Population pharmacokinetics of propofol in Chinese patients

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ABSTRACT

AIM: To analyze population pharmacokinetics of propofol in Chinese surgical patients using a nonlinear mixed-effect model (NONMEM) program and to quantitate the effects of covariance of gender, age, and body weight. **METHODS:** The population pharmacokinetics of propofol was investigated in 76 selective surgical patients (37 males and 39 females aged 19-77 a, weighing 39-86 kg). A total of 1439 blood samples were analyzed using NONMEM (NONMEM Project Group, University of California, San Francisco, CA). Interindividual variability was estimated for clearances and distribution volumes. The effects of age, body weight, and gender were investigated. **RESULTS:** The pharmacokinetics of propofol in Chinese patients was best described by a three-compartment pharmacokinetic model. Body weight was found to be a significant factor for the elimination clearance, the two inter-compartmental clearances, and the volume of the central compartment. The volumes of the shallow peripheral compartment and deep peripheral compartment remain constant for all individuals. The estimates of these parameters for a 60-kg adult were 1.56 L/min, 0.737 L/min, 0.360 L/min, 12.1 L, 43 L, and 213 L, respectively. For old patients, the elimination clearance and volume of the central compartment decreased. **CONCLUSION:** The pharmacokinetics of propofol in Chinese patients can be well described by a standard three-compartment pharmacokinetic model. Inclusion of age and body weight as covariances significantly improved the model. Adjusting pharmacokinetics to the individual patients should improve the precision of target-controlled infusion system.

INTRODUCTION

Since its introduction into China at the beginning of nineties of last century, propofol has become increasingly popular for the induction and maintenance of general anesthesia. This popularity stems from both the pharmacokinetic and pharmacodynamic properties of propofol. 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

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infusion system for propofol (Diprifusor-TCI, Zeneca Pharmaceuticals, Macclesfield, UK) is now available in China and it has begun to be used clinically in large hospitals. Such systems require appropriate pharmacokinetic data to ensure that the desired concentration is achieved. During the past 15 years, the pharmacokinetics of propofol has been well studied in different population[7-15]. Recently Schüttler and Ihmsen[16] performed a population pharmacokinetic analysis with data from five research groups. The aims of this study were to estimate the pharmacokinetics of propofol with respect to the covariances of gender, age, and body weight and to evaluate the inter- and intra-individual variability in Chinese patients.

SUBJECTS AND METHODS

Subjects and samples Thirty-seven male and thirty-nine female ASA grade I-III patients with no severe cardiovascular, hepatic, renal, hematological, or metabolic disorder, aged 19-77 a (49±15), weighing 39-86 kg (61±11) were studied (Tab 1). The patients were undergoing intra-abdominal (69), orthopedic (2), nose (2), and other (3) surgery under total intravenous anesthesia (TIVA). The study was approved by the hospital Ethics Committee and signed consent was obtained from the patients.

All patients were premedicated with 0.1 g phenobarbital and 0.3 mg scopolamine intramuscularly, 1 h before operation. In the operating room, one iv cannula was inserted into a large forearm vein for the infusion of propofol only and another in the contralateral arm for the transfusion of fentanyl and vecuronium. A radial artery was cannulated for the continuous measurement of arterial blood pressure and the collection of blood samples for determination of blood propofol concentrations. The ECG, arterial pressure, heart rate, end-tidal carbon dioxide partial pressure and oxyhenoglobin saturation (Spo_2) were monitored continuously throughout the study.

Before induction of anesthesia, patients received crystalloid solution (Ringer' s solution) 20 mL/kg body weight. With the patients breathing 100 % oxygen, anesthesia was induced by a manually controlled infusion (Graseby 3500 pump, Graseby Medical, Watford, UK) with a bolus dose of propofol (Disoprivan or Diprivan; Zeneca Pharmaceuticals, Macclesfield, UK) 1-2.5 mg/kg (2.0±0.4) for 0.5-4 min (2.0±0.8) followed by fixed infusion rate of 3-8 mg· kg^{-1}· h^{-1} (6.0±1.0) that was maintained constant until skin closure. The duration of infusion ranged from 58.5 to 380 min (175±62) and total dose from 400.93 to 3308.42 mg (1285±483). When consciousness was lost, vecuronium 0.1 mg/kg was given iv and the trachea was intubated. The lungs of the patients were then ventilated with oxygen in air (1:2) and the ventilation was adjusted to maintain the end-tidal carbon dioxide partial pressure between 4-4.5 kPa. In addition, patients received a bolus dose of fentanyl 3 μg/kg for 30 s followed by a continuous infusion (Graseby 3100 pump, Medical, Watford, UK) of fenta-

Tab 1. Demographic data for study patients. *n*=76. Data are expressed as range and mean±SD.

Demographic characteristics	All patients
Administration mode	Bolus and continuous infusion
Number of individual	76 Patients
Number of samples	1439
Sampling side	Arterial
Age/a	19 - 77 (49±15)
Body weight/ kg	39-86 (61±11)
Gender (M:F)	37:39
Type of surgery	Intraabdominal (69) others (7)
Duration of propofol administration/min	58.5-380 (175±62)
Bolus dose of propofol/(mg· kg^{-1})	1-2.5 (2.0±0.4)
Bolus time of propofol/min	0.5-4 (2.0±0.8)
Maintenance rate of propofol/mg· kg^{-1}· h^{-1}	3-8 (6.6±1.0)
Duration of infusion of propofol/min	58.5-380 (175±62)
Total dose of propofol/mg	401.0-3308.4 (1285±483)
Total sampling time/min	181.5-1506.0 (1268±257)

nyl 2 μg· kg^{-1}· h^{-1} for 30 min and 1.5 μg· kg^{-1}· h^{-1} from 31 to 150 min and 1 μg· kg^{-1}· h^{-1} iv until 30 min before skin closure. Post-operative pain relief was provided with morphine or tramadol by patient control analgesia (PCA) for 48 h postoperatively.

Blood (5 mL) was taken from an indwelling radial arterial cannula prior to the infusion of propofol and then at 1.5-120 min intervals until the end of the infusion. Arterial blood was also collected post infusion. The total sampling time ranged from 181.50 to 1506.00 min (1268±257). All samples were collected in heparinized tubes and centrifuged within 30 min after collection. The plasma was transferred to polypropylene tubes and frozen at -20 °C until assay. Propofol concentrations in plasma were measured within 14 weeks by high-pressure liquid chromatography with fluorescence detection[17]. The linear ranges of propofol detected were 16-10000 mg/L and the lower limit of detection was approximately propofol 2 mg/L plasma. The coefficient of variation of the HPLC method did not exceed 10 % in the concentration range encountered in this study. Drug metabolites and commonly coadministered drugs did not affect the assay results. We analyzed 1439 blood samples from 76 individuals.

Pharmacokinetic analysis The population pharmacokinetics analyses were performed using NONMEM program (version V, Lever 1.1)[18]. 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 covariances such as body weight, age, and gender.

Pharmacokinetic model Pharmacokinetics was assumed to be linear with 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 covariances, additional parameters were successively included in the model.

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 lognormal model:

$$\ln q_i = \ln \bar{q} + h_i \quad (1)$$

in which q_i is the individual value of the parameter q, $\bar{q}$ is the mean population value of this parameter, and h_i is a random variable with mean zero and variance w^2.

The intraindividual variability describes the residual errors resulting from assay errors, time-recording inaccuracies, model misspecification, and so forth. We used the exponential model:

$$\ln C_{ij} = \ln CP_{ij} + e_{ij} \quad (2)$$

in which C_{ij} is jth measured concentration of ith individual and CP_{ij} is the corresponding predicted concentration. Again, e_{ij} is random variable with mean zero and variance s^2. NONMEM estimates the mean pharmacokinetic parameters of the population, the interindividual variances e^2, and the intraindividual variances s^2, including estimates of the standard errors and correlation coefficients for all parameters.

Data analysis Firstly, individual Bayesian estimates of pharmacokinetic parameters of each individual were obtained using a three-compartment model without any covariances. The individual estimated parameters were plotted independently against each covariance (age, body weight, and gender) to identify the influence of the covariances and the shape of the curve parameter-covariance relationships. Subsequently, we performed a population analysis of all data, beginning with a simple model without any covariances and successively incorporating additional parameters. The effects of covariances were tested for statistical significance using the NONMEM objective function (which is -2 lg L_{max}) and the standard errors of the additional parameters. An additional parameter was included in the model if the decrease of the objective function was 3.84 (P<0.05) and the 95 % confidence interval of the additional parameter (mean± 2SEM) did not include zero (null hypothesis value). In addition, the inter- and intra-individual variabilities should decrease as an additional covariance 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. As used previously[10], we described the goodness of fit using the weighted residual (WR) and the absolute weighted-residual (AWR) for each sample:

$$WR_{ij} = \frac{C_{ij} - CP_{ij}}{CP_{ij}} \quad AWR_{ij} = \frac{\left|C_{ij} - CP_{ij}\right|}{CP_{ij}} \quad (4)$$

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 weighted residual (MWR) calculated as the median WR of all the observations, is a measure of bias. The median absolute weighted residual (MAWR) calculated as the median of absolute value of the WR, is a measure of inaccuracy of the fit. Interindividual and intraindividual variabilities were expressed as % CV, calculated as square roots of the variances of the corresponding *h* and *e*.

Simulations To illustrate the pharmacokinetic findings, simulations were carried out. Using the estimated parameters of the final model we calculated the time for a 50 % decrease in concentration after continuous infusion (context-sensitive half-time)[19]. To show the effect of age on dosing we computed the infusion rates necessary to maintain a defined concentration. Both simulations were performed with Microsoft Excel 97.

RESULTS

The individual estimates revealed an influence of body weight and age on all clearances and V_1. V_2 and V_3 were almost constant in all subjects. As an example, the individual estimates of CL_1 were found to be a function of body weight. The shapes of the relationship curve suggested that the body weight should not be incorporated into the model in a linear fashion, but should be incorporated as a power function with a positive exponent smaller than one (Fig 1). In the population analysis, these effects were modeled by incorporating additional parameters. The results of this procedure are shown in Tab 2. In which OBJ denotes the value of objective function (-2 lg L_{max}), describing the goodness of fit. As mentioned previously, a decrease of -2 lg L_{max} means an improvement of fit. Significant effects were retained in regression subsequent procedure. At the end the pharmacokinetic parameters of the final model were demonstrated in Tab 3.

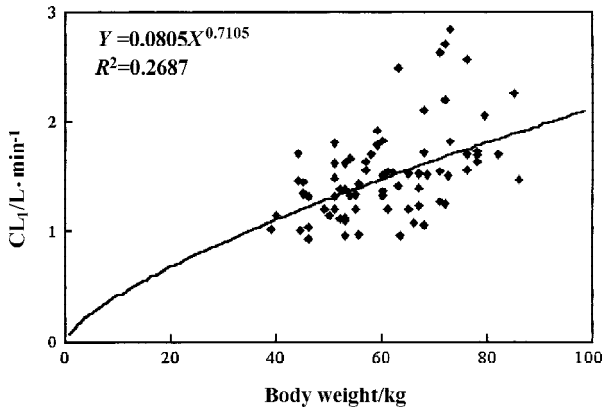

Fig 1. Plot of the individual Bayesian estimates of the elimination clearance (CL_1) *versus* body weight for a three-compartment model without any covariances. A power function (line) yielded the best results in regression analysis.

Number of compartments Initially, a simple two-compartment model was assumed, however, the resulting fit was rather poor. A three-compartment model markedly improved the fit (Tab 2), because of the long sampling period in this study.

Influence of covariances The population parameter estimates arising from the basic pharmacokinetic structural model are 1.62 L/min for CL_1, 0.752 L/min for CL_2, 0.343 for CL_3, 12.0 L for V_1, 43.7 L for V_2, and 194 L for V_3. As suggested from the individual estimates, we found effects of body weight on CL_1, CL_2, CL_3, and V_1. The influence was best modeled by a power function. As an example, Tab 2 shows the results for a simple weight normalization of CL_1 (model 3) and the power function (model 4). This means that the weight-normalized parameter (parameter divided by the body weight) increases with decreasing weight, while V_2 and V_3 did not vary with age and body weight. For older patients the elimination clearance and the volume of the central compartment decreased with age if divided by body weight. This led to a worse fit if CL_1 and V_1 were modeled by weight proportionally (model 6). Inclusion of age and weight as a power function, however, improved the model (model 7). No influence of gender could be found for the analyzed subjects.

The estimates of all parameters and their standard errors, interindividual and intraindividual variabilities were summarized (Tab 3). Fixing of any additional parameter to zero led to a significant decrease in goodness of fit, indicating that all additional parameters were required. The weighted residuals calculated with kinetic parameters of the final model were median values of 5.57 % (MWR) and 26.91 % (MAWR). The predicted propofol concentration calculated with the parameters derived from the final model was plotted against the measured propofol concentrations (Fig 2). The weighted residual was calculated for each sample and plotted against the corresponding predicted concentration (Fig 3)

Simulations We performed several simulations for three types of individuals (average adult, obese adult and elderly) using the estimated pharmacokinetic pa-

Tab 2. Results of the regression procedure.

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
θ_1	0.0642	1.62	1.58	1.58	1.59	1.56	1.55	1.56
θ_2	0.0361	12	11.6	11.7	11.4	14.1	14.5	12.1
θ_3	0.0039	0.343	0.366	0.367	0.369	0.361	0.357	0.360
θ_4	22.6	194	199	208	210	218	212	213
θ_5	0	0.752	0.769	0.777	0.795	0.737	0.737	0.737
θ_6	0	43.7	41.6	42	41.7	43.8	43.1	43.0
θ_7	0	0	0.676	0.794	0.858	0.861	0.86	0.899
θ_8	0	0	0	1.03	1.17	1.12	1.1	1.15
θ_9	0	0	0	0	0.944	0.347	0.364	0.483
θ_{10}	0	0	0	0	0	-0.45	-0.86	-0.98
θ_{11}	0	0	0	0	0	0	-0.108	-0.154
θ_{12}	0	0	0	0	0	0	0	-1.35
OBJ	-518.6	-1132.2	-1189.8	-1213.2	-1224.4	-1240.4	-1246.5	-1284.1
ΔOBJ	0	613.67	57.602	23.377	11.206	15	6.145	37.574
MWR (%)	-7.53	9.5	6.65	6.08	6.17	3.29	3.19	5.57
MAWR (%)	28.6	29.56	28.69	27.83	28.09	26	25.5	26.91

(1) Two-compartment model, (2) three-compartment model, (3) $TVCL_1=\theta_1\cdot(BW/60)^{\theta_7}$, (4) $TVCL_2=\theta_3\cdot(BW/60)^{\theta_8}$, (5) $TVCL_3=\theta_5\cdot(BW/60)^{\theta_9}$, (6) $TVCL_1=\theta_2\cdot(BW/60)^{\theta_{10}}$, (7) $TVCL=\theta_1\cdot(BW/60)^{\theta_7}\cdot(AGE/50)^{\theta_{11}}$, (8) $TVV_1=\theta_2\cdot(BW/60)^{\theta_{10}}\cdot(AGE/50)^{\theta_{12}}$. θ_1, θ_2, θ_3, θ_4, θ_5, and θ_6 are structural parameters of three-compartment model. θ_1 stands for CL_1, θ_2 for V_1, θ_3 for CL_3, θ_4 for V_3, θ_5 for CL_2, and θ_6 for V_2, respectively, MWR=median weighted residual, MAWR=median absolute weighted residual. OBJ is the value of the objective function ($-2\lg L_{max}$), ΔOBJ is the difference of objective function between full regression model and restricted regression model.

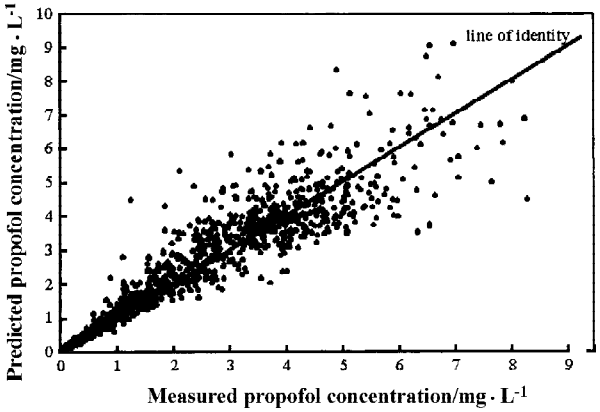

Fig 2. Scatter plot of propofol concentrations predicted by the full model *versus* the measured propofol concentrations.

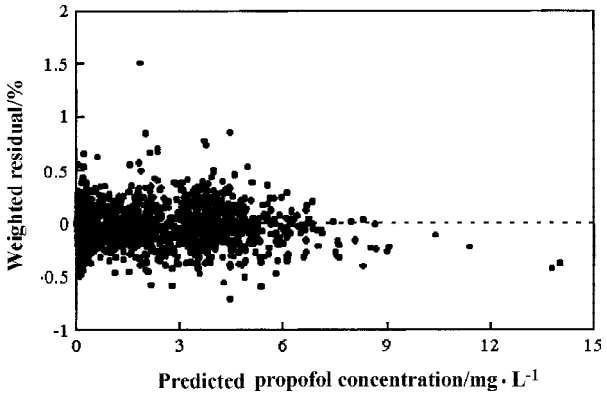

Fig 3. Weighted residual (%) against the predicted propofol concentration (mg/L).

rameters of the final model (Tab 4). The propofol infusion rates necessary to maintain a propofol concentration of 1 mg/L for 2 h were calculated and depicted against the time for the three types of individuals (Fig 4). The total doses, including the loading dose, were 2.7 $mg\cdot kg^{-1}\cdot h^{-1}$ for the average adult, 2.1 $mg\cdot kg^{-1}\cdot h^{-1}$ for the obese adult and 1.4 $mg\cdot kg^{-1}\cdot h^{-1}$ for the elderly individual. The context-sensitive half-times of the three types of individuals were plotted against the different infusion times (Fig 5). The half-time was nearly the same for the first two types of adults, but markedly increased for the 70-year-old subject.

DISCUSSION

We have analyzed Chinese patients with a wide range of ages and weights. In order to describe the effects of all the covariances on the pharmacokinetics of propofol, we have incorporated additional parameters.

Tab 3A. Pharmacokinetic parameters for the final model (1).

Model parameter	Value	CV/%
CL_1	$\theta_1 \cdot (BW/60)^{\theta_7} \cdot (AGE/50)^{\theta_{11}}$	24.5
V_1	$\theta_2 \cdot (BW/60)^{\theta_{10}} \cdot (AGE/50)^{\theta_{12}}$	27.4
CL_2	$\theta_5 \cdot (BW/60)^{\theta_9}$	45.5
V_2	θ_6	62.8
CL_3	$\theta_3 \cdot (BW/60)^{\theta_8}$	30.8
V_3	θ_4	27.7

Tab 3B. Pharmacokinetic parameters for the final model (2).

Parameter estimates	Value	SEM
θ_1	1.56 L/min	0.0658
θ_2	12.1 L	2.08
θ_3	0.360 L/min	0.0276
θ_4	213 L	24.5
θ_5	0.737 L/min	0.0612
θ_6	43 L	4.45
θ_7	0.899	0.154
θ_8	1.15	0.306
θ_9	0.483	0.477
θ_{10}	-0.98	0.567
θ_{11}	-0.514	0.0627
θ_{12}	-1.35	0.189
Intraindividual variability	26.3 %	
MWR	5.57 %	
MAWR	26.91 %	

Interindividual and intraindividual variabilities are expressed as % CV, calculated as square roots of the variance of the corresponding *h* and *e*.

Tab 4. Pharmacokinetic parameters for three typical individuals, calculated with the estimates of the final model.

	Adult		Elderly
	40 a, 60 kg	40 a, 80 kg	70 a, 50 kg
CL_1(mL· min^{-1}· kg^{-1})	29.2	28.3	21.9
CL_2(mL· min^{-1}· kg^{-1})	12.3	10.6	12.3
CL_3(mL· min^{-1}· kg^{-1})	6.0	6.3	6.0
V_1 (L/kg)	0.273	0.154	0.128
V_2 (L/kg)	0.717	0.538	0.717
V_3 (L/kg)	3.550	2.663	3.550
V_{dss} (L/kg)	4.539	3.354	4.395
$T_{1/2\alpha}$ (min)	2.95	2.36	3.49
$T_{1/2\beta}$ (min)	47.8	34.9	42.6
$T_{1/2\gamma}$ (min)	485	382	518

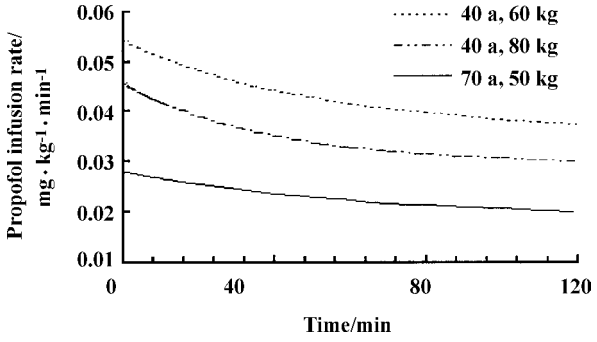

Fig 4. Propofol infusion rates required maintaining a concentration of 1 mg/L in an adult of average weight (40 a, 60 kg), an obese adult (40 a, 80 kg), and an elderly individual (70 a, 50 kg). The infusion rates were calculated using the parameters of final model (Tab 4).

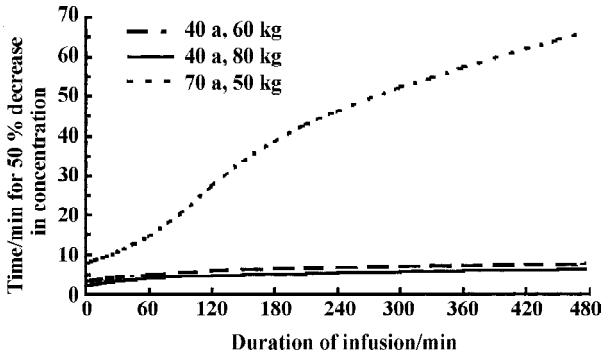

Fig 5. Time required for a 50 % decrease in concentration after variable duration of continuous infusion (context-sensitive half-time). Simulations were performed for an adult of average weight (40 a, 60 kg), an obese adult (40 a, 80 kg), and an elderly individual (70 a, 50 kg), based on the final model parameters (Tab 4).

The final model is able to describe the pharmacokinetics of the population with sufficient precision, as indicated by the values of MWR and MAWR for all data. The plot of predicted *versus* measured concentrations (Fig 2) shows a good fit up to the highest concentration in our data achieved with continuous infusion, which indicates that within the clinically relevant range, the pharmacokinetics of propofol are linear for clinically relevant infusion rate. Nonlinear pharmacokinetics of propofol have been investigated previously, with controversial results. Evidence for nonlinearity was discussed recently by Coetzee *et al*[20], Vuyk *et al*[21], and Schüttler *et al*[16]; while Bailey *et al*[22] and Schnider *et al*[23] found no indication of nonlinearity. A linear relationship between concentration at steady state and infusion rate was also found in patients during regional

anesthesia[9]. It is known that propofol reduces the liver blood flow, particularly at high concentrations such as in cases found shortly after bolus administration[24]. We also know that an induction bolus dose has a statistically significantly different kinetic profile than infusion and the concentration measurements after the bolus dose are significantly underpredicated by the parameters obtained from the infusion data[16,23]. But its effect in predicting a measured concentration is small compared with the overall pharmacokinetic variability of propofol among different patients.

The estimates of the pharmacokinetic parameters for an adult as revealed in this study were similar to those found by other investigators[5,8,13-16]. One major aim of the present study was to quantitate the effect of covariances on pharmacokinetics of propofol. Body weight was obviously the covariance that influenced all parameters with the exception of V_2 and V_3. The influence of weight is best described by a power function; in most previously published models, the pharmacokinetic parameters were weight-proportional[5,6,10]. The result are based on analysis of rather homogenous groups of patients, including, for example, only average 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, which 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_1). For the central volume of distribution (V_1), a power function for weight and age revealed the best results. In older subjects, we found a marked decrease in the elimination clearance CL_1 and V_1, which is best described by a power function with a negative exponent[9,16]. Although weight and age are irrelative to each other (r=0.028), inclusion of both covariances improved the fit significantly compared with inclusion of only weight or age. Particularly for V_1, simple weight normalization led to a worse fit.

For clinical practice, the knowledge of 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 mg/L in three individuals of an average adult, an obese adult, and an old patient were plotted (Fig 4). If normalized to weight, the total doses required for a period of 120 min are higher for an average adult and smaller for an obese adult. But for elderly patients, the total dose was clearly smaller than younger patients, as reported by SchÜttler *et al*[16]. Because an obese adult needs less than an average adult, simple weight-normalization of the dose (as it is used in the common target-controlled infusion pumps) would lead to overdosing for such a patient. In clinical practice, the propofol dosing in elderly patients should be reduced for both pharmacodynamic and pharmacokinetic reasons, because elderly patients are more sensitive to hypnotic and EEG effects of propofol than younger persons[25]. To evaluate the effect of covariances on recovery, we estimated the time required for a 50 % decrease in propofol concentration after a constant infusion of variable length (Fig 5). This context-sensitive half-time is clearly prolonged in elderly individuals but is nearly identical for adults of different weights, similar to that reported by Schüttler *et al*[16]. It should be emphasized that this prolonged half-time does occur, although the kinetic parameters were adjusted for age and weight. This means that the adjustment of pharmacokinetics can help to avoid misdoing, but difference with respect to the recovery cannot be overcome if we have not incorporated the pharmacodynamic factors.

Even with the inclusion of covariances, the interindividual variabilities remained relatively large, indicating a large variance of pharmacokinetics among patients. 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 these population-based pharmacokinetic parameters may help to further improve the accuracy of target-controlled drug-delivery system and promote the application of such system in clinical practice.

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