	0.22	0.41	0.64	0.91	1.20

$C_{max,\ PropofolGPI}$ = maximum $propofol_{GPI}$ plasma concentration.

Table 10. BIS at $T_{Cmax,\ PropofolGPI}$ and Minimal BIS as Predicted by the Population Pharmacokinetic–Pharmacodynamic Model

	Cohort 1 (n = 6)	Cohort 2 (n = 6)	Cohort 3 (n = 6)	Cohort 4 (n = 6)	Cohort 5 (n = 6)	Cohort 6 (n = 6)
Predicted BIS at $T_{Cmax,\ PropofolGPI}$	98.6	82.2	56.7	40.6	32.5	28.2
Predicted BIS_{peak}	96.2	76.1	53.8	39.9	32.4	28.1

BIS = Bispectral Index; BIS_{peak} = lowest BIS value; $T_{Cmax,\ PropofolGPI}$ = time to reach maximum $Propofol_{GPI}$ plasma concentration.

constant. The model-predicted relation between the effect site concentration and BIS is shown in figure 9. It can be observed that by giving an AQUAVAN® Injection bolus dose of 15 mg/kg, the EC_{50} of clinical effect is reached, and by giving a bolus dose of 30 mg/kg, the clinical effect comes close to the maximum plateau.

Classically, the equilibration rate constant between the plasma and the effect site, called k_{e0}, is concentration independent and, as such, is presented as a constant value.[19] For $Propofol_D$, Schnider *et al.*[20] reported that age was the only covariate for k_{e0}. In the pharmacokinetic–pharmacodynamic model for $Propofol_{GPI}$, k_{e0} was found to be proportional to plasma $Propofol_{GPI}$ concentration, as shown in table 9. This means that for small $Propofol_{GPI}$ plasma concentrations, the equilibration time between plasma and the effect site is longer than for higher concentrations, as illustrated in figure 10. The underlying mechanism of this concentration-dependent behavior of k_{e0} is unknown. To the best of our knowledge, no literature exists on the concentration dependency of k_{e0} value.

Classically, k_{e0} is seen as an important parameter because it explains the delay between the plasma concentration and the onset of clinical effect. When administering a bolus of AQUAVAN® Injection, the concentration dependency of k_{e0} might be seen as a complicating factor. However, for all doses, a very small difference is observed between predicted BIS values at $T_{Cmax,\ PropofolGPI}$ and BIS_{peak}, as shown in table 10. This indicates that at the moment of maximum plasma $Propofol_{GPI}$ concentration, equilibration between the plasma and the effect site has already been achieved. The mismatch between plasma and effect site concentration is only very temporary in the initial phase after bolus injection. As such, for clinical use of the drug, plasma concentration is a good estimation of the effect site concentration, and k_{e0} might even be seen as a misleading parameter for estimating the time course of the clinical effect.

In conclusion, pharmacodynamics and safety of AQUAVAN® Injection and comparison with the propofol lipid emulsion showed that the bolus administration of AQUAVAN® Injection resulted in a dose-dependent hypnotic effect as measured by BIS. After bolus injection of AQUAVAN, LOC_{verbal} was achieved at a similar time as after an equipotent dose of $Propofol_D$ administered at 50 mg/min, but AQUAVAN® Injection revealed a longer time to peak BIS and a prolonged pharmacodynamic effect compared with $Propofol_D$. Hemodynamic stability was similar for both drugs, except for an initial tachycardia in the $Propofol_{GPI}$ group. $Propofol_D$ showed more pain on injection and apnea than AQUAVAN® Injection. In contrast, AQUAVAN® Injection revealed short-lasting transient paresthesias and pruritus. The predictive population pharmacokinetic–pharmacodynamic model was developed for AQUAVAN® Injection and its liberated $Propofol_{GPI}$. This model was best described by a nonlinear, six-compartment pharmacokinetic model with an effect site compartment. We found that $Propofol_{GPI}$ plasma concentration is a good predictor of the effect site concentration and the effect. The effect site concentration follows plasma concentration with the delay that is smaller for the higher doses and larger for the smaller doses. This is reflected in the unusual dependency of the k_{e0} value on the $Propofol_{GPI}$ plasma concentration.

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