Anesthesiology
2000; 92:727–38

Population Pharmacokinetics of Propofol

A Multicenter Study

Jürgen Schüttler, M.D., Harald Ihmsen, M.Sc.†*

Background: **Target-controlled infusion is an increasingly common type of administration for propofol. This method requires accurate knowledge of pharmacokinetics, including the effects of age and weight. The authors performed a multicenter population analysis to quantitate the effects of covariates.**

Methods: **The authors analyzed 4,112 samples of 270 individuals (150 men, 120 women, aged 2–88 yr, weighing 12–100 kg). Population pharmacokinetic modeling was performed using NONMEM (NONMEM Project Group, University of California, San Francisco, CA). Inter- and intraindividual variability was estimated for clearances and volumes. The effects of age, weight, type of administration and sampling site were investigated.**

Results: **The pharmacokinetics of propofol were best described by a three-compartment model. Weight was found to be a significant covariate for elimination clearance, the two intercompartmental clearances, and the volumes of the central compartment, the shallow peripheral compartment, and the deep peripheral compartment; power functions with exponents smaller than 1 yielded the best results. The estimates of these parameters for a 70-kg adult were 1.44 l/min, 2.25 l/min, 0.92 l/min, 9.3 l, 44.2 l, and 266 l, respectively. For patients older than 60 yr the elimination clearance decreased linearly. The volume of the central compartment decreased with age. For children, all parameters were increased when normalized to body weight. Venous data showed a decreased elimination clearance; bolus data were characterized by increases in the volumes of the central and shallow peripheral compartments and in the rapid distribution clearance (Cl_2) and a decrease in the slow distribution clearance (Cl_3).**

Conclusions: **Pharmacokinetics of propofol can be well described by a three-compartment model. Inclusion of age and weight as covariates significantly improved the model. Adjusting pharmacokinetics to the individual patient should improve the precision of target-controlled infusion and may help to broaden the field of application for target-controlled infusion systems. (Key words: Age; body weight; children; elderly; NONMEM.)**

PROPOFOL is widely used for both induction and maintenance of general anesthesia. Its tremendous body uptake as well as the rapid elimination caused by a huge apparent volume of distribution and a high clearance make propofol the best controllable intravenous hypnotic from a pharmacokinetic point of view.[1]

Based on the pharmacokinetic properties of propofol, drug-administration schemes have been developed that allow a defined concentration to be rapidly achieved and held constant. Target-controlled infusion was introduced for research purpose years ago, with computer-driven infusion pumps using two- or three-compartment models.[2–6] A commercial target-controlled infusion system for propofol is now available (Diprifusor-TCI, Zeneca Pharmaceuticals, Macclesfield, UK). Such systems require appropriate pharmacokinetic data to ensure that the desired concentration is achieved. In the past 15 yr, several studies on the pharmacokinetics of propofol have been performed to derive pharmacokinetic parameters not only for adult patients[7–16] but also for elderly patients,[17] children,[6,18–21] and patients with diseases influencing propofol metabolism.[22,23] Propofol has also been used for sedation of patients in intensive care medicine.[24–26]

In this study we performed a population pharmacokinetic analysis with data from five research groups (J. Schüttler,[7] University of Erlangen-Nuremberg, Germany; I. Cockshott,[17,18] Zeneca Pharmaceuticals, UK; P. Glass,[27] Duke University, Durham, NC; M. White,[3,6] Academisch Ziekenhuis Leiden, The Netherlands; and S. Shafer,[21] Stanford University, Palo Alto, CA). Population analysis allows us to quantitate the variability of the parameters between individuals (interindividual) as well as within any patient (intraindividual) and to investigate the influence of covariates. The aims of this study were to estimate the pharmacokinetics of propofol with special respect to the covariates age, body weight, and

* Professor of Anesthesiology and Chairman.

† Research Assistant.

Received from the Department of Anesthesiology, Friedrich-Alexander-University of Erlangen-Nuremberg, Erlangen, Germany. Submitted for publication August 10, 1998. Accepted for publication November 3, 1999. Supported in part by grant no. 35868 from Zeneca Pharmaceuticals, Macclesfield, United Kingdom.

Address reprint requests to Dr. Schüttler: Department of Anesthesiology, Krankenhausstr. 12, D-91054 Erlangen, Germany. Address electronic mail to: juergen.schuettler@kfa.imed.uni-erlangen.de

Table 1. Complete Data Set of the Propofol Population (270 individuals, 4,112 samples)

Principal Investigator	Group	Administration Mode	No. of Individuals	No. of Samples	Sampling Site	Sampling Period (min)*	Age (years)*	Weight (kg)*	Gender (m/f)
Schüttler[7]	1	Single bolus	8 patients; 8 volunteers	332	Arterial	480–720 585 ± 122	20–51 31 ± 10	57–94 69 ± 10	8/8
	2	Continuous infusion	6 volunteers	298	Arterial	267–558 362 ± 102	24–28 25 ± 2	57–82 70 ± 9	4/2
	3	Continuous infusion	10 patients	98	Arterial	30–70 53 ± 12	66–82 73 ± 6	51–73 62 ± 8	4/6
Cockshott[17,18]	4	Single bolus	10 patients	187	Venous	240–1530 1,126 ± 538	4–7 5 ± 1	17–24 19 ± 2	7/3
	5	Single bolus	24 patients	554	Venous	1,153–1,442 1,428 ± 57	19–77 49 ± 22	43–85 64 ± 10	9/15
Glass[27]	6	Continuous infusion	28 patients	451	Arterial	59–397 165 ± 93	18–49 32 ± 9	54–96 72 ± 14	13/15
White[3,6]	7	Continuous infusion	90 patients	1266	Venous	18–266 55 ± 35	17–88 47 ± 17	42–100 69 ± 13	45/45
	8	Continuous infusion	33 patients	269	Venous	15–120 57 ± 21	2–10 5 ± 2	12–30 19 ± 5	32/1
Shafer[21]	9	Continuous infusion	53 patients	657	Venous	52–811 214 ± 144	3–11 7 ± 3	15–61 26 ± 10	28/25

* Values are mean ± SD and range.

gender and to evaluate the inter- and intraindividual variability.

Materials and Methods

Samples

We analyzed 4,112 concentrations of 270 individuals. Two-hundred fifty-six were patients undergoing surgery; 14 were volunteers (table 1). Propofol (Disoprivan or Diprivan; Zeneca Pharmaceuticals, Macclesfield, United Kingdom) was administered as a bolus or using continuous infusion, with the infusions computer-controlled in groups 2 and 4–8. The sampling period was in the range of 0.25–24 h. Propofol concentrations were measured from arterial (groups 1, 2, 3, and 6) and venous samples (groups 4, 5, and 7–9). Propofol concentrations were measured in whole blood (groups 1–8) and plasma (group 9) using high-pressure liquid chromatography (groups 1–6 and 9) and gas–liquid chromatography (groups 7 and 8) with fluoreometric or electrochemical detection.[28]

Pharmacokinetic Analysis

The propofol concentration data were analyzed with NONMEM (version V, double precision).[29] NONMEM allows multiple nonlinear regression of population data simultaneously, which means that not only the mean kinetic parameters but also inter- and intraindividual variability can be estimated. In addition, it is possible to quantitate the influence of covariates such as body weight, age, and gender. Another advantage of the population approach is that the number of observations per individual can be kept relatively small.

Pharmacokinetic Model

Pharmacokinetics were assumed to be linear with two- or three-compartments and elimination from the central compartment. The elimination clearance (Cl_1), the intercompartmental clearances (Cl_2, Cl_3), and the volumes of the central compartment (V_1), the shallow peripheral compartment (V_2), and the deep peripheral compartment (V_3) were chosen as pharmacokinetic parameters to be estimated. To investigate the effect of covariates, additional parameters were successively included in the model (see Regression Procedure).

Interindividual and Intraindividual Variability

One major advantage of NONMEM is that interindividual and intraindividual variability can be quantified. The interindividual variability describes the variance of a

pharmacokinetic parameter among different subjects. We estimated the variability of all clearances and volumes using a log-normal model. This means for the *i*th individual

$$\theta_i = \bar{\theta} \cdot e^{\eta_i} \text{ or } \log \theta_i = \log \bar{\theta} + \eta_i \quad (1)$$

in which Θ_i is the individual value of the parameter Θ, $\bar{\Theta}$ is the mean population value of this parameter, and η_i is a random variable with mean zero and variance ω_η^2. For the intraindividual variability that describes the residual errors resulting from assay errors, time-recording inaccuracy, model misspecification, and so forth, we used a constant coefficient of variation model:

$$c_{ij} = cp_{ij} \cdot (1 + \epsilon_{ij}) \quad (2)$$

in which c_{ij} is the *j*th measured concentration of the *i*th individual and cp_{ij} is the corresponding predicted concentration. Again, ϵ_{ij} is a random variable with mean zero and variance σ_ϵ^2. NONMEM estimates the mean pharmacokinetic parameters of the population, the interindividual variances ω_η^2, and the intraindividual variances σ_ϵ^2, including estimates of the standard errors and correlation coefficients for all parameters.

Regression Procedure

The complete data set was randomly divided into two subsets containing 135 individuals each. The subjects of each subset were comparable with respect to age, weight, gender, sampling site, and administration mode. The first subset was used for the development of the model as described subsequently. The predictive accuracy of the model was then tested with the second subset. In a first step, individual Bayesian estimates of the pharmacokinetic parameters of each individual were obtained using a three-compartment model without any covariates. The estimated parameters were plotted independently against body weight, age, and gender to identify the influence of the covariates and the shape of the parameter–covariate relationships. Subsequently, we performed a population analysis of all data, beginning with a simple model without any covariates and successively incorporating additional parameters. The effects of covariates were tested for statistical significance using the NONMEM objective function (which is $-2 \cdot$ log-likelihood) and the standard errors of the additional parameters. An additional parameter was included in the model if the decrease of the objective function was at least 7.8 ($P < 0.005$) and the 95% confidence interval of the additional parameter (mean $\pm 2 \cdot$ SE) did not include zero (null hypothesis value). In addition, the inter- and intraindividual variabilities should decrease as an additional covariate parameter explains the difference between individuals. To exclude covariate correlations, we tested whether deletion of any additional parameter from the full model resulted in a decreased goodness of fit. To estimate the accuracy of the model we calculated the weighted residual (WR) and the absolute weightedresidual (AWR) for each sample:

$$WR_{ij} = \frac{c_{ij} - cp_{ij}}{cp_{ij}} \quad AWR_{ij} = \frac{| c_{ij} - cp_{ij} |}{cp_{ij}} \quad (3)$$

in which c_{ij} is the *j*th measured concentration of the *i*th individual and cp_{ij} denotes the corresponding predicted value. The median population values of WR (median weighted residual, MWR) and AWR (median absolute weighted residual, MAWR) were used as overall measures for goodness of fit.

Finally, we calculated MWR and MAWR for the remaining subset of individuals who were not included during model development, using the estimated parameters of the full model. This gives additional information about the ability of the final model to predict propofol concentrations.

Simulations

To illustrate the pharmacokinetic findings, various simulations were carried out. Using the estimated parameters we calculated the time for a 50% decrease in concentration after continuous infusion (context-sensitive half-time).[30] To show the effect of age on dosing we computed the infusion rates necessary to maintain a defined concentration. The interindividual variability was illustrated by calculating the context-sensitive halftime for a population of 100 subjects whose pharmacokinetic parameters were log-normally distributed with means and variances as estimated for the full model. To demonstrate the influence of the administration mode (bolus *vs.* infusion) we simulated the concentration course after a bolus dose using the kinetic parameters for bolus and infusion, respectively. All simulations were performed with software written by the authors.

Results

The individual estimates revealed an influence of body weight and age on all clearances, V_1, and V_2; V_3 was almost constant in all subjects. As an example, figure 1 shows the individual estimates of Cl_1 as a function of

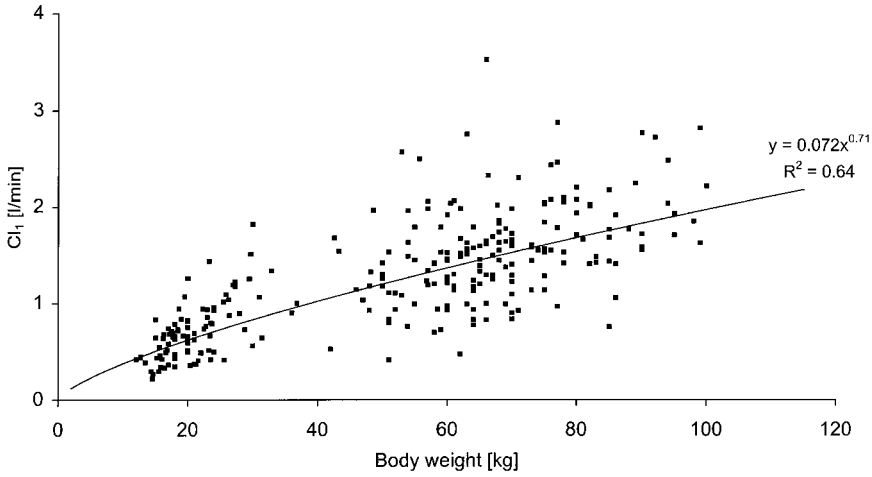

Fig. 1. Plot of the individual Bayesian estimates of the elimination clearance (Cl_1) *versus* body weight for a three-compartment model without any covariates. A power function (line) yielded the best results in regression analysis.

body weight. The shapes of the relationships suggested that body weight should not be incorporated into the model in a linear fashion but as a power function with a positive exponent smaller than one. V_1 was almost constant in adults but decreased in children. If divided by the body weight, V_1 showed a clear relationship with age, which could be described by a power function with negative exponent. The effect of age on Cl_1 was a linear decrease for patients older than 60 yr. The predictive accuracy of the individual Bayesian estimates was quite high (MWR = −1.5%, MAWR = 9.6%; fig. 2).

In the subsequent population analysis, these effects were modeled by incorporating additional parameters. The results of this procedure are shown in table 2, in which *−2LL* denotes the value of the objective function (−2 log-likelihood), describing the goodness of fit. As mentioned previously, a decrease of −2 log-likelihoods means an improvement of fit. Significant effects were retained in the subsequent regressions. The pharmacokinetic parameters of the final model are shown in table 3.

Number of Compartments

Initially, a simple two-compartment model was assumed, but the resulting fit was quite poor. A three-compartment model markedly improved the fit, because of the long sampling period in some groups (1, 4, and 5).

Influence of Covariates

As suggested from the individual estimates, we found effects of body weight on Cl_1, Cl_2, Cl_3, V_1, and V_2. The influence was best modeled by a power function with an exponent smaller than 1. As an example, table 2 shows the results for a simple weight normalization of Cl_1

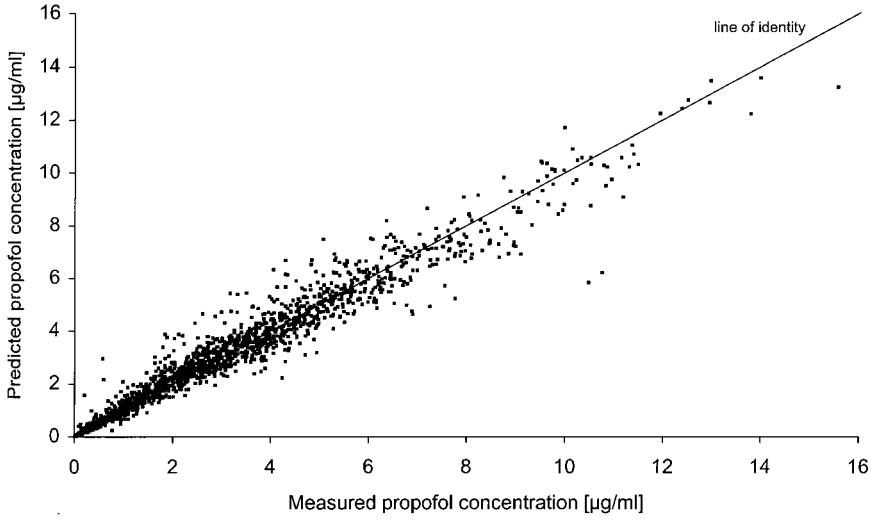

Fig. 2. Plot of the propofol concentrations predicted by the individual Bayesian estimates of a three-compartment model without any covariates *versus* the measured propofol concentrations of the first subset.

Table 2. Results of the Regression Procedure

	θ_1	θ_2	θ_3	θ_4	θ_5	θ_6	θ_7	θ_8	θ_9	θ_{10}	θ_{11}	θ_{12}	θ_{13}	θ_{14}	θ_{15}	θ_{16}	θ_{17}	θ_{18}	MWR (%)	MAWR (%)	−2LL*
(1)	0.34	11.5	1.21	81.3	—	—	0	0	0	0	0	0	0	0	0	0	0	0	−62	62	−12
(2)	0.84	12.8	1.48	47.5	0.39	204	0	0	0	0	0	0	0	0	0	0	0	0	−32	41	−1144
(3)	1.25	12.4	1.86	62.1	0.45	315	0	0	0	0	0	0	0	0	0	0	0	0	−14	28	−1545
(4)	1.32	12.1	1.81	59.5	0.42	268	0.89	0	0	0	0	0	0	0	0	0	0	0	−13	27	−1553
(5)	1.20	11.3	2.67	64.4	0.34	188	0.85	0.79	0	0	0	0	0	0	0	0	0	0	−18	29	−1768
(6)	1.17	10.5	2.91	79.1	0.37	223	0.61	0.99	0.82	0	0	0	0	0	0	0	0	0	−15	27	−1912
(7)	1.46	10.4	2.47	67.2	0.42	211	0.75	0.88	0.72	0.048	0	0	0	0	0	0	0	0	−7.9	26	−2174
(8)	1.45	10.2	2.40	62.9	0.52	217	0.71	0.86	0.66	0.050	0.37	0	0	0	0	0	0	0	−7.5	25	−2196
(9)	1.56	26.1	3.41	51.6	0.73	253	0.81	1.10	0.51	0.056	0.61	0	0	0	0	0	0	0	−6.5	30	−2070
(10)	1.45	10.9	2.38	63.2	0.51	217	0.71	0.85	0.63	0.050	0.37	0.49	−0.31	0	0	0	0	0	−8.6	25	−2204
(11)	1.48	10.9	2.85	62.4	0.53	219	0.72	0.73	0.62	0.052	0.39	0.56	−0.36	−0.30	0	0	0	0	−7.3	25	−2221
(12)	1.44	9.3	2.25	44.2	0.92	266	0.75	0.62	0.62	0.045	0.55	0.71	−0.39	−0.40	1.61	2.02	0.73	−0.48	−3.4	25	−2455

(1) two-compartment model; (2) three-compartment model; (3) $Cl_1 = \theta_1 \cdot (BW/70)$; (4) $Cl_1 = \theta_1 \cdot (BW/70)^{\theta_7}$; (5) $Cl_2 = \theta_3 \cdot (BW/70)^{\theta_8}$; (6) $V_2 = \theta_4 \cdot (BW/70)^{\theta_9}$; (7) $Cl_1 = \theta_1 \cdot (BW/70)^{\theta_7} - (age - 60) \cdot \theta_{10}$; (8) $Cl_3 = \theta_5 \cdot (BW/70)^{\theta_{11}}$; (9) $V_1 = \theta_2 \cdot (BW/70)$; (10) $V_1 = \theta_2 \cdot (BW/70)^{\theta_{12}} \cdot (age/30)^{\theta_{13}}$; (11) Cl_2 changed for venous samples as noted in table 3; (12) Cl_2, Cl_3, V_1, and V_2 changed for bolus data as noted in table 3; MWR = median weighted residual; MAWR = median absolute weighted residual.

* −2LL is the value of the objective function (−2 log likelihood).

(model 3) and the power function (model 4). This means that the weight-normalized parameter (parameter divided by body weight) increases with decreasing weight (*e.g.*, for children). V_3 did not vary with age and body weight. The elimination clearance decreased linearly in individuals older than 60 yr. The volume of the central compartment decreased with age if divided by body weight. This led to a worse fit if V_1 was modeled weight-proportionally (model 9, table 2). Inclusion of age and weight as a power function, however, improved the model (model 10, table 2). No influence of gender could be found for the analyzed subjects.

Influence of Sampling Site

An influence of different sampling sites was found only for Cl_2, which was smaller for venous samples; no other parameter was altered significantly.

Influence of Mode of Administration

Nearly all parameters with the exception of Cl_1 and V_3 were found to be altered with bolus administration compared with infusion data. Whereas V_1, V_2, and Cl_2 were larger than after infusion, Cl_3 was decreased.

The estimates of all parameters and their standard errors are summarized in table 3. Fixing of any additional parameter to zero led to a significant decrease in goodness of fit (increase of −2 log-likelihood), indicating that all additional parameters were required. Calculation of the weighted residuals revealed median values of −3.4% (MWR) and 24.9% (MAWR) for the first subset. The prediction errors for the second subset calculated with the estimated kinetic parameters were similar (MWR = −0.4%, MAWR = 25.5%). Figure 3 shows the predicted concentrations, as calculated with the parameters derived from the first subset, plotted against the measured concentrations of the second subset. The ratio of measured:predicted concentration was calculated for each sample and plotted against time for each individual (fig. 4).

Simulations

We performed several simulations for five typical individuals (child, lean adult, average adult, obese adult, and elderly) using the estimated pharmacokinetic parameters of the full model (table 4). Figure 5 shows that the propofol infusion rate maintains a propofol concentration of 1 μg/ml for 2 h. The total doses, including the loading dose, were 3.7 $mg \cdot kg^{-1} \cdot h^{-1}$ for the child, 2.6 $mg \cdot kg^{-1} \cdot h^{-1}$ for the lean adult, 2.3 $mg \cdot kg^{-1} \cdot h^{-1}$ for the average adult, 1.9 $mg \cdot kg^{-1} \cdot h^{-1}$ for the obese adult, and 1.5 $mg \cdot kg^{-1} \cdot h^{-1}$ for the elderly individual. The context-sensitive half-times for these five individuals are depicted in figure 6. The half-times are nearly the same for the child and the adults but markedly increased for the 80-yr-old subject. Figure 7 depicts the context-sensitive half-times for 100 individuals, calculated with kinetic parameters that were log-normally distributed with the mean values of a 30-yr-old adult with average weight (table 4) and variances as estimated for the full model (table 3). Figure 8 shows the effect of the administration

Table 3. Pharmacokinetic Parameters for the Final Model

Model Parameter	Value	% CV
Cl_1	$\theta_1 \cdot (BW/70)^{\theta_7}$ if age ≤ 60 $\theta_1 \cdot (BW/70)^{\theta_7} - (age - 60) \cdot \theta_{10}$ if age > 60	37.4
Cl_2	$\theta_3 \cdot (BW/70)^{\theta_8} \cdot (1 + ven \cdot \theta_{14}) \cdot (1 + bol \cdot \theta_{16})$	51.9
Cl_3	$\theta_5 \cdot (BW/70)^{\theta_{11}} \cdot (1 + bol \cdot \theta_{18})$	50.9
V_1	$\theta_2 \cdot (BW/70)^{\theta_{12}} \cdot (age/30)^{\theta_{13}} \cdot (1 + bol \cdot \theta_{15})$	40.0
V_2	$\theta_4 \cdot (BW/70)^{\theta_9} \cdot (1 + bol \cdot \theta_{17})$	54.8
V_3	θ_6	46.9

Parameter Estimates	Value	SE
θ_1	1.44 l/min	0.09
θ_2	9.3 l	0.9
θ_3	2.25 l/min	0.31
θ_4	44.2 l	6.1
θ_5	0.92 l/min	0.15
θ_6	266 l	43
θ_7	0.75	0.06
θ_8	0.62	0.09
θ_9	0.61	0.11
θ_{10}	0.045	0.012
θ_{11}	0.55	0.13
θ_{12}	0.71	0.26
θ_{13}	−0.39	0.15
θ_{14}	−0.40	0.10
θ_{15}	1.61	0.36
θ_{16}	2.02	0.41
θ_{17}	0.73	0.23
θ_{18}	−0.48	0.12
Intraindividual variability	17.6%	
MWR	−3.4%	
MAWR	24.9%	

Interindividual and intraindividual variabilities are expressed as % CV, calculated as square roots of the variances of the corresponding η and ϵ. Ven and bol are indicator variables: ven = 1 for venous samples, ven = 0 for arterial samples; bol = 1 for bolus data, bol = 0 for infusion data.

mode. The concentration course after a bolus dose of 100 mg propofol was calculated using the kinetic parameters obtained from bolus and infusion data, respectively. Use of the infusion kinetics leads to an overestimation of the concentration during the first 10 min and an underprediction during the following 4 h.

Discussion

We analyzed a quite unhomogeneous population with different modes of administration (bolus dose and continuous infusion), different sampling sites (venous and arterial), and a wide range of ages and weights. There-

Table 4. Pharmacokinetic Parameters for Five Typical Individuals, Calculated with the Estimates of the Final Model

	Child 5 yr, 20 kg	Adult			Elderly 80 yr, 65 kg
		30 yr, 50 kg	30 yr, 70 kg	30 yr, 110 kg	
Cl_1 (ml · min^{-1} · kg^{-1})	28	22	21	18	8
Cl_2 (ml · min^{-1} · kg^{-1})	52	37	32	27	33
Cl_3 (ml · min^{-1} · kg^{-1})	23	15	13	11	14
V_1 (l/kg)	0.38	0.15	0.13	0.12	0.09
V_2 (l/kg)	1.0	0.7	0.6	0.5	0.6
V_3 (l/kg)	13.3	5.3	3.8	2.4	4.1
V_{dss} (l/kg)	14.7	6.2	4.6	3.1	4.8
$T_{1/2\ \alpha}$ (min)	2.39	1.30	1.33	1.37	1.12
$T_{1/2\ \beta}$ (min)	29.7	27.4	27.0	26.5	34.6
$T_{1/2\ \gamma}$ (min)	760	413	335	259	664

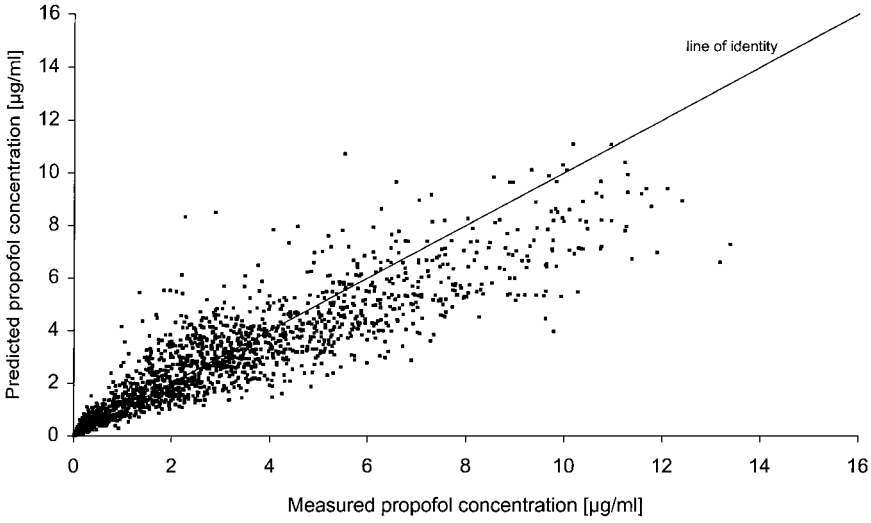

Fig. 3. Plot of the propofol concentrations predicted by the final model *versus* the measured propofol concentrations of the second subset.

fore we had to incorporate additional parameters to describe all effects of covariates on the pharmacokinetics of propofol. The final model was able to describe the pharmacokinetics of the population with sufficient precision, as indicated by the values of MWR and MAWR for both data subsets. A precision of about 25% is typical for pharmacokinetic models.[31–33] The plot of predicted *versus* measured concentrations (fig. 3), however, shows a good correlation for concentrations up to 8 μg/ml, but a lack of fit for higher concentrations in which the model underestimates the measured concentration. Consideration should be given to the fact that the model for intraindividual variability assumes that the error increases with increasing concentrations, but this error should be centered around zero, whereas we observed only a positive deviation (measured > predicted). This underestimation may indicate nonlinear pharmacokinetics of propofol, in the sense that the total body clearance decreases with increasing concentration. Nonlinear pharmacokinetics of propofol have been investigated previously, with controversial results. Coetzee *et al.*[31] and Vuyk *et al.*[32] suggested that propofol may have nonlinear kinetics; Bailey *et al.*[34] and Schnider *et al.*[35] did not find any indication of nonlinearity. It is known that propofol reduces liver blood flow, particularly at high concentrations such as are found shortly after bolus administration.[36] The very high concentrations in our data were achieved with continuous infusion, which

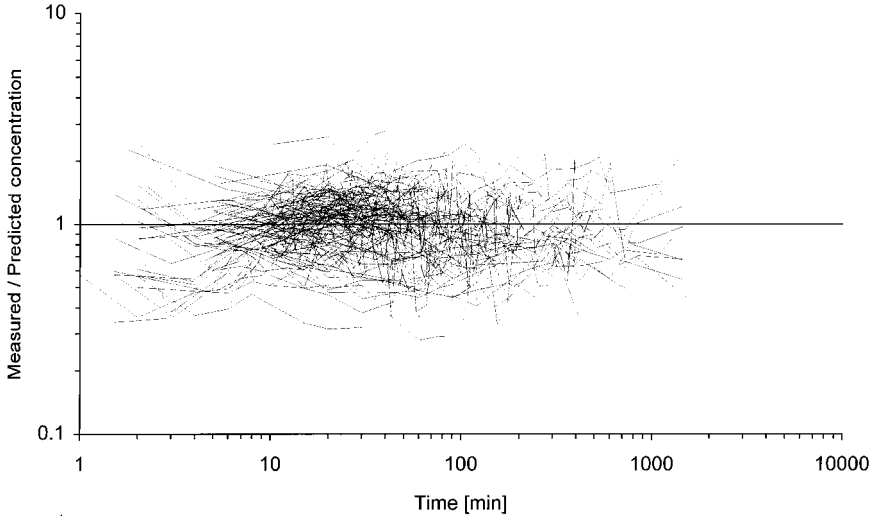

Fig. 4. Ratio of measured to predicted propofol concentrations for the second subset as a function of time. Predictions were calculated with the parameters derived form the first subset.

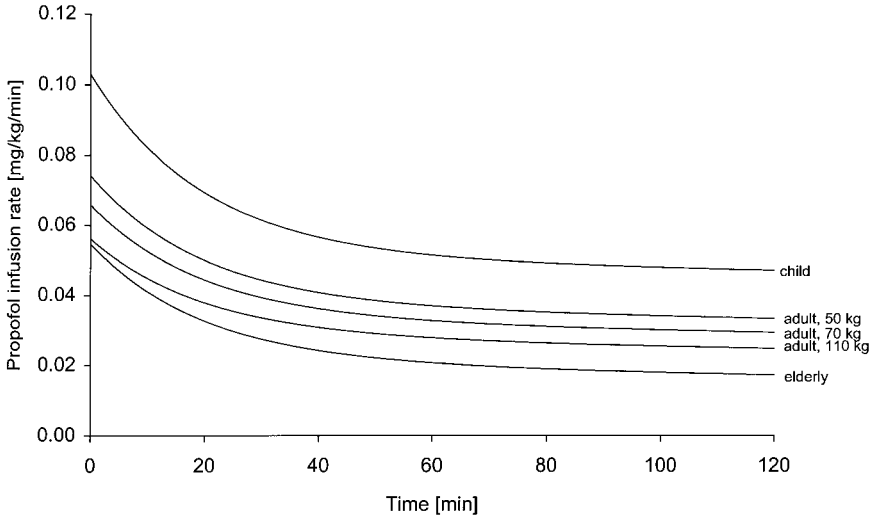

Fig. 5. Propofol infusion rates required to maintain a concentration of 1 μg/ml in a child (20 kg body weight, 5 yr of age), a lean adult (50 kg, 30 yr), an adult of average weight (70 kg, 70 yr), an obese adult (110 kg, 30 yr) and an elderly individual (65 kg, 80 yr). The infusion rates were calculated using the parameters of the final model (table 4).

also may cause a reduced blood flow and therefore a reduction of clearance. One general problem with compartment models is that they assume instantaneous mixing in the central compartment, which is obviously a simplification. Major *et al.* found considerable differences between venous and arterial samples during the first 60 s after administration of a propofol bolus dose, indicating that instantaneous mixing does not occur.[37] Therefore, it is possible that incomplete mixing in case of high infusion rates causes unexpectedly high propofol concentrations.

Whereas there was only a slight effect of the sampling site, the mode of administration (bolus *vs.* infusion) did significantly affect the pharmacokinetics (fig. 8). Similarly, Schnider *et al.* reported an overestimation of the early concentrations after bolus administration, followed by an underprediction using kinetic parameters evaluated from infusion data.[35] A possible reason for this phenomenon may be model misspecification, because the conventional compartment model assumes instantaneous mixing and does not consider recirculation effects. On the other hand, it must be taken into account that the sampling in bolus studies is quite different from that used in infusion studies, in which there are not so many samples in the very early time and therefore less information about the initial distribution process. At least the bolus data that were included in our analysis were characterized by a very long sampling time. There-

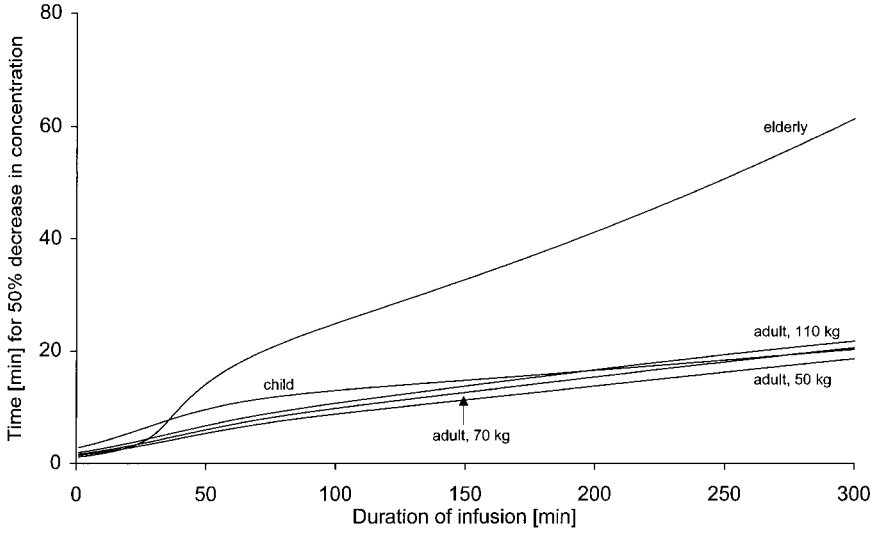

Fig. 6. Time required for a 50% decrease in concentration after continuous infusion of variable length (context-sensitive half-time). Simulations were performed for a child (20 kg body weight, 5 yr of age), a lean adult (50 kg, 30 yr), an adult of average weight (70 kg, 30 yr), an obese adult (110 kg, 30 yr), and an elderly individual (65 kg, 80 yr), based on the final model parameters (table 4).

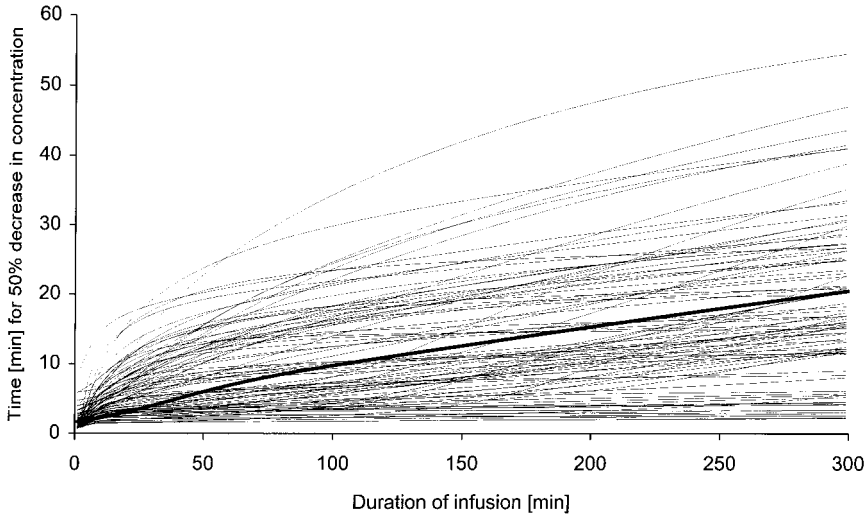

Fig. 7. Simulations showing the interindividual variability of the context-sensitive half-time for a population of 100 individuals using the pharmacokinetic parameters for an adult of 70 kg aged 30 yr (table 4) and the interindividual variances estimated in the study. The bold line depicts the context-sensitive half-time for the typical individual (70 kg body weight, 30 yr of age).

fore, it is quite reasonable that Cl_3 was reduced compared with infusion pharmacokinetics, which means a slowed transfer back from the deep third compartment and in consequence higher concentrations in the terminal phase as shown in figure 8.

In addition, it should be considered that differences in the propofol assays may be a source of intraindividual error. All propofol concentrations were measured with assays based on the same method,[28] but with some modifications. In groups 7 and 8, propofol was analyzed with gas–liquid chromatography rather than high-pressure liquid chromatography, which was used for all other data. Analysis of group 9 used propofol plasma concentrations; the propofol concentrations of the remaining groups were measured in whole blood. Fan *et al.* did not find significant differences between propofol concentrations measured with high-pressure liquid chromatography and gas chromatography, respectively, but the plasma concentrations during infusions were higher than those from whole blood.[38]

The estimates of the pharmacokinetic parameters for an adult as revealed in this study are similar to those found by other investigators,[5,8–11,15] with the exception of V_1, which was smaller in our analysis. The central volume is more difficult to determine than the clearance, because it depends on the mode of administration, the sampling site, and the number of compartments. The very first concentration values after the start of adminis-

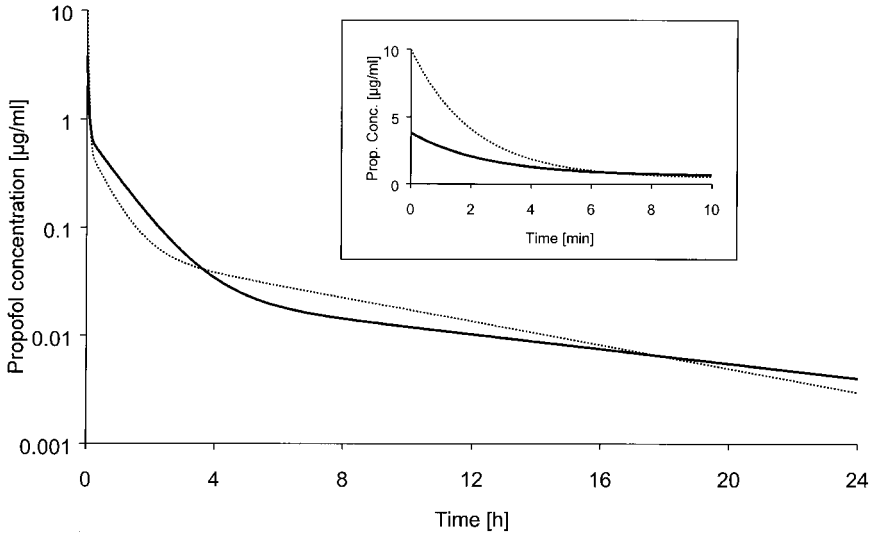

Fig. 8. Concentration course after a propofol bolus of 100 mg, calculated with the pharmacokinetic parameters for infusion (thin dashed line) and bolus administration (bold line). The small picture shows the concentration course for the first 10 min.

tration are essential for the consistent estimation of the central volume. Because we had only few data from the first minutes, and because these were mainly from bolus administration, there might be a model misspecification.

One major aim of the present study was to quantitate the effect of covariates on the pharmacokinetics of propofol. Body weight was obviously the covariate that influenced all parameters with the exception of V_3. Interestingly, the influence of weight was best described by a power function; in most previously published models the pharmacokinetic parameters were weight-proportional.[5,6,21] The combination of children and adults in our data may explain these results, because other authors analyzed more homogenous groups of only adults or children. The power function for weight may therefore describe not only the influence of body weight but also partly the effect of age. This is supported by the fact that for nearly all parameters for which the influence of body weight was modeled as a power function (Cl_1, Cl_2, Cl_3, and V_2), no additional parameters for children were necessary. All estimated exponents of the power functions were smaller than 1, which means that the corresponding parameters were higher for children if normalized for body weight, as reported by other authors.[18,20,21] For the central volume of distribution (V_1), a power function for weight and age revealed the best results. This also means an increase of the weight-normalized V_1 for children. In subjects older than 60 yr, we found a marked linear decrease of the elimination clearance Cl_1 and a slight decrease of V_1, which was best described by a power function with a negative exponent. The reduction of the elimination clearance and V_1 in elderly have also been observed in other studies.[17] Although weight and age are correlated, inclusion of both covariates improved the fit significantly compared with inclusion of only weight or age. Particularly for V_1, simple weight normalization led to a worse fit, but the inclusion of weight and age improved the fit. In several studies on population pharmacokinetics, lean body mass was found to be a significant covariate for pharmacokinetics.[35,39] Unfortunately, we could not model the effect of lean body mass, because we had not the heights of all subjects. Furthermore, a formula for lean body mass of children is not available. For those adults whose heights were known, the individual pharmacokinetic parameters did not correlate better with lean body mass than with body weight. The power function of weight, however, may reflect in part the influence of height, because the absolute dose for an obese adult, for example, is increased compared with an adult of average weight, but the weight-normalized dose is smaller than for an average adult (table 4). Generally, one has to consider that the estimated effects of age are valid only for that range investigated in our study (2–88 yr). For patients older than 90 yr, Cl_1 would become almost zero or negative, and V_1 increases toward infinity the younger the patient is (the effect of body weight on V_1, however, may compensate for this).

For clinical practice, the effects of body weight and age allow the dosing to be adjusted to the individual patient. The different infusion schemes necessary to maintain a propofol concentration of 1 μg/ml in three adults who are thin, of average weight, and obese, an 80-yr-old patient, and a 5-yr-old child of 20 kg body weight are plotted in figure 5. If normalized to weight, the total doses required for a period of 120 min are quite higher for children and smaller for elderly individuals. Because an obese adult needs less than an average adult, simple weight-normalization of the dose (as it is used for example in the common target-controlled infusion pumps) would lead to overdosing for such a patient. To evaluate the effect of covariates on recovery, we estimated the time required for a 50% decrease in propofol concentration after a constant infusion of variable length (fig. 6). This context-sensitive half-time is clearly prolonged in elderly individuals and nearly identical for children and the adults of different weights. It should be emphasized that this prolonged half-time for elderly individuals does occur, although the kinetic parameters were adjusted for age and weight. This means that the adjustment of pharmacokinetics can help to avoid misdosing, but differences with respect to the recovery cannot be overcome.

Even with inclusion of covariates, the interindividual variabilities remained relatively large, indicating a large variance of pharmacokinetics among patients. This leads to a broad range of context-sensitive half-times (fig. 7), which masks the small differences between children and adults but not the differences between adults and elderly. The relatively large interindividual error may be considered a limiting factor for target-controlled infusion and open-loop control of anesthesia, which are based on pharmacokinetic models. Clinical practice, however, has shown that effective and safe anesthesia can be achieved with infusion schemes based on pharmacokinetic models, because titration of the target concentration may help to overcome the problem of interindividual variability of pharmacokinetics and pharmacodynamics.[2–6] The use of population-based pharmacokinetic parameters is likely to further improve the accuracy of target-con-

trolled drug-delivery systems. Moreover, the field for target-controlled infusion may be broadened using our results for application in children and elderly patients.

References

1. Cockshott ID: Propofol pharmacokinetics and metabolism: An overview. Postgrad Med J 1985; 61:45–50

2. Schüttler J, Schwilden H, Stoeckel H: Total intravenous anaesthesia with propofol and alfentanil by computer-assisted infusion. Anaesthesia 1988; 43(suppl):341–5

3. White M, Kenny GN: Intravenous propofol anaesthesia using a computerised infusion system. Anaesthesia 1990; 45:204–9

4. Chaudri S, White M, Kenny GN: Induction of anaesthesia with propofol using a target-controlled infusion system. Anaesthesia 1992; 47:551–3

5. Tackley RM, Lewis GT, Prys-Roberts C, Boaden RW, Dixon J, Harvey JT: Computer controlled infusion of propofol. Br J Anaesth 1989; 62:46–53

6. Marsh B, White M, Morton N, Kenny GN: Pharmacokinetic model driven infusion of propofol in children. Br J Anaesth 1991; 67:41–8

7. Schuttler J, Stoeckel H, Schwilden H: Pharmacokinetic and pharmacodynamic modelling of propofol ("Diprivan") in volunteers and surgical patients. Postgrad Med J 1985; 61(suppl 3):53–4

8. Shafer A, Doze VA, Shafer SL, White PF: Pharmacokinetics and pharmacodynamics of propofol infusions during general anesthesia. ANESTHESIOLOGY 1988; 69(3):348–56

9. Gepts E, Camu F, Cockshott ID, Douglas EJ: Disposition of propofol administered as constant rate intravenous infusions in humans. Anaesth Analg 1987; 66:1256–63

10. Gepts E, Jonckheer K, Maes V, Sonck W, Camu F: Disposition kinetics of propofol during alfentanil anaesthesia. Anaesthesia 1988; 43(suppl):8–13

11. Kay NH, Sear JW, Uppington J, Cockshott ID, Douglas EJ: Disposition of propofol in patients undergoing surgery: A comparison in men and women. Br J Anaesth 1986; 58:1075–9

12. Jacobs JR: Intravenous anesthetic drugs: Infusion pharmacology. Int Anaesthesiol Clin 1991; 29:53–71

13. Gin T, Gregory MA, Chan K, Buckley T, Oh TE: Pharmacokinetics of propofol in women undergoing elective caesarean section. Br J Anaesth 1990; 64:148–53

14. Gill SS, Wright EM, Reilly CS: Pharmacokinetic interaction of propofol and fentanyl: Single bolus injection study. Br J Anaesth 1990; 65:760–5

15. Cockshott ID, Briggs LP, Douglas EJ, White M: Pharmacokinetics of propofol in female patients: Studies using single bolus injection. Br J Anaesth 1987; 59:1103–10

16. Morgan DJ, Campbell GA, Crankshaw DP: Pharmacokinetics of propofol when given by intravenous infusion. Br J Clin Pharmacol 1990; 30:144–8

17. Kirkpatrick T, Cockshott ID, Douglas EJ, Nimmo WS: Pharmacokinetics of propofol (diprivan) in elderly patients. Br J Anaesth 1988; 60:146–50

18. Saint-Maurice C, Cockshott ID, Douglas EJ, Richard MO: Pharmacokinetics of propofol in young children after a single dose. Br J Anaesth 1989; 63:667–70

19. Vandermeersch E, van Hemelrijck J, Byttebier G, van Aken H: Pharmacokinetics of propofol during continuous infusion for pediatric anesthesia. Acta Anaesthesiol Belg 1989; 40:161–5

20. Jones RD, Chan K, Andrew LJ: Pharmacokinetics of propofol in children. Br J Anaesth 1990; 65:661–7

21. Kataria BK, Ved SA, Nicodemus HF, Hoy GR, Lea D, Dubois MY, Mandema JW, Shafer SL: The pharmacokinetics of propofol in children using three different data analysis approaches. ANESTHESIOLOGY 1994; 80:104–22

22. Servin F, Desmonts JM, Haberer JP, Cockshott ID, Plummer GF, Farinotti R: Pharmacokinetics and protein binding of propofol in patients with cirrhosis. ANESTHESIOLOGY 1988; 69:887–91

23. Kirvela M, Olkkola KT, Rosenberg PH, Yli-Hankala A, Salmela K, Lindgren L: Pharmacokinetics of propofol and haemodynamic changes during induction of anaesthesia in uraemic patients. Br J Anaesth 1992; 68:178–82

24. Albanese J, Martin C, Lacarelle B, Saux P, Durand A, Gouin F: Pharmacokinetics of long-term propofol infusion used for sedation in ICU patients. ANESTHESIOLOGY1990; 73:214–7

25. Bailie GR, Cockshott ID, Douglas EJ, Bowles BJ: Pharmacokinetics of propofol during and after long-term continuous infusion for maintenance of sedation in ICU patients. Br J Anaesth 1992; 68:486–91

26. Frenkel C, Schüttler J, Ihmsen H, Heye H, Rommelsheim K: Pharmacokinetics and pharmacodynamics of propofol/alfentanil infusions for sedation in ICU patients. Intensive Care Med 1995; 21:981–8

27. Smith C, McEwan AI, Jhaveri R, Wilkinson M, Goodman D, Smith LR, Canada AT, Glass PS: The interaction of fentanyl on the Cp50 of propofol for loss of consciousness and skin incision. Anesthesiology 1994; 81:820–8

28. Plummer GF: Improved method for the determination of propofol in blood by high performance liquid chromatography with fluorescence detection. J Chromatogr 1987; 421:171–6

29. Beal SL, Sheiner LB: NONMEM User's Guide. San Francisco, University of California San Francisco, 1998

30. Hughes MA, Glass PS, Jacobs JR: Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs. ANESTHESIOLOGY 1992; 76:334–41

31. Coetzee JF, Glen JB, Wium CA, Boshoff L: Pharmacokinetic model selection for target controlled infusions of propofol. Assessment of three parameter sets. ANESTHESIOLOGY 1995; 82:1328–45

32. Vuyk J, Engbers FHM, Burm AGL, Vletter AA, Bovill JG: Performance of computer-controlled infusion of propofol: An evaluation of five pharmacokinetic parameter sets. Anesth Analg 1995; 81:1275–82

33. Fechner J, Albrecht S, Ihmsen H, Knoll R, Schwilden H, Schuttler J: Predictability and precision of "target-controlled infusion" (TCI) of propofol with the "Disoprifusor TCI" system. Anaesthesist 1998; 47:663–8

34. Bailey JM, Mora CT, Shafer SL: Pharmacokinetics of propofol in adult patients undergoing coronary revascularization. ANESTHESIOLOGY 1996; 84:1288–97

35. Schnider TW, Minto CF, Gambus PL, Andresen C, Goodale DB, Shafer SL, Youngs EJ: The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. ANESTHESIOLOGY 1998; 88:1170–82

36. Lange H, Stephan H, Rieke H, Kellermann M, Sonntag H, Bircher J: Hepatic and extrahepatic disposition of propofol in patients undergoing coronary bypass surgery. Br J Anaesth 1990; 64:563–70

37. Major E, Aun C, Yate PM, Savege M, Verniquet AJW, Adam H, Douglas EJ: Influence of sample site on blood concentrations of ICI 35868. Br J Anaesth 1983; 55:371–5

38. Fan SZ, Yu HY, Chen YL, Liu CC: Propofol concentration monitoring in plasma or whole blood by gas chromatography and high-performance liquid chromatography. Anest Analg 1995; 81:175–8

39. Minto CF, Schnider TW, Egan TD, Youngs E, Lemmens HJM, Gambus PL, Billard V, Hoke, JF, Moore KHP, Hermann DJ, Muir KT, Mandema JW, Shafer SL: Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. ANESTHESIOLOGY 1997; 86:10–23

Appendix

Participants of the multicenter study: Ian D. Cockshott, Ph.D., Zeneca Pharmaceuticals, Macclesfield, United Kingdom; Peter S. Glass, M.D., Professor, Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina; Jürgen Schüttler, M.D., Professor and Chairman, Department of Anesthesiology, Friedrich-Alexander-University of Erlangen-Nuremberg, Erlangen, Germany; Steven L. Shafer, M.D., Professor, Department of Anesthesiology, Stanford University School of Medicine, Palo Alto, California; and Martin White, Ph.D., Staff Anesthesiologist, Department of Anaesthesiology, Academisch Ziekenhuis Leiden, Leiden, The Netherlands.