

Pharmacokinetics and Clinical Pharmacodynamics of the New Propofol Prodrug GPI 15715 in Volunteers

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Background: GPI 15715 (AQUAVAN injection) is a new water-soluble prodrug which is hydrolyzed to release propofol. The objectives of this first study in humans were to investigate the safety, tolerability, pharmacokinetics, and clinical pharmacodynamics of GPI 15715.

Methods: Three groups of three healthy male volunteers (aged 19–35 y, 67–102 kg) received 290, 580, and 1,160 mg GPI 15715 as a constant rate infusion over 10 min. The plasma concentrations of GPI 15715 and propofol were measured from arterial and venous blood samples up to 24 h. Pharmacokinetics were analyzed with compartment models. Pharmacodynamics were assessed by clinical signs.

Results: GPI 15715 was well tolerated without pain on injection. Two subjects reported a transient unpleasant sensation of burning or tingling at start of infusion. Loss of consciousness was achieved in none with 290 mg and in one subject with 580 mg. After 1,160 mg, all subjects experienced loss of consciousness at propofol concentrations of $2.1 \pm 0.6 \mu\text{g/ml}$. A two-compartment model for GPI 15715 (central volume of distribution, 0.07 l/kg; clearance, $7 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$; terminal half-life, 46 min) and a three-compartment model for propofol (half-lives: 2.2, 20, 477 min) best described the data. The maximum decrease of blood pressure was 25%; the heart rate increased by approximately 35%. There were no significant laboratory abnormalities.

Conclusions: Compared with propofol lipid emulsion, the potency seemed to be higher with respect to plasma concentration but was apparently less with respect to dose. Pharmacokinetic simulations showed a longer time to peak propofol concentration after a bolus dose and a longer context-sensitive half-time.

PROPOFOL (Diprivan® Injectable Emulsion, AstraZeneca, London, UK), a potent intravenous sedative-hypnotic agent that is widely used for general anesthesia and sedation,¹ is a substance with very slight solubility in water and, thus, is formulated as an oil-in-water emulsion. Possible disadvantages associated with the lipid emulsion formulation of propofol are the lipid intake, particularly in patients receiving long-term intensive care unit sedation,^{2,3} risk of infection due to reduced bacterial clearance,⁴ and aggravated pain on injection.⁵ In

addition, the direct cardiovascular effects of propofol may be influenced by the lipid solvent.^{6,7} GPI 15715 (AQUAVAN injection, 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. GPI 15715 is chemically described as phosphono-O-methyl-2,6-diisopropylphenol, disodium salt ($\text{C}_{13}\text{H}_{19}\text{O}_5\text{PNa}_2$). Phosphono-O-methyl prodrugs undergo hydrolysis most notably by endothelial cell surface alkaline phosphatases liberating propofol, the active metabolite; phosphate; and formaldehyde (fig. 1). This approach theoretically should lead to rapid intravascular liberation of the active drug and has been applied to the marketed product fosphenytoin. The prodrug is expected to produce an exposure to propofol equivalent to an equimolar dose of propofol emulsions with altered distribution kinetics due to hydrolysis of the prodrug, but with similar disposition of the liberated propofol. From the molecular weights of 332.24 for the GPI 15715 disodium salt and 178.27 for propofol, one would expect that 1 mg of GPI 15715 would liberate 0.54 mg of propofol. The aim of this first study in humans was to investigate the safety, tolerability, pharmacokinetics, and clinical pharmacodynamics of GPI 15715 in volunteers.

Materials and Methods

The study protocol was approved by the local Medical Ethics Review Committee, and the study was conducted in accordance with the Declaration of Helsinki and its amendments.

Subjects

After written informed consent, nine healthy male volunteers (aged 19–35 yr; body weight, 67–102 kg, 77 ± 10 kg, mean \pm SD) were enrolled in the study. Subjects had to be aged at least 18 yr and not more than 45 yr and they had to be nonsmokers for at least 6 months before the start of the study. The volunteers had to be healthy as assessed by medical history and physical examination. Exclusion criteria were a body weight of more than 20% outside the normal range (according to the Metropolitan Life Insurance Company table); documented drug allergies; alcohol, drug, or medication abuse; medication with a pronounced effect on the central nervous system; medication altering the pharmacokinetics of the investigated drugs (e.g., enzyme-inducing or enzyme-inhibiting compounds); and participation in investigational drug

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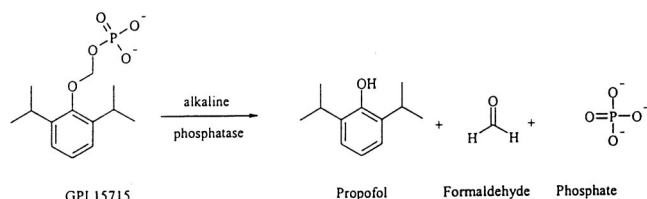


Fig. 1. Chemical structure of GPI 15715 and the scheme of its hydrolysis to propofol.

studies within 1 month before the start of this study. Subjects were required to fast for at least 8 h before drug administration.

Study Procedure

Subjects underwent a physical/neurologic examination 2 h before administration of the study drug. A venous catheter was inserted in the dominant arm for drug administration and an arterial catheter was inserted into the radial artery of the contralateral arm for collection of blood samples.

GPI 15715 (20 mg/ml) was administered as a constant rate infusion over 10 min using a syringe pump (Braun perfusor fm; Braun, Melsungen, Germany). The investigation was conducted as dose escalation study with loss of consciousness (LOC), defined as loss of response to a loud verbal command, as endpoint. LOC was assessed every 90 s until the subject lost consciousness or until 20 min had elapsed. The nine volunteers were studied in three dose groups of three subjects each. The initial dose for the first three volunteers was 290 mg. If no more than one subject attained the defined endpoint (LOC), the dose for the next three volunteers was increased by 100%. If two subjects attained the defined endpoint, the dose was increased by 50%. If all three subjects lost consciousness, the dose for the subsequent group was decreased by 25%. Three dose groups were to be assessed in this study.

Blood Sampling and Drug Analysis

Blood samples of 3 ml each to determine the concentrations of GPI 15715 and propofol were collected from the indwelling arterial and venous catheters. A control sample was drawn before the start of drug administration. After the start of infusion, arterial samples were taken every 2 min for 30 min and at 60, 120, and 240 min. The arterial line was then removed, and venous samples were taken at 240, 360, and 1,440 min after start of infusion. The blood samples were collected in sodium heparin glass vials that were prefilled with 30 mg sodium ortho-vanadate to inhibit alkaline phosphatase and stored on ice for up to 1 h. After centrifugation at 1,200 revolutions per minute for 15 min, the plasma was transferred into transport vials and stored at -70°C .

GPI 15715 plasma analysis was performed using a validated high-performance liquid chromatography with

mass spectrometric detection (LC/MS/MS) assay. Human plasma (50 μl) to which ^{13}C -GPI 15715 (internal standard prepared in 1.0 M ammonium acetate buffer) was added was subsequently extracted using a solid phase extraction. Cartridges were conditioned by gravity with methanol and 1.0 M ammonium acetate buffer. The samples were loaded on the cartridges, washed with water and 10% methanol/water, and eluted with methanol. The tubes were then evaporated under nitrogen and the sample was resolubilized with 50/50 methanol/25 mM ammonium acetate. The sample was injected onto a reversed phase high performance liquid chromatographic column and detected using MS/MS detection. The analytical range of this method was 5–1,000 ng/ml with a coefficient of variation of 10.5, 3.2, and 2.9% in the low, medium, and high part of the concentration range, respectively. Propofol analysis was performed using a reversed phase high-performance liquid chromatography with fluorescence detection, modified from the method of Plummer.⁸ The analytical range of this method was 5–2,000 ng/ml with a coefficient of variation of 3.9%.

Pharmacokinetic Modeling

The concentrations of propofol and GPI 15715 were analyzed using linear models with two or three compartments each, whereby the elimination from the central compartment of GPI 15715 was used as input for the central compartment of propofol (fig. 2). The propofol drug input into the central compartment of propofol was calculated as $F \cdot k_{10}^G \cdot m_1^G$, where m_1^G is the amount of GPI 15715 in its central compartment, k_{10}^G is the elimination rate constant of GPI 15715, and F is the fraction of the dose of GPI 15715 metabolized to propofol, including molar conversion factors. From the molecular weights of 332.24 for the GPI 15715 disodium salt and 178.27 for propofol and assuming a complete conver-

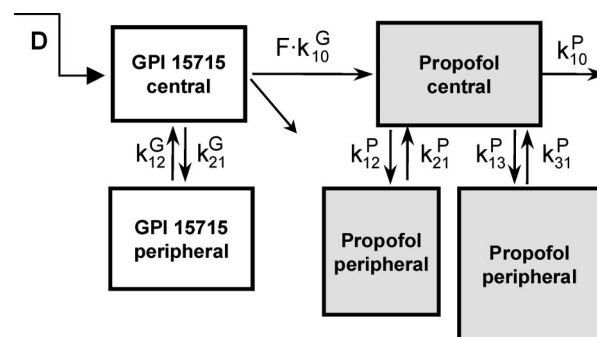


Fig. 2. Pharmacokinetic/dynamic model for GPI 15715 and propofol. k_{12} , k_{21} , k_{13} , k_{31} = transfer rate constants between the central and the peripheral compartments; k_{10} = elimination rate constant. The superscripts G and P denote whether the parameters are with respect to GPI 15715 or propofol. The conversion factor F is the fraction of GPI 15715, which is metabolized to propofol. A lag time between the central compartments of GPI 15715 and propofol was assumed for the process of hydrolysis.

sion, one would expect a value of $F = 0.54$, and this value was used for the pharmacokinetic analysis. The differential equations and their analytical solutions are given in the Appendix, as well as a method to derive the infusion rate of GPI 15715 necessary to achieve a constant propofol concentration. The following parameters were estimated for both submodels: the central volume of distribution (V_c), the elimination clearance (CL), and the transfer rate constants k_{ij} . To account for a possible delay of hydrolysis, a lag time between the two submodels was included in the model. In the first step, the plasma concentrations of GPI 15715 were analyzed for each subject. The estimated individual pharmacokinetic parameters of GPI 15715 were then used for the individual and population pharmacokinetic analyses of propofol. Model estimation was performed by nonlinear regression using NONMEM® (GloboMax LLC, Hanover, MD) assuming log-normally distributed inter- and intra-individual errors. To estimate the accuracy of the model, we calculated the weighted residual $WR_{ij} = (c_{ij} - cp_{ij}) / cp_{ij}$ and the absolute weighted residual $AWR_{ij} = \text{Abs}(c_{ij} - cp_{ij}) / cp_{ij}$ for each sample, where c_{ij} is the j^{th} measured concentration of the i^{th} individual and cp_{ij} is the corresponding prediction. The predictions were calculated with the individual pharmacokinetic parameters and, in addition, with the mean pharmacokinetic parameters to assess also the accuracy of the "mean model." The median values of WR (median weighted residual, MWR) and AWR (median absolute weighted residual, MAWR) were used as overall measure for goodness of fit. Different models were tested for statistical significance using $-2 \log$ likelihood ($-2LL$), which is supplied by the value of the NONMEM® objective function.

Graphical Representations

To visualize the results of the pharmacokinetic analysis, we used graphical representations. The accuracy of the "mean models," *i.e.*, the models with the mean pharmacokinetic parameters of GPI 15715 and propofol, was represented by plotting the ratio measured/predicted concentration *versus* time. As the intraindividual error was assumed to be log-normally distributed, the ratio was plotted on a logarithmic scale. Using the estimated mean pharmacokinetic parameters, we simulated the time course of the propofol concentration after a bolus dose of GPI 15715 and the time required for a 50% decrease of propofol concentration as a function of infusion duration ("context-sensitive half-time").⁹ We also plotted the unit disposition function of the propofol submodel to assess whether the pharmacokinetics of the liberated propofol are similar to those of the known propofol emulsion. For the propofol emulsion, we used the pharmacokinetic data published by Gepts *et al.*¹⁰

Pharmacodynamics

The volunteer's response to a loud verbal command was tested every 90 s and was continued until the subject had lost the ability to respond (*i.e.*, LOC) or until 20 min had elapsed. Once LOC had occurred, the corneal reflex (eyelid closure reflex) was tested by rubbing a wisp of cotton across the cornea. The volunteer's ability to respond was further tested every 90 s until the ability was regained. Once the ability was regained, sedation was further assessed using the Observer's Assessment of Alertness/Sedation Scale. If the subject had continued to respond for 20 min, the Observer's Assessment of Alertness/Sedation Scale rating started 20 min after start of infusion. The scale rating was applied at 2, 5, 10, 20, 60, 120, and 240 min after having regained the ability to respond, or after end of the 20-min period, respectively. The scale evaluates responsiveness, quality of speech, facial expression, and expression of eyes with a composite score level ranging from 1 (deep sleep) to 5 (alert).¹¹ This assessment was discontinued after two consecutive ratings were assessed as alert.

In each volunteer, we determined the maximum propofol concentration with LOC = 0 (response to verbal command) and the minimum propofol concentration with LOC = 1 (no response to verbal command). From these data, the probability of LOC as a function of propofol plasma concentration was assessed by probit analysis (STATISTICA 6.0, StatSoft, Inc., Tulsa, OK).

Blood pressure, heart rate, pulse oximetry, and electrocardiogram were monitored continuously during and after drug administration (SC9000, Siemens, Munich, Germany), and were recorded every 2 min for 30 min, and at 60, 120, 240, and 360 min after start of infusion. When the oxygen saturation (SpO_2) dropped below 93%, the volunteer received 3 l/min oxygen through a nasal cannula. Body temperature was recorded at 10, 30, 60, and 360 min after start of administration. An arterial blood sample of 10 ml was taken 10 min after start of infusion to be analyzed for blood gases, ionized calcium, and electrolytes. At 360 min, a venous sample for clinical laboratory evaluation was drawn. On the morning following the study drug infusion and on the fourth day, subjects underwent a full clinical assessment. Any adverse events were documented and volunteers were asked about unpleasant sensations during or after drug administration.

Results

All subjects enrolled in the trial completed all prescribed assessments. None of the first three volunteers who received 290 mg GPI 15715 reached loss of response to verbal command (*i.e.*, LOC). Thus, the dose for the following three subjects was increased to 580 mg. In this second group, only one volunteer experienced LOC.

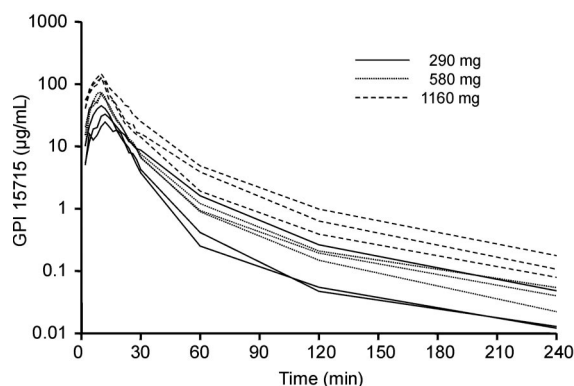


Fig. 3. Plot of the measured GPI 15715 concentrations after administration of 290, 580, and 1,160 mg GPI 15715. Each line shows the values of one individual volunteer.

Therefore, the dose was further increased to 1,160 mg for the last three volunteers. All three subjects in this group lost response to verbal command. GPI 15715 was well tolerated with no pain on injection. One subject receiving 290 mg and another subject receiving 1,160 mg reported a transient unpleasant sensation of burning or tingling of moderate severity in the anal and genital region, which lasted 5 min at the low and 2 min at the high dose. This sensation was accompanied by a transient increase of heart rate to values of about 100 beats per minute. In both cases, these sensations completely resolved without therapy. There were no significant laboratory abnormalities. Both calcium and inorganic phosphate were normal (range, 2.0–2.4 mm and 2.6–4.0 mg/dl, respectively). There was no indication of increased formate (range, <15–49 µg/ml), which is rapidly formed from the formaldehyde liberated by prodrug hydrolysis.

Pharmacokinetics

The time courses of the mean plasma concentrations of GPI 15715 and propofol for the three dosing groups are shown in figures 3 and 4. The maximum concentrations and the areas under the curves increased approximately proportional to the applied dose (table 1). GPI 15715 reached its maximum concentration at the end of the infusion, whereas propofol further increased until the twelfth to twentieth minute (table 1). After cessation of the infusion, GPI 15715 decreased rapidly. At 240 min, the plasma concentration of GPI 15715 was approximately 1,000 times less than the maximum concentration, and at 24 h the concentration was below the detection limit. Propofol decreased more slowly than GPI 15715; in two volunteers who had received 580 mg and in all volunteers who had received 1,160 mg GPI 15715, propofol could be determined 24 h after start of infusion. As the plasma concentrations at 360 and 1,440 min were measured from venous samples and the venous concentrations of GPI 15715 at 240 min were much higher than the arterial (median relative differ-

ence, 88%), we used only the arterial plasma concentrations of GPI 15715 for the determination of pharmacokinetics. For propofol, the arteriovenous difference at 240 min was much smaller (median relative difference, 15%), and therefore we included the venous concentrations at 360 and 1,440 min into the pharmacokinetic analysis.

The arterial plasma concentrations of GPI 15715 were best described with a two-compartment model. The hydrolysis half-life was 7.2 ± 1.1 min. The median residuals of the individual fits were MWR = 0.08% and MAWR = 7.7%; for the mean pharmacokinetic parameters the residuals were -1.9 and 18.3%. Table 2 summarizes the results of the individual fits and figure 5 shows the ratio measured/predicted concentration for the mean pharmacokinetic parameters.

For the liberated propofol, we performed two analyses: one included only the arterial concentrations until 240 min, and the other was performed with all data, including the venous concentrations at 360 and 1,440 min. The arterial propofol concentrations were best described with a two-compartment model. A lag time for the transfer between the central compartments of GPI 15715 and propofol was necessary to appropriately describe the propofol concentrations at the beginning of the infusion. Table 3 shows the results of the individual analyses of the arterial concentrations. The residuals of these individual propofol fits were MWR = 0.2 and

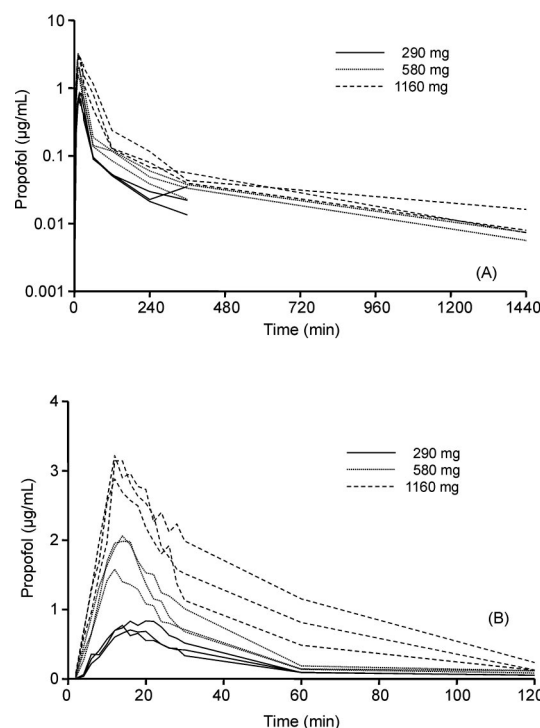


Fig. 4. Plot of the measured propofol concentrations after administration of 290, 580 and 1,160 mg GPI 15715. Each line shows the values of one individual volunteer. The top panel shows the complete time courses; the bottom panel shows plotting of the first 2 h.

Table 1. Time until Maximum Concentration was Reached, Measured Maximum Concentrations, and AUC

Dose (mg)	GPI 15715			Propofol		
	T _{max} (min)	C _{max} (μg/ml)	AUC _∞ (μg · ml ⁻¹ · min)	T _{max} (min)	C _{max} (μg/ml)	AUC _∞ (μg · ml ⁻¹ · min)
290	11.3 ± 1.2	34.3 ± 10.2	651 ± 222	16.7 ± 3.1	0.77 ± 0.07	38 ± 5
580	10.0 ± 0.0	71.6 ± 3.0	1,113 ± 33	13.3 ± 1.2	1.87 ± 0.26	89 ± 21
1160	10.0 ± 0.0	133 ± 12	2,334 ± 480	12.0 ± 0.0	3.08 ± 0.18	182 ± 37

Values are expressed as mean ± SD.

AUC = areas under the curve.

MAWR = 7.1%. Figure 6 (*top*) shows the ratio measured/predicted propofol concentration for the mean pharmacokinetic parameters of the two-compartment models for propofol and GPI 15715. As the propofol concentrations at 360 and 1,440 min were not included into the analysis, these concentrations were significantly underpredicted by this model, whereas for the arterial concentrations until 240 min the accuracy of the mean model was MWR = 0.7 and MAWR = 16.2%. For the complete propofol data, including the venous concentrations at 360 and 1,440 min, we performed a population analysis with all volunteers because propofol concentrations at 1,440 min were obtained in only five of nine volunteers. A three-compartment model was significantly better than the two-compartment model (difference in the objective function = 159, $P < 0.0001$). The results of the population analysis are given in table 4, and figure 6 (*bottom*) shows the ratio measured/predicted concentration for the population pharmacokinetic parameters of propofol and the mean pharmacokinetic parameters of GPI 15715. The accuracy of the three-compartment model was MWR = -2.6 and MAWR = 15.7%.

Using the results of the pharmacokinetic analyses of GPI 15715 and propofol, we simulated the expected propofol concentration course after a bolus dose of 1,000 mg GPI 15715 (fig. 7). From these data one would expect a maximum propofol concentration of 3.3 ± 0.6 μg/ml at 7.4 ± 1.2 min after bolus administration.

The decrease of propofol concentration after continuous infusion of GPI 15715 is shown in figure 8. The time for a 50% decrease of propofol concentration (context-sensitive half-time) is approximately 10–20 min longer than for propofol formulated as lipid emulsion. The unit disposition function of the propofol liberated from GPI 15715 is plotted in figure 9, together with the disposition function of propofol as lipid emulsion.

Pharmacodynamics

LOC and recovery of response to a loud verbal command (ROC) were the main pharmacodynamic endpoints. LOC was achieved in one volunteer after 580 mg GPI 15715 and in all three volunteers who received 1,160 mg GPI 15715. The corneal reflex was lost in only one volunteer who had received 1,160 mg. Table 5 shows the times and the corresponding propofol concentrations (as predicted by the individual pharmacokinetic models) for the different clinical endpoints. Because of the different doses, the clinical endpoints were observed at different times but at similar propofol plasma concentrations. The administered dose of GPI 15715 at LOC was 870 ± 237 mg (mean ± SD). Figure 10 shows the individual responses to verbal command and the corresponding propofol plasma concentrations. Probit analysis revealed an EC₅₀ of 2.2 ± 0.4 μg/ml (estimate ± standard error).

Table 2. Pharmacokinetic Parameters of GPI 15715

No.	Dose (mg)	K ₁₂ (min ⁻¹)	K ₂₁ (min ⁻¹)	K ₁₀ (min ⁻¹)	CL (ml · kg ⁻¹ · min ⁻¹)	V _c (ml/kg)	V _{ss} (ml/kg)	T _{1/2α} (min)	T _{1/2β} (min)
1	290	0.0018	0.011	0.088	6.78	77	91	7.7	67
2	290	0.0086	0.019	0.076	5.07	67	97	8.0	43
3	290	0.0023	0.012	0.089	8.09	91	109	7.6	61
4	580	0.0079	0.021	0.115	6.68	58	80	5.6	36
5	580	0.0094	0.017	0.101	7.41	73	114	6.2	46
6	580	0.0074	0.017	0.104	8.71	84	121	6.2	45
7	1,160	0.0118	0.019	0.083	6.16	74	120	7.1	42
8	1,160	0.0239	0.025	0.112	7.56	68	132	4.9	35
9	1,160	0.0115	0.019	0.111	6.46	58	94	5.6	42
Mean		0.0094	0.018	0.098	6.99	72	107	6.5	46
SD		0.0065	0.004	0.014	1.09	11	17	1.1	11

Estimations from the arterial concentrations (2–240 min after start of infusion) of GPI 15715.

CL = elimination clearance; K₁₂, k₂₁ = transfer rate constants between central and peripheral compartments; k₁₀ = elimination rate constant; T_{1/2α} fast half-life; T_{1/2β} = terminal half-life; V_c = central volume of distribution; V_{ss} = volume of distribution at steady state.

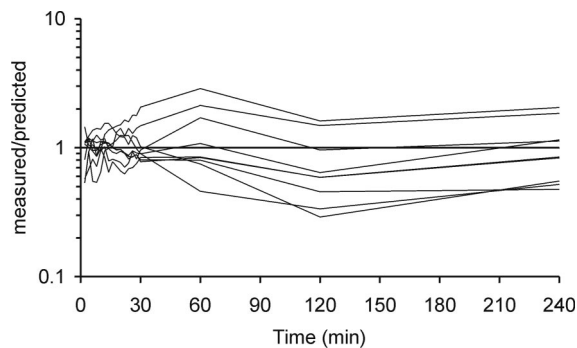


Fig. 5. Residual errors for GPI 15715, expressed as measured/predicted concentration. The predictions were calculated using the mean pharmacokinetic parameters for a two-compartment model of GPI 15715. Each line shows the values of one individual volunteer.

Hemodynamics and Respiration

In one volunteer who received 580 mg GPI 15715, the systolic blood pressure was increased during the complete study period. In all other volunteers, a decrease of the systolic and the diastolic blood pressure was observed with the minimum values at 20 ± 8 min after start of infusion. Blood pressure reached the baseline approximately 60 min after start of infusion. Heart rate increased to maximum values at 12 ± 8 min after start of GPI 15715 infusion and returned to the baseline level approximately 30 min after start of infusion. Table 6 summarizes the effects on hemodynamics with respect to dose. The three volunteers who received 1,160 mg GPI 15715 required a temporary insufflation (14 ± 7 min, beginning at stop of the infusion) of oxygen through a nasal cannula. In all volunteers, the oxygen saturation decreased slightly to a minimum of $94.6 \pm 1.6\%$ that was reached 15 ± 3 min after start of administration. Apnea was not observed. At the end of the infusion period, the P_{aCO_2} showed a dose-dependent rise to 38.2 ± 2.7 , 42.9 ± 0.9 , and 47.1 ± 4.8 mmHg after administration of 290, 580, and 1,160

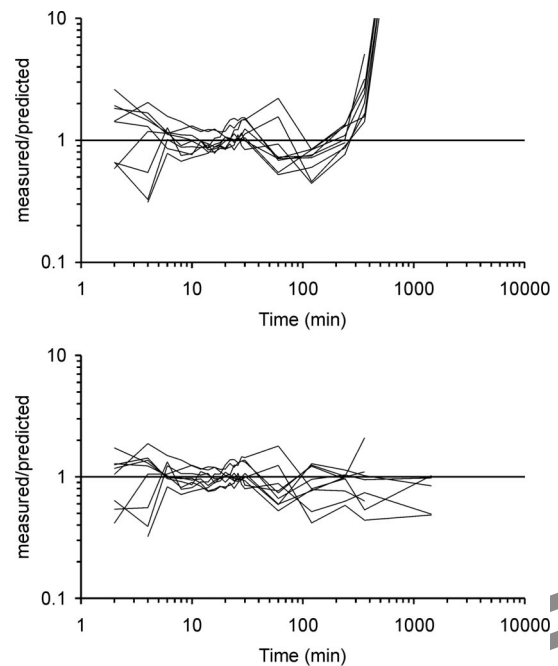


Fig. 6. Residual errors for propofol, expressed as measured/predicted concentration. The predictions were calculated using the mean pharmacokinetic parameters for a two-compartment model (top) estimated from the arterial concentrations until 240 min, and a three-compartment model (bottom) estimated from the arterial and venous concentrations until 1,440 min. Each line shows the values of one individual volunteer.

mg GPI 15715, respectively. Body temperature remained stable at $36.2 \pm 0.4^\circ\text{C}$.

Discussion

Pharmacokinetics

The parent drug GPI 15715 showed a relatively fast distribution and elimination and small volumes of distribution, whereas the liberated propofol exhibited the well-known lipophilic pharmacokinetics with large pe-

Table 3. Pharmacokinetic Parameters for a Two-compartment Model of Propofol

No.	Dose (mg)	K_{12} (min^{-1})	K_{21} (min^{-1})	K_{10} (min^{-1})	CL ($\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	V_c (L/kg)	V_{ss} (L/kg)	$T_{1/2\alpha}$ (min)	$T_{1/2\beta}$ (min)	T_{lag} (min)
1	290	0.14	0.014	0.16	67	0.41	4.5	2.3	94	2.5
2	290	0.11	0.008	0.13	66	0.50	7.4	2.8	160	1.5
3	290	0.06	0.010	0.10	59	0.57	4.0	4.1	111	1.4
4	580	0.12	0.013	0.14	62	0.45	4.7	2.6	103	1.2
5	580	0.11	0.009	0.16	52	0.32	3.9	2.6	124	1.4
6	580	0.10	0.009	0.19	75	0.40	4.9	2.4	118	1.6
7	1,160	0.20	0.032	0.16	63	0.39	2.8	1.8	51	1.3
8	1,160	0.31	0.066	0.11	44	0.40	2.3	1.5	45	1.1
9	1,160	0.12	0.021	0.14	54	0.39	2.6	2.6	63	1.1
Mean		0.14	0.020	0.14	60	0.43	4.1	2.5	97	1.4
SD		0.07	0.019	0.03	9	0.07	1.5	0.7	38	0.4

Estimations from the arterial concentrations (2–240 min after start of infusion) of propofol. V_c , V_{ss} , and CL are given assuming a metabolism factor of 0.54 for the fraction of the dose of GPI 15715 metabolized to propofol.

CL = elimination clearance; K_{12} , K_{21} = transfer rate constants between the central and the peripheral compartment; K_{10} = elimination rate constant; $T_{1/2\alpha}$ = fast half-life; $T_{1/2\beta}$ = terminal half-life; T_{lag} = lagtime for the transfer between the central compartments of GPI 15715 and propofol; V_c = central volume of distribution; V_{ss} = volume of distribution at steady state.

Table 4. Pharmacokinetic Parameters for a Three-compartment Model of Propofol

Parameter	Estimate	SE	% iiv	Propofol Emulsion
K_{12} (min^{-1})	0.087	0.031	—	0.11 ± 0.10
K_{21} (min^{-1})	0.051	0.0053	—	0.055 ± 0.06
K_{13} (min^{-1})	0.079	0.011	—	0.042 ± 0.016
K_{31} (min^{-1})	0.0026	0.00033	—	0.0033 ± 0.0013
K_{10} (min^{-1})	0.12	0.02	—	0.12 ± 0.04
CL (l/min)	4.14	0.25	16.6	1.77 ± 0.32
V_c (l)	33.1	3.9	18.9	16.9 ± 7.0
V_{ss} (l)	1,183	90	—	287 ± 213
$T_{1/2\alpha}$ (min)	2.2	0.2	—	2.8 ± 1.2
$T_{1/2\beta}$ (min)	20.4	2.8	—	31.4 ± 14.7
$T_{1/2\gamma}$ (min)	477	31	—	355 ± 227
T_{lag} (min)	1.30	0.06	12.0	—

Estimations from population analysis of the arterial concentrations (2–240 min after start of infusion) and the venous concentrations at 360 and 1,440 min. V_c , V_{ss} , and CL are given assuming a metabolism factor of 0.54 for the fraction of the dose of GPI 15715 metabolized to propofol. The percent interindividual variability (% iiv) is the square root of the variance of η . The values for propofol emulsion were published by Gepts *et al.*¹⁰

CL = elimination clearance; K_{12} , K_{21} , K_{13} , K_{31} = transfer rate constants between the central and the peripherals compartments; K_{10} = elimination rate constant; $T_{1/2\alpha}$ = fast half-life; $T_{1/2\beta}$ = intermediate half-life; $T_{1/2\gamma}$ = terminal half-life; T_{lag} = lagtime for the transfer between the central compartments of GPI 15715 and propofol; V_c = central volume of distribution; V_{ss} = volume of distribution at steady state.

ripheral compartments. As the concentrations were approximately proportional to the applied doses the pharmacokinetics of both propofol and GPI 15715 seemed to be linear over the dose range studied. The pharmacokinetics of the prodrug GPI 15715 and its main active metabolite propofol could be well described with two linked linear models. However, the maximum propofol concentration was reached earlier at higher doses (table 1), and there was an increase of k_{12} of GPI 15715 for higher doses of GPI 15715 (table 2). The mean values of this parameter for the three dosing groups were 0.0042, 0.0082, and 0.016 min^{-1} . This could be an indicator for a nonlinear distribution but it could also indicate that the applied model was too simplistic. As GPI 15715 is metabolized to propofol not only in the liver (like most intravenous drugs and propofol as well) but also by endothelial cell surface phosphatases anywhere in the body, it might be appropriate to assume an additional

elimination rate constant k_{20} rather than only one elimination pathway as described by k_{10} (fig. 1). Unfortunately, it is not possible to obtain independent, uncorrelated estimates of k_{10} and k_{20} from measured plasma concentrations of GPI 15715 and propofol, and therefore it is impossible to determine such a model from the given data. However, even the simple model with the averaged parameters was quite able to sufficiently describe the plasma concentrations of both the parent drug and propofol.

It was expected that the disposition of the liberated propofol should be similar to the disposition of the known propofol lipid emulsion. When comparing the results of the pharmacokinetic analysis with the pharmacokinetics of a known propofol lipid emulsion as published in previous studies,^{12–15,10} there are some differences (table 4). For propofol lipid emulsion, the central volume of distribution (V_c) for an adult was estimated at

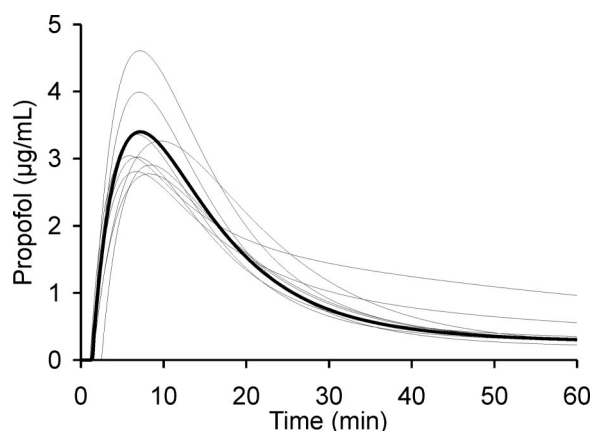


Fig. 7. Simulated propofol concentration course after a bolus dose of 1,000 mg GPI 15715. Each *thin line* shows the propofol concentration predicted by the individual pharmacokinetic parameters for two-compartment models of GPI 15715 and propofol. The *bold line* shows the predicted propofol concentration using the mean pharmacokinetic parameters.

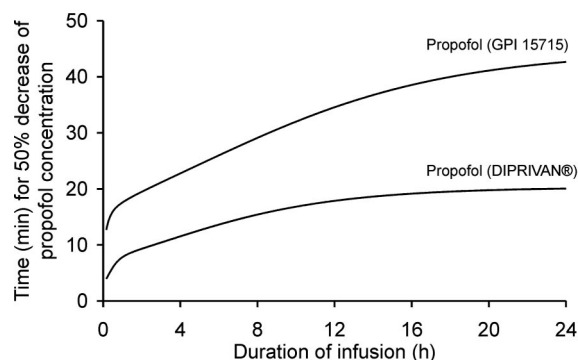


Fig. 8. Time for a 50% decrease of propofol plasma concentration after continuous infusion (context-sensitive half-time) of GPI 15715 and propofol emulsion (Diprivan®). Calculations for GPI 15715 were made with the mean pharmacokinetic parameters (two-compartment model for GPI 15715, three-compartment model for propofol), as estimated in this study. The context-sensitive half-time for the propofol emulsion was obtained using the results for a three-compartment model, as published by Gepts *et al.*¹⁰

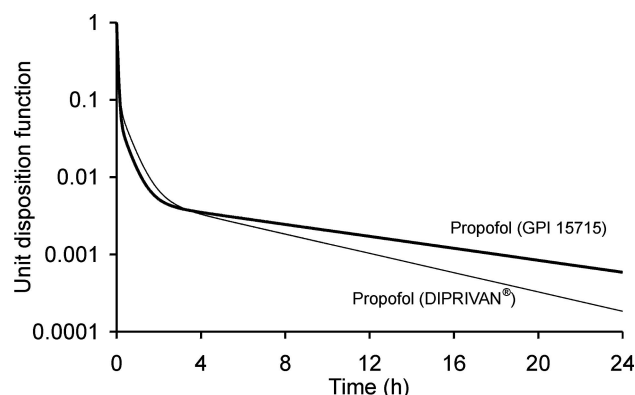


Fig. 9. Unit disposition functions of propofol from GPI 15715 calculated with the population pharmacokinetic parameters for a three-compartment model parameters (**bold line**) and with the data for propofol emulsion (Diprivan®) as reported by Gepts *et al.* (**thin line**).¹⁰

values of 4.3,¹³ 9.3,¹⁴ 16.9,¹⁰ and 26.3 l.¹² For the volume at steady state, previous studies found values of 280,¹³ 430,¹⁴ 287¹⁰ and 771 l.¹² Compared with these results, propofol from GPI 15715 showed higher values (33 and 1183 l, respectively). However, the results for V_c , V_{ss} , and clearance depend on the assumed value for the metabolism factor F ; in other words, we cannot determine V_c , V_{ss} , CL , and F but only V_c/F , V_{ss}/F , and CL/F . Using a value of $F = 0.54$, the resulting clearance of propofol from GPI 15715 ($52 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) is much higher than the clearance of propofol lipid emulsion ($28 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). If one claimed that the clearances of propofol should be identical, one would have to assume $F = 0.30$ or an apparent “bioavailability” for propofol from GPI 15715 of 54%. The corresponding values for the volumes of distribution would then be $V_c = 17.8$ and $V_{ss} = 639 \text{ l}$, which would be similar to the values for propofol lipid emulsion. Conversely, Dutta and Ebling demonstrated that the volumes of distribution in rats were much higher for a lipid-free propofol than for propofol lipid emulsion and that this was caused by a higher uptake of propofol lipid emulsion in the lungs.^{16,17} Such formulation-dependent pharmacokinetics could also be the reason for the higher volumes of distribution of propofol from GPI 15715. The elimination rate constant k_{10} , the transfer rates constants and

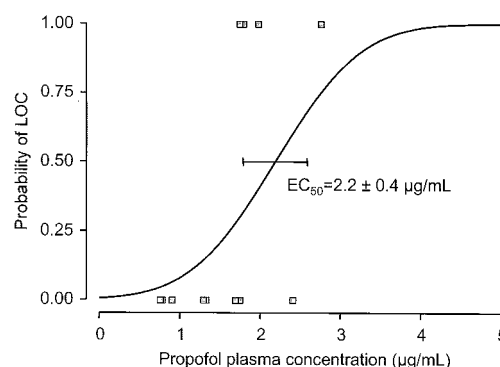


Fig. 10. Probability of loss of consciousness (LOC) as a function of the propofol plasma concentration. The **filled squares** denote the propofol plasma concentrations (estimated from the individual pharmacokinetic analyses) and the corresponding responses. In each volunteer, we determined the maximum propofol concentration with LOC = 0 (response to verbal command) and the minimum propofol concentration with LOC = 1 (no response to verbal command). The **line** shows the result of probit analysis.

the half-times of propofol were similar when compared with estimates for propofol lipid emulsion. This is also evident from the unit disposition functions for the propofol from GPI 15715 and for Diprivan® (fig. 9), which are quite similar with exception of the late phase ($> 10 \text{ h}$), when the propofol from GPI 15715 shows a slower decrease. However, one has to consider that in the study of Gepts *et al.*¹⁰ propofol was measured only until 480 min after the end of infusion, so that the shorter elimination half-life for propofol lipid emulsion in their study is not surprising.

Pharmacodynamics

One major aim of the study was to determine the dose required to achieve LOC. At the end of the 10 min infusion interval LOC was attained in three cases with a dose of 1,160 mg GPI 15715 and in one case with 580 mg GPI 15715. The corresponding propofol plasma concentrations were approximately 2 µg/ml and probit analysis revealed an EC_{50} of approximately 2 µg/ml . However, as propofol is characterized by a distinct hysteresis between plasma concentration and effect, it is necessary to discriminate between plasma and effect site concentration, unless a steady state is reached. If

Table 5. Clinical Pharmacodynamics

GPI 15715 dose (mg)	LOC		ROC		OAA/S = 5 (alert)	
	Time (min)	Cp (µg/ml)	Time (min)	Cp (µg/ml)	Time (min)	Cp (µg/ml)
290	—	—	—	—	25 ± 5	0.55 ± 0.04
580	12	2.0	22	1.3	63 ± 49	0.34 ± 0.23
1,160	9 ± 3	2.1 ± 0.6	24 ± 2	2.0 ± 0.03	112 ± 72	0.49 ± 0.62

Time (min after start of infusion) and corresponding propofol plasma concentrations (C_p) for the investigated clinical endpoints in the three dosing groups (mean ± SD). Propofol plasma concentrations were obtained from the individual pharmacokinetic models. Because only one subject experienced loss of consciousness after 580 mg, there were no standard deviations available for LOC and ROC in this group.

LOC = loss of response to verbal command; OAA/S = Observer's Assessment of Alertness/Sedation Scale; ROC = recurrence of response to verbal command.

Table 6. Hemodynamics

GPI 15715 dose	290 mg	580 mg	1,160 mg
Heart rate (bpm), baseline	62 ± 7	62 ± 5	60 ± 15
Heart rate (bpm), maximum	80 ± 17 (36 ± 17%)	82 ± 9 (32 ± 4%)	89 ± 13 (52 ± 35%)
Systolic BP (mmHg), baseline	137 ± 12	134 ± 17	138 ± 12
Systolic BP (mmHg), minimum	113 ± 17 (-18 ± 7%)	108 ± 13 (-18 ± 15%)	107 ± 4 (-25 ± 8%)
Diastolic BP (mmHg), baseline	62 ± 15	71 ± 4	62 ± 10
Diastolic BP (mmHg), minimum	60 ± 16 (-13 ± 9%)	50 ± 5 (-29 ± 7%)	43 ± 2 (-28 ± 9%)

Mean ± SD. Changes are given in % compared to baseline.

BP = blood pressure; bpm = beats per minute.

one assumes an equilibration half-time $t_{1/2k_{e0}}$ of about 2 min,^{18,19} the effect site concentration at LOC would be approximately 1.5 µg/ml. For the known propofol lipid emulsion, the concentration to achieve LOC showed a large variation, both interindividual and between studies. Schuttler *et al.* reported a range of 1.6–6.3 µg/ml,²⁰ Forrest *et al.* found an EC_{50} of 1.8–2.7 µg/ml²¹ and Smith *et al.* estimated an EC_{50} of 3.3 µg/ml and an EC_{95} of 5.4 µg/ml.²² Compared to these results, propofol from GPI 15715 seemed to show a higher potency than propofol lipid emulsion with respect to concentration. Similarly, Dutta and Ebling found a smaller EC_{50} for lipid-free propofol in rats and a higher brain:plasma partition coefficient for the lipid free propofol which could explain the higher potency.^{16,17} Assuming complete conversion and $F = 0.54$, GPI 15715 is apparently less potent than propofol lipid emulsion with respect to dose, even when using molar units. Forrest *et al.*²¹ achieved LOC in 95% of the patients with a propofol dose of approximately 450 mg (= 2.5 mmol) administered in 30 min, whereas we achieved LOC with a mean dose of 870 mg GPI 15715 (= 2.6 mmol) administered over a period of 8–10 min.

Interestingly, in the three volunteers who received 1,160 mg, the propofol plasma concentrations at recurrence of response were nearly identical to those at loss of response (table 5). This could indicate that for propofol from GPI 15715 the hysteresis between plasma and effect site concentration is very small; otherwise, the plasma concentration at ROC should be lower than at LOC. The propofol concentrations of approximately 0.5 µg/ml at regaining full alertness in the present study were similar to those reported by Shafer *et al.* for propofol lipid emulsion (0.38–0.43 µg/ml).²³

Hemodynamics

Concerning the hemodynamic effects of propofol, it was expected that the propofol from GPI 15715 might cause less pronounced depression. The maximum decrease of blood pressure was approximately 20–25% and the maximum increase of heart rate was approximately 35%. This includes a volunteer in dosing group 3

(1,160 mg) who showed an extreme increase from a relatively slow baseline value of 43 to a maximum of 83 beats per minute. When comparing these results with those published for the known propofol lipid emulsion, it is difficult to obtain comparable data, as the hemodynamic effects may also depend on the age of the subjects, the delivery rate (bolus, rapid infusion, or slow infusion), the applied dose, the achieved concentration, and, for studies in patients, concomitantly administered drugs. After an infusion of 30 min with a total dose of 500 mg propofol, which resulted in a propofol concentration of approximately 3 µg/ml and caused LOC, Forrest *et al.*²¹ found a decrease of systolic and diastolic blood pressure from 131 and 81 mmHg to 103 and 67 mmHg (22 and 28% decrease, respectively) and an increase of heart rate from 69 to 77 (12%) beats per minute. With an electroencephalogram-controlled continuous infusion of propofol during the induction, Struys *et al.*²⁴ observed a decrease of systolic blood pressure from 122 ± 15 to a minimum of 93 ± 8 mmHg (24%). Kazama *et al.*¹⁹ modeled the pharmacodynamics of systolic blood pressure and found a decrease of about 15% for a propofol concentration of 3 µg/ml. For linearly increasing propofol concentrations, Schuttler²⁵ observed a maximum decrease of 15% for the mean arterial pressure and a maximum increase of 15% for heart rate with maximum propofol plasma concentrations of 5–6 µg/ml. From these results and with the limitations mentioned before, one may conclude that the hemodynamic effects after administration of GPI 15715 are not different from those of the known propofol lipid emulsion. Bolus application might produce other results as the conversion process would lead to lower propofol peak concentrations and a less rapid increase of propofol (fig. 7), which could reduce cardiovascular depression. The delay of the maximum cardiovascular depression, which occurred approximately 10 min after the maximum hypnotic effect, is in agreement with the results of Kazama *et al.*¹⁹ for propofol lipid emulsion.

In conclusion, GPI 15715, a water-soluble prodrug of propofol, produced LOC and was well tolerated. Due to the conversion process of the prodrug to propofol, the

time to peak of propofol concentration after a bolus and the elimination of propofol after infusion is longer than for propofol formulated in a lipid emulsion (figs. 7 and 8). Therefore, the most appropriate use of the prodrug may be maintenance of anesthesia and particularly sedation, where the missing lipid load and the potentially lower risk of infection is a clear advantage compared with propofol emulsion.²⁻⁴ The slower decrease of propofol concentration after bolus dose might be also an advantage for short procedures of 30–40 min duration, where a single bolus dose of GPI 15715 could probably provide sufficient hypnosis. Due to the short infusion period and the moderate dose, the potential risk of the metabolites formaldehyde, which is converted to formate, and phosphate could only be partially assessed in the present study. The clinical benefit of GPI 15715 as a propofol prodrug for the application in general anesthesia and sedation is to be investigated in further studies.

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Appendix

For the linked compartment models as shown in figure 2, the mass transfer is given by the following differential equations:

$$\begin{aligned} \text{GPI 15715:} \quad \frac{dm_1^G}{dt} &= -(k_{10}^G + k_{12}^G) \cdot m_1^G + k_{21}^G \cdot m_2^G + I(t) \\ \frac{dm_2^G}{dt} &= k_{12}^G \cdot m_1^G - k_{21}^G \cdot m_2^G \\ \text{Propofol:} \quad \frac{dm_1^P}{dt} &= -(k_{10}^P + k_{12}^P + k_{13}^P) \cdot m_1^P + k_{21}^P \cdot m_2^P + k_{31}^P \cdot m_3^P + F \cdot k_{10}^G \cdot m_1^G \\ \frac{dm_2^P}{dt} &= k_{12}^P \cdot m_1^P - k_{21}^P \cdot m_2^P \\ \frac{dm_3^P}{dt} &= k_{13}^P \cdot m_1^P - k_{31}^P \cdot m_3^P \end{aligned}$$

The superscripts G and P denote whether the parameters and masses are with respect to GPI15715 or propofol. The conversion factor F is the fraction of GPI15715 that is metabolized to propofol.

Each of both submodels can be described by the well-known multi-exponential disposition functions:

GPI 15715:

$$C^G(t) = \sum_{i=1}^2 A_i \cdot e^{-\alpha_i t},$$

and for propofol:

$$C^P(t) = \sum_{i=1}^3 B_i \cdot e^{-\beta_i t}$$

whereby the coefficients A and B and the exponents α and β can be calculated from the transfer constants k_{ij} and the central volume of distribution V_c .

The disposition function of propofol after bolus dose of GPI 15715 is:

$$C(t) = F \cdot k_{10}^G \cdot V_c \cdot \sum_{i=1}^2 \sum_{j=1}^3 \frac{A_i \cdot B_j}{\beta_j - \alpha_i} (e^{-\alpha_i t} - e^{-\beta_j t})$$

From this set of differential equations it is also possible to derive the infusion rate of GPI 15715, which results in a constant propofol concentration. However, even with a bolus dose of GPI 15715, it is not possible to achieve instantaneously a defined concentration in the central compartment of propofol. Therefore, it is useful to choose the following exponentially increasing form for the target concentration of propofol: $C(t) = C_{\text{Target}} \cdot (1 - e^{-\lambda t})$, whereby the exponent λ defines how fast the target is reached. This concentration course can be achieved with a combination of a bolus, a constant infusion, and

exponentially declining terms. For a two-compartment model of both GPI 15715 and propofol one yields:

$$I(t) = C_{\text{Target}} \cdot V_C^P \cdot \{\delta(t) \cdot (s_0 + s_1 + s_2) + k_{10}^P + s_3 \cdot e^{-k_{21}^G \cdot t} + s_4 \cdot e^{-k_{21}^P \cdot t} + s_5 \cdot e^{-\lambda \cdot t}\} / F$$

with

$$\begin{aligned} s_0 &= \frac{k_{10}^P}{k_{10}^G} \\ s_1 &= \frac{\lambda \cdot k_{12}^P}{k_{10}^G \cdot (\lambda - k_{21}^P)} \\ s_2 &= (\lambda - k_{12}^P - k_{10}^P + \frac{k_{12}^P \cdot k_{21}^P}{(k_{21}^P - \lambda)}) / k_{10}^G \\ s_3 &= s_0 \cdot k_{12}^G + s_1 \cdot \frac{k_{12}^G \cdot k_{21}^G}{k_{21}^G - k_{21}^P} + s_2 \cdot \frac{k_{12}^G \cdot k_{21}^G}{k_{21}^G - \lambda} \\ s_4 &= s_1 \cdot (k_{10}^G + k_{12}^G - k_{21}^P - \frac{k_{12}^G \cdot k_{21}^G}{k_{21}^G - k_{21}^P}) \\ s_5 &= s_2 \cdot (k_{10}^G + k_{12}^G - \lambda - \frac{k_{12}^G \cdot k_{21}^G}{k_{21}^G - \lambda}) \end{aligned}$$

This infusion rate can become negative, depending on the pharmacokinetic parameters and the parameter λ . As one can realize only a stop of infusion, there might occur an overshoot, particularly at the beginning. The GPI 15715 infusion rate which achieves a propofol concentration of 1.0 $\mu\text{g}/\text{mL}$, using the mean pharmacokinetic parameters estimated for two-compartment models (tables 2 and 3) and an increase parameter $\lambda = 1.0 \text{ min}$, is plotted in figure 11. The administration starts with a rapid infusion (4 mg/kg in 2 min), and after a short break of 1 min follows a declining infusion rate that reaches a steady state of approximately $7 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ at the end of the 2h-infusion

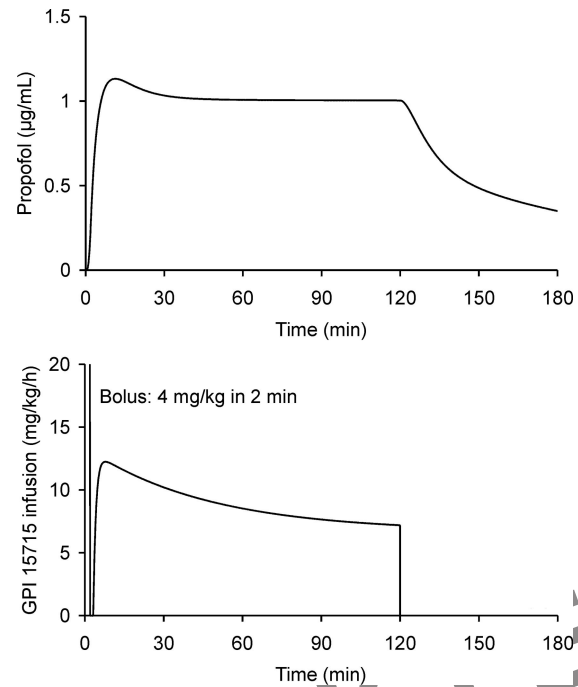


Fig. 11. Target-controlled infusion of GPI 15715 to rapidly achieve and maintain a propofol plasma concentration of 1 $\mu\text{g}/\text{mL}$. The top panel shows the resulting propofol concentration; the bottom panel shows the infusion rate as derived from the pharmacokinetic model (see Appendix).

period. The break at the beginning is necessary to reduce the overshoot. With this infusion scheme, the target concentration is reached in approximately 5 min, with a small overshoot of 10%.