Influence of Different Fat Emulsion-Based Intravenous Formulations on the Pharmacokinetics and Pharmacodynamics of Propofol

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Purpose. The influence of different intravenous formulations on the pharmacokinetics and pharmacodynamics of propofol was investigated using the effect on the EEG (11.5-30 Hz) as pharmacodynamic endpoint.

Methods. Propofol was administered as an intravenous bolus infusion (30 mg/kg in 5 min) or as a continuous infusion (150 mg/kg in 5 hours) in chronically instrumented male rats. Propofol was formulated as a 1% emulsion in an Intralipid 10%®-like fat emulsion (Diprivan-10®, D) or as a 1%- or 6% emulsion in Lipofundin® MCT/LCT-10% (Pl% and P6%, respectively). EEG was recorded continuously and arterial blood samples were collected serially for the determination of propofol concentrations using HPLC.

Results. Following bolus infusion, the pharmacokinetics of the various propofol emulsions could adequately be described by a two-compartmental pharmacokinetic model. The average values for clearance (Cl), volume of distribution at steady-state ($V_{d,ss}$) and terminal half-life ($t_{1/2,\lambda 2}$) were 107 ± 4 ml/min/kg, 1.38 ± 0.06 l/kg and 16 ± 1 min, respectively (mean±S.E., n = 22). No significant differences were observed between the three propofol formulations. After continuous infusion these values were 112 ± 11 ml/min/kg, 5.19 ± 0.41 l/kg and 45 ± 3 min, respectively (mean±S.E., n = 20) with again no statistically significant differences between the three propofol formulations. Comparison between the bolus- and the continuous infusion revealed a statistically significant difference for both $V_{d,ss}$ and $t_{1/2,\lambda 2}$ ($p < 0.05$), whereas Cl remained unchanged. In all treatment groups infusion of propofol resulted in a burst-suppression type of EEG. A profound hysteresis loop was observed between blood concentrations and EEG effect for all formulations. The hysteresis was minimized by a semi-parametric method and resulted in a biphasic concentration-effect relationship of propofol that was described non-parametrically. For P6% a larger rate constant onset of drug effect ($t_{1/2,keo}$) was observed compared to the other propofol formulations ($p<0.05$).

Conclusions. The pharmacokinetics and pharmacodynamics of propofol are not affected by to a large extent the type of emulsion nor by the concentration of propofol in the intravenous formulation.

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INTRODUCTION

Propofol is an unique highly lipophilic anesthetic which has the desirable properties of rapid onset and offset of effect upon intravenous infusion and which is widely used as a versatile sedative agent in the intensive care unit (1). Propofol is formulated as an intravenous emulsion of 1% propofol in an Intralipid 10%®-like fat emulsion (Diprivan-10®), containing long chain triglycerides (LCT). The major side effects of this formulation are pain at the site of injection and a considerable fat load (2). For these reasons, alternative formulations of propofol need to be developed (3). Fat load can be decreased by using more concentrated formulations of propofol. Furthermore, it has been shown that the pain at the site of injection is related to the propofol concentration in the aqueous phase of the formulation. Recently it has been demonstrated that the use of a mixture of medium and long chain triglycerides, Lipofundin® MCT/LCT-10%, results in a decreased propofol concentration in the aqueous phase of the fat emulsion (4). In order to minimize both side effects of intravenous fat emulsions of propofol, a new formulation has been developed containing 6% (g/v) propofol in Lipofundin® MCT/LCT-10% (3).

The composition of the intravenous fat emulsion, however, may potentially affect both the pharmacokinetics and the pharmacodynamics of propofol, as has been shown for several other drugs, such as cyclosporin (5), paclitaxel (6), doxorubicin/doxorubicinol (7) and phenytoin (8). The purpose of the present study was to characterize the pharmacokinetics and the pharmacodynamics of propofol in rats using different intravenous propofol formulations: 1%-propofol in an Intralipid 10%®-like fat emulsion (Diprivan-10®, D), 1% (P1%)- and 6% (P6%) in Lipofundin® MCT/LCT-10%. The pharmacokinetics of propofol were investigated upon both a bolus infusion and a continuous infusion of 5 hours. For the pharmacodynamics, the effect on the electroencephalogram (EEG, 11.5-30 Hz) was used as the pharmacodynamic endpoint.

METHODS

Study Design

The pharmacokinetics and pharmacodynamics of propofol were determined in four groups of 6–9 chronically instrumented rats receiving 30 mg/kg propofol as a 1% emulsion in an Intralipid10%®-like fat emulsion (Diprivan-10®, D), a 1% (P1%) or 6% (P6%) emulsion in Lipofundin® MCT/LCT-10%, or Lipofundin® MCT/LCT-10% only (placebo) in 5 min (bolus infusion experiment). In addition, the pharmacokinetics of the three different formulations of propofol were determined in three groups of 5–8 rats receiving 150 mg/kg propofol in 5 hours (continuous infusion experiment).

Drugs

Diprivan-10® was obtained from Zeneca, Ridderkerk, The Netherlands, P1% and P6% were obtained from the Department

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of Clinical Pharmacy, St. Antonius Hospital, Nieuwegein, The Netherlands and were prepared as described by Koster *et al.* (3).

Animals

Male Wistar rats with a body weight between 250 and 300 g at the time of the experiment were used (Broekman, Someren, The Netherlands). The rats were housed individually in plastic cages at constant temperature of 21°C and a controlled light-dark cycle (lights on: 7.00 a.m. to 7.00 p.m.). Food (Standard Laboratory Rat Mouse and Hamster Diets, RMH-TM, Hope Farms, Woerden, The Netherlands) and tap water were available *ad libitum.* One week before the bolus infusion experiment, four groups of rats had 7 cortical EEG electrodes implanted under fentanyl/fluanisone anaesthesia (Hypnorm^R, Janssen Pharmaceutica BV, Beerse, Belgium) as described before (9). One day prior to the experiment two indwelling cannulas were implanted, one in the left femoral artery and one in the right jugular vein. The cannula in the right jugular vein was used for drug administration, while the left femoral artery cannula was used for the serial collection of blood samples. Three groups of rats that were enrolled in the continuous infusion experiment, were used only for pharmacokinetic studies and had therefore only the venous- and arterial cannulas implanted one day prior to the experiment. The research adhered to the "Principles of Laboratory Animal Care" (NIH publication #85-23, revised, 1985).

Bolus Infusion Experiment

The pharmacokinetics and pharmacodynamics of propofol were determined after an intravenous infusion of 30 mg/kg propofol in 5 min. For the rats receiving the preparations containing 1% propofol, the total administered volume was 3 ml/kg. For the rats receiving the preparation with 6% propofol this volume was 0.5 ml. The placebo group received 3 ml/kg of the fat emulsion (Lipofundin®). The propofol emulsions were administered using a Harvard-22 infusion pump (Harvard Apparatus Inc., South Natick, MA). To determine the pharmacokinetics of propofol, arterial blood samples of 100 μl were collected at the following time intervals: 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 15, 20, 25, 30, 35, 45, 60, 75 and 90 min after the start of the propofol infusion. In the placebo group blood samples were obtained according to the same schedule as in the rats receiving propofol. Blood samples were immediately hemolyzed with 0.5 ml of deionized water and stored at 4°C until analysis. EEG recording and analysis was performed as described previously (10). For each 5-sec epoch the amplitude in the beta frequency range (11.5–30 Hz) of the power spectrum of the EEG was used as pharmacodynamic endpoint. Reduction of EEG data was performed by averaging spectral parameter values over predetermined time intervals.

Continuous Infusion Experiment

The pharmacokinetics of propofol were determined upon intravenous administration of 150 mg/kg propofol in 300 min. The propofol emulsions were administered using a Harvard-22 infusion pump, (Harvard Apparatus Inc., South Natick, MA). Arterial blood samples of 100 μl were collected at the following time intervals: 5, 10, 20, 30, 45, 60, 120, 180, and 300 min after the start of the infusion and 1, 3, 5, 7.5, 10, 15, 20, 30, 40, 50, 60 and 70 min after the termination of the infusion. Blood samples were immediately hemolyzed with 0.5 ml of deionized water and stored at 4°C until analysis.

Drug Assay

Propofol concentrations in whole blood samples were measured by High Performance Liquid Chromatography (HPLC) with fluorescence detection (11). Briefly, 50 or 5000 ng of thymol (internal standard) in 250 μl of acetonitrile was added to the haemolyzed blood sample. The mixture was vortexed for 2 min. and subsequently centrifuged for 5 minutes at 4000 rpm. 50 μl of the supernatant was injected into the HPLC. The HPLC system consisted of a Waters 600 MS system controller, a Waters inline degasser, a Waters 717 plus autosampler, a Merck-Hitachi F 1000 fluorescence detector and a 125 mm x 4.0 mm i.d. LiChrospher 100 RP-18 (5 μm) column (Merck Darmstadt, Germany). The mobile phase, a mixture of acetonitrile, distilled water and trifluoroacetic acid (60:40:0.1 v/v/v) was eluted at 1.5 ml/min. The excitation and emission wavelength of the detector were set at 276 and 310 nm respectively. The signals were recorded and processed by Millenium Session Manager version 2.10 (Waters, Etten Leur, The Netherlands). The coefficient of variation of the assay was less than 10% over the concentration range studied (0.4-40 μg/ml) and the lower limit of quantification was 0.4 μg/ml.

Data Analysis

The pharmacokinetics and pharmacodynamics of propofol were quantified for each individual rat. The blood concentration-time profiles during and after infusion were characterized by a poly-exponential equation:

$$C(t) = \sum_{i=1}^{n} \frac{C_i}{\lambda_i \cdot T}(1 - e^{-\lambda_i \cdot t}) \; t < T \qquad (1A)$$

$$C(t) = \sum_{i=1}^{n} \frac{C_i}{\lambda_i \cdot T} \cdot (1 - e^{-\lambda_i \cdot T}) \cdot e^{-\lambda_i \cdot (t-T)} \; t \geq T \qquad (1B)$$

where C(t) is the blood concentration of propofol at time t, T is the duration of the infusion and C_i and λ_i are the coefficients and the exponents of the equation, respectively. Different models were investigated and tested according to the Akaike Information Criterion and according to the precision of the parameter estimates obtained, as determined by their standard errors. The values of the various pharmacokinetic parameters (clearance, volume of distribution at steady-state and elimination half-life) were calculated from the coefficients and exponents of the fitted functions by standard methods or directly from the concentration-time data. The pharmacokinetic data were analyzed using the data analysis program Siphar, version 3.0 (Simed, Creteil, France). The wake-up concentration of propofol was calculated on the basis of the wake-up time recorded during the bolus infusion experiment and the set of exponents and coefficients obtained for each individual rat in the pharmacokinetic data analysis (Equation 1).

Hysteresis in the EEG effect *versus* blood concentration curve was minimized by a semi-parametric approach. Propofol blood concentrations were calculated with the estimated coefficients and exponents (Equation 1) obtained from each individual

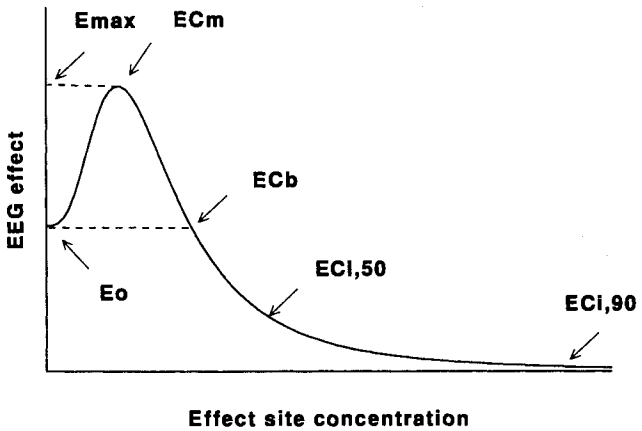

Fig. 1. Model independent pharmacodynamic parameters to characterize the biphasic concentration-EEG effect relationship of propofol (13).

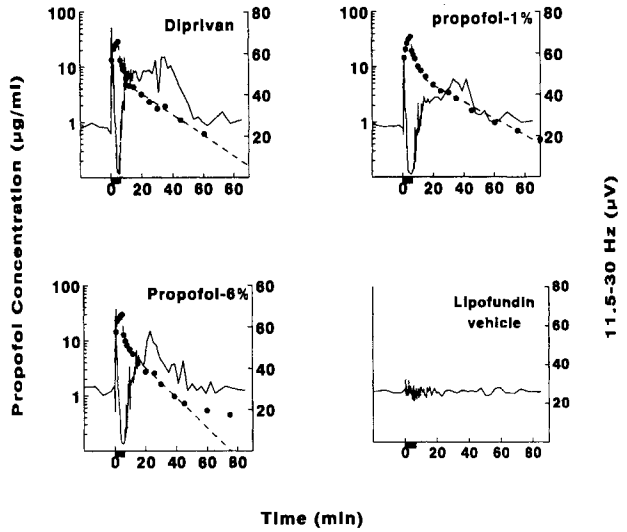

Fig. 2. Propofol blood concentrations (●) and EEG effect (—, change in the amplitudes in the 11.5-30 Hz frequency band) *versus* time profiles in four representative rats which received 30 mg/kg propofol (D, P1% or P6%) or Lipofundin® MCT/LCT-10% only (vehicle) intravenously in 5 min. The dashed lines fitted to the blood concentrations represent the best fit according to the pharmacokinetic model. The solid bar represents the duration of infusion.

rat. For the hysteresis minimization a FORTRAN written program was used (12). The EEG effect *versus* effect-site concentration curve was characterized non-parametrically using descriptors which are represented in Figure 1 (13). These parameters are: the baseline effect (E_0), the maximal activation of the EEG effect (E_{max}), the concentration required to produce the maximal activation (EC_m), the concentration required to produce the baseline effect between maximal activation and maximal inhibition (EC_b) and the concentrations required to obtain 50% and 90% reduction of EEG effect below baseline ($EC_{i,50}$ and $EC_{i,90}$, respectively). The pharmacodynamic parameters were directly obtained from the high resolution effect-site concentration-EEG effect data using the Matlab software package for numerical computation (version 4.0, The Math Works, Natick, MA). E_0, E_{max} and EC_m were directly obtained from the data, whereas C_b, $EC_{i,50}$ and $EC_{i,90}$ were derived by linear interpolation between the two closest data points.

Pharmacokinetic and pharmacodynamic estimates of the different treatment groups were compared statistically with the Fisher's Least Significant Difference test using Epistat Statistical Package, version 3.0 (T.L. Gustafson, Wound Rock, TX). A confidence level of 5 % was considered to be statistically significant.

RESULTS

The whole blood concentration *versus* time profiles of propofol after the bolus infusion of 30 mg/kg in 5 min in representative rats of the four different treatment groups are represented in Figure 2. The pharmacokinetics of propofol were most adequately described using a bi-exponential equation. The pharmacokinetic parameters of propofol were calculated for each rat in the different treatment groups and are summarized in Table 1. The average values for clearance (Cl), volume of distribution at steady-state ($V_{d,ss}$) and elimination half-life ($t_{1/2,\lambda 2}$) of propofol observed in the three treatment groups were 107 ± 5 ml/min/kg, 1.38 ± 0.06 l/kg and 16 ± 1 min, respectively (mean ± S.E., n = 22) and no significant differences were observed between the three treatment groups. The distributional half-life ($t_{1/2,\lambda 1}$) for P6% was significantly smaller than for the other formulations.

Upon continuous infusion of 150 mg/kg propofol in 5 hours, an apparent steady-state concentration of approximately 5 µg/ml was reached after 120 min for each of the three formulations. Thereafter, a continued increase in propofol concentration was observed (Figure 3). Consequently, the entire data set obtained upon 5-hour infusion could not be analyzed on basis of the two-compartment pharmacokinetic model. Therefore, non-compartmental pharmacokinetic parameter estimates were calculated from the full data set by statistical moment analysis. The half-lifes related to the different phases in the decline of propofol concentrations were determined from the post-infusion data. The post-infusion data were adequately described using a bi-exponential function. The average values for Cl, $V_{d,ss}$, $t_{1/2,\lambda 2}$ and $t_{1/2,\lambda 1}$ of propofol observed in the three treatment groups were 112 ± 11 ml/min/kg, 5.19 ± 0.41 l/kg, 45 ± 3 min and 3.3 ± 0.4 min, respectively (mean ± S.E., n = 20) and no significant differences were observed between the three treatment groups (Table 2). Comparison of the pharmacokinetic parameter estimates between the bolus infusion and the continuous infusion revealed statistically significant differences in both $V_{d,ss}$, $t_{1/2,\lambda 1}$ and $t_{1/2,\lambda 2}$, whereas Cl remained unchanged.

During the propofol bolus infusion typical changes in the EEG pattern were observed (Figure 4). Initially an increase

Table 1. Pharmacokinetic Parameter Estimates of Propofol for the Three Preparations (mean±S.E.) upon a Bolus Infusion of 30 mg/kg Propofol in 5 min

	D	P1%	P6%
Number of animals	7	6	9
Cl (ml/min/kg)	101 ± 10	97 ± 11	119 ± 15
$V_{d,ss}$ (l/kg)	1.32 ± 0.11	1.31 ± 0.19	1.46 ± 0.24
$t_{1/2,\lambda 1}$ (min)	1.2 ± 0.2	1.4 ± 0.2	0.6 ± 0.2[a]
$t_{1/2,\lambda 2}$ (min)	18 ± 3	18 ± 2	14 ± 2

[a] $p < 0.05$.

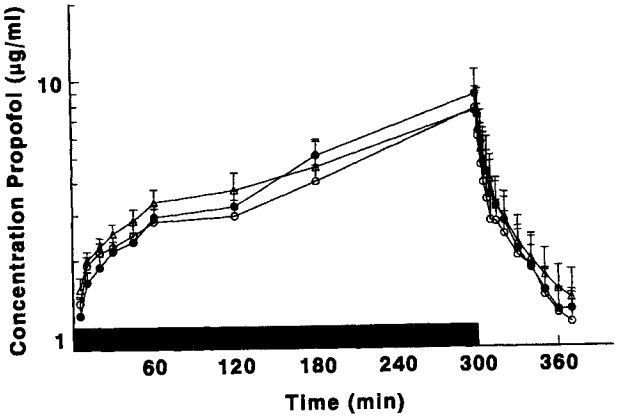

Fig. 3. Propofol blood concentrations *versus* time profiles in rats which received 150 mg/kg propofol as a continuous infusion as D (●), P1% (○) or P6% (△). The solid bar represents the duration of infusion.

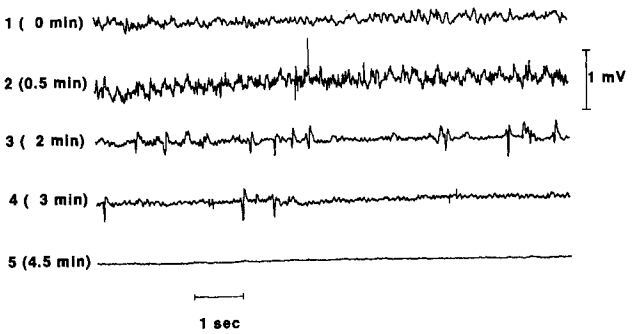

Fig. 4. Characteristic EEG changes in the central-occipital lead of the left hemisphere (C_1-O_1) induced by increasing propofol concentrations during an intravenous bolus infusion of 30 mg/kg in 5 min in a typical rat. Before administration of propofol (1) the EEG is characterized by predominant high theta, low alpha activity (6-10 Hz). During infusion of propofol initially an increase in high-frequency activity is observed (2). As propofol concentrations increase further, this pattern gradually changes into a burst-suppression type of EEG pattern (3 and 4) and finally results in an iso-electric EEG at the end of the infusion (5).

in high frequency (beta) activity was observed. As propofol concentrations increased further, this pattern gradually changed into a burst-suppression type of EEG and finally resulted in an iso-electric EEG pattern at the end of the infusion. After termination of the infusion the same pattern was observed in a reversed manner. These EEG changes were characterized on basis of changes in the amplitude of the 11.5–30 Hz frequency band of the EEG power spectrum (Figure 2). When the EEG effect observed after bolus infusion was plotted versus the propofol blood concentration a profound hysteresis loop was observed for all propofol formulations (Figure 5a). Hysteresis was successfully minimized by a semi-parametric method. In all treatment groups this resulted in a biphasic effect-site concentration-EEG effect relationship of propofol (Figure 5b). At lower propofol concentrations an activation on the 11.5-30 Hz frequency band of the EEG was observed, whereas a further increase of the propofol concentration showed an inhibition of the beta EEG effect, resulting in an amplitude value of approximately zero. This biphasic concentration-EEG effect relationship was characterized by non-parametric descriptors (Figure 1). The pharmacodynamic parameter estimates of propofol obtained for the different formulations are represented in Table 3.

DISCUSSION

The main objective of the present investigations was to determine whether differences in pharmacokinetics and phar-

Table 2. Pharmacokinetic Parameter Estimates of Propofol for the Three Preparations (mean±S.E.) upon a Continuous Infusion of 150 mg/kg Propofol in 5 hr

	D	P1%	P6%
Number of animals	5	7	8
Cl (ml/min/kg)	96 ± 19	107 ± 11	127 ± 22
$V_{d,ss}$ (l/kg)	5.03 ± 0.56	5.61 ± 0.64	4.91 ± 0.76
$t_{1/2,\lambda 1}$ (min)	3.1 ± 0.8	3.0 ± 0.5	3.7 ± 0.6
$t_{1/2,\lambda 2}$ (min)	44 ± 5	43 ± 5	48 ± 4

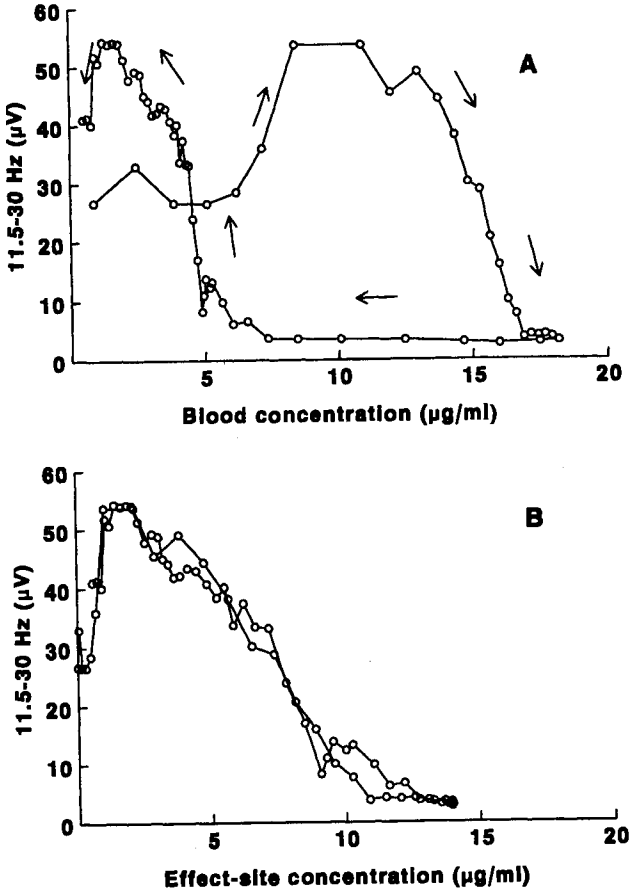

Fig. 5. EEG effect *versus* blood concentration profile of propofol in a representative rat. The arrows indicate time course of the changes of propofol blood concentrations and EEG effect. A profound hysteresis loop is observed. (B) EEG effect *versus* effect-site concentration time profile in the same rat after semiparametric hysteresis minimization.

Table 3. Pharmacodynamic Parameter Estimates of Propofol for the Three Treatment Groups upon a Bolus Infusion of 30 mg/kg Propofol in 5 min (mean ± S.E.)

	D	P1%	P6%
Number of animals	7	6	8
E_0 (μV)	24 ± 1	29 ± 2	24 ± 2
E_{max} (μV)	57 ± 2	53 ± 2	55 ± 3
EC_m (μg/ml)	2.48 ± 0.26	1.83 ± 0.45	2.45 ± 0.12
EC_b (μg/ml)	19.5 ± 1.1[a]	14.5 ± 0.6	13.5 ± 0.5
$EC_{i,50}$ (μg/ml)	25.3 ± 1.0[a]	21.8 ± 0.5[a]	16.7 ± 0.6[a]
$EC_{i,90}$ (μg/ml)	30.0 ± 1.0	29.3 ± 0.7	22.5 ± 0.6[a]
$C_{wake\text{-}up}$ (μg/ml)	2.23 ± 0.4	2.11 ± 0.4	2.45 ± 0.9
$t_{1/2,keo}$ (min)[a]	0.93 ± 0.09	1.05 ± 0.09	1.52 ± 0.05[a]

[a] $p < 0.05$.

macodynamics exist between different formulations of propofol. In this context the influence of different fat emulsions (an Intralipid®-10%-like fat emulsion *versus* Lipofundin® MCT/LCT-10%) and of different concentrations of propofol (1% *versus* 6%) were tested. The pharmacokinetics of propofol have been determined following both an intravenous bolus infusion and a continuous infusion. Between the different pharmaceutical formulations no statistically significant differences in pharmacokinetic parameters were observed, indicating that at least from a pharmacokinetic point of view the formulations are bio-equivalent. Between the bolus infusion and the continuous infusion, however, some marked differences in pharmacokinetic parameter estimates were observed. Particularly, the larger volume of $V_{d,ss}$ upon continuous infusion is of interest. A similar observation has been obtained in humans (14).

Following the intravenous bolus infusion, the pharmacokinetics were described on the basis of a two-compartment pharmacokinetic model. In this way pharmacokinetic parameter estimates were obtained that are in agreement with values previously reported for propofol in rats administered as a 2% emulsion with 10% Cremophor (15) or as Diprivan-10® (16,17). Cockshott *et al.* have proposed that a three compartment pharmacokinetic model may be more appropriate to characterize the pharmacokinetics of propofol in the rat (18). In their study no serial blood sampling was conducted, but destructive sampling was applied instead. In each individual rat one large blood sample was obtained by cardiac puncture. In this way a detection limit of 0.01 μg/ml was obtained, which allowed determination of blood concentrations of propofol up to 24 hours after administration of a dose of 9.3 mg/kg. This resulted in an estimate of the terminal half-life of 6 hours. The existence of a slow third phase in the pharmacokinetics of propofol may explain why during continuous infusion steady-state concentrations are not attained at 2 hours of infusion, but that blood concentrations continue to increase between 2 and 5 hours of infusion. Another factor however may be time dependent alterations of the propofol pharmacokinetics. In this respect it is of interest that some pharmacokinetic rate constants obtained after termination of the continuous infusion are significantly different from those observed following the bolus infusion, such despite the fact that they were obtained in the same concentration range. Propofol-induced changes in hepatic blood flow and/or slight changes in body temperature may have contributed to this observation (19). At any rate, not only following bolus infusion, but also following the continuous infusion nearly identical pharmacokinetic parameter estimates of propofol were obtained for the different formulations. This justifies the conclusion that nor the type of fat emulsion nor the propofol concentration in the fat emulsion influences the pharmacokinetic characteristics of propofol.

In order to evaluate the effect of different intravenous formulations on the pharmacodynamics of propofol, a quantitative effect measure is needed that is continuous, sensitive and objective (20). Quantitative parameters derived from the EEG have been used previously to characterize the *in vivo* pharmacodynamics of several classes of CNS active drugs, such as barbiturates (9,13), benzodiazepines (21), baclofen (22) and synthetic opioids (10). Propofol induces a burst-suppression type of changes in the EEG in a concentration dependent manner, similar to the EEG effect of barbiturates (13). This EEG effect has been demonstrated in a number of species, such as rats (16,17), cats (23), rabbits (24) and humans (25). Also, this effect is observed in a wide clinically relevant concentration range, ranging from post-operative sedation to induction and maintenance of peri-operative anesthesia (26). In the present study the equivalent ampitude of the 11.5-30 Hz (beta) frequency band of the power spectrum of the EEG was used to relate the pharmacological effect to the propofol concentration. Compared to other frequency bands, propofol induced the most robust effect on the beta frequency over the entire concentration range.

When the EEG effect was related to propofol blood concentrations, a biphasic relationship was observed, with an increase of the beta effect at low propofol concentrations, and a decrease in beta effect at higher concentrations. Also, profound hysteresis was observed between blood concentration and EEG effect (Figure 5a). In order to obtain a unique concentration-EEG effect relationship of propofol, hysteresis was minimized by a semiparametric approach. This method was preferred over other approaches by considering the following criteria with respect to the pharmacokinetic model, the pharmacodynamic model and the model linking the effect compartment to the blood compartment. Because the blood concentration *versus* time profile of propofol in all treatment groups could adequately be described on the basis of a two-compartmental pharmacokinetic model (Figure 2), a parametric approach was used with respect to the pharmacokinetic model. With respect to the pharmacodynamic model, a non-parametric approach was preferred because of the complex pattern of the biphasic concentration-effect relationship of propofol. Finally,with respect to the model linking propofol concentrations in a hypothetical effect compartment to propofol concentrations in the blood, a simple first order model was used. This model was adequate in minimizing the hysteresis observed in the blood concentration-EEG effect relationship of propofol (Figure 5b) and therefore more complex models (27) did not offer any advantages. The effect-site concentration *versus* EEG effect relationship of propofol in the different treatment groups was characterized for each individual rat by non-parametric descriptors (13, see Figure 1). As can be seen from Table 3, some minor differences were observed between the three propofol formulations. However, these differences were not consistent for one type of emulsion. The values for the different descriptors of the effect-site concentration-EEG effect relationship previously reported (16,17) were lower than in the present study: 0.66- and 2.34 μg/ml for EC_m and

$EC_{i,50}$, respectively. This difference may be attributed to the excessive blood sampling in the study by Dutta *et al.* (17). Over a time period of two hours 6.4 ml of total blood was drawn from a male Wistar rat of 500 gr (compared to 2 ml in the present study). It is very likely that hemodilution has resulted in a decrease of the concentration of plasma proteins. Since propofol is highly bound to albumin (28), this may have resulted in increased free propofol concentrations in the body and therefore in lower values of the descriptors of the concentration-EEG effect of propofol. Also, the amount of blood drawn by Dutta *et al.* (17) is nearly the same as the amount of blood drawn that is needed to induce acute hypovolemia (29, approximately 30% of total blood volume). The latter study showed that the sensitivity of the CNS for phenobarbital is increased in the situation of hypovolemia. It can not be excluded that this is also the case for propofol. The average wake-up concentration of 2.28 μg/ml observed in the present study is in agreement with the values observed previously (15,18). Recently, a close correlation has demonstrated between the time of peak EEG activity and offset of sleep (17) and this is in agreement with the similar values for EC_m and wake-up concentration of propofol for the different formulations (Table 3). Interestingly, similar wake-up concentrations have been observed in humans (30, 2.3 μg/ml).

A significantly larger time delay between blood concentration and effect ($t_{1/2,keo}$) was observed for P6% when compared to the 1% formulations (Table 3). The values of $t_{1/2,keo}$ obtained for the two 1% formulations of propofol in the present study are in agreement with values reported for a number of 1% formulations of propofol in rats using different types of fat emulsions (16,17). Since no differences in $t_{1/2,keo}$ were observed between different types of 1% emulsions of propofol, the differences observed in the P6% group can only be accounted for by the difference in the propofol concentration in the formulation and not by the type of fat emulsion used.

In summary it can be concluded that the pharmacokinetics and the pharmacodynamics of propofol are not affected by the fat emulsion formulation used for the intravenous administration of propofol. Only minor differences were observed for P6% with respect to the rate of equilibrium with the site of action of propofol. The 6% propofol emulsion in Lipofundin® MCT/LCT-10% may therefore be further developed as a possible alternative for Diprivan-10®.

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