

## The Influence of Method of Administration and Covariates on the Pharmacokinetics of Propofol in Adult Volunteers

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**Background:** Unresolved issues with propofol include whether the pharmacokinetics are linear with dose, are influenced by method of administration (bolus *vs.* infusion), or are influenced by age. Recently, a new formulation of propofol emulsion, containing disodium edetate (EDTA), was introduced in the United States. Addition of EDTA was found by the

manufacturer to significantly reduce bacterial growth. This study investigated the influences of method of administration, infusion rate, patient covariates, and EDTA on the pharmacokinetics of propofol.

**Methods:** Twenty-four healthy volunteers aged 26–81 yr were given a bolus dose of propofol, followed 1 h later by a 60-min infusion. Each volunteer was randomly assigned to an infusion rate of 25, 50, 100, or 200  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . Each volunteer was studied twice under otherwise identical circumstances: once receiving propofol without EDTA and once receiving propofol with EDTA. The influence of the method of administration and of the volunteer covariates was explored by fitting a three-compartment mamillary model to the data. The influence of EDTA was investigated by direct comparison of the measured concentrations in both sessions.

**Results:** The concentrations of propofol with and without EDTA were not significantly different. The concentration measurements after the bolus dose were significantly underpredicted by the parameters obtained just from the infusion data. The kinetics of propofol were linear within the infusion range of 25–200  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . Age was a significant covariate for Volume<sub>2</sub> and Clearance<sub>2</sub>, as were weight, height, and lean body mass for the metabolic clearance.

**Conclusions:** These results demonstrate that method of administration (bolus *vs.* infusion), but not EDTA, influences the pharmacokinetics of propofol. Within the clinically relevant range, the kinetics of propofol during infusions are linear regarding infusion rate. (Key words: Age; EDTA; linearity; population.)

THE pharmacokinetics of propofol have been widely studied and reported.<sup>1–7</sup> An unresolved issue in these reports is whether the pharmacokinetics of propofol change with dose and method of administration. The clearance of drugs with hepatic extraction ratios approaching 1 is limited by blood flow in the liver. For drugs with flow-dependent clearance, such as propofol, changes in blood flow in the liver cause proportional changes in clearance. Most anesthetic agents, including propofol, reduce blood flow in the liver. It is probable, *a priori*, that propofol changes its own clearance. This has been found in dogs<sup>8</sup> but has not been reported

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in humans, although there have been some suggestive studies.<sup>9</sup>

The influence of age on propofol pharmacokinetics remains unresolved. Several studies, including prior work from our laboratory,<sup>2,10</sup> have suggested that the pharmacokinetics of propofol are age-dependent. Other investigators have not found an effect of age.<sup>1,4,5,7</sup> One possible explanation for the differences in results in prior studies might be the influence of dose, the effect of age possibly being limited to higher or lower doses of propofol.

Between June 1990 and February 1993, the Centers for Disease Control and Prevention conducted investigations at seven hospitals because of unusual outbreaks of bloodstream infections, surgical site infections, and acute febrile episodes after surgical procedures. Only exposure to Diprivan<sup>®</sup> (propofol in a lipid emulsion) was significantly associated with the postoperative complications at all investigated hospitals.<sup>11</sup> The lipid vehicle of Diprivan supports rapid bacterial growth at room temperature.<sup>12-15</sup> To reduce the rate of infection, Zeneca Pharmaceuticals Group (Wilmington, DE), the manufacturer of propofol, issued new guidelines for aseptic handling of propofol. These guidelines reduced but did not eliminate the incidence of infection related to propofol emulsion. Zeneca found that the addition of disodium edetate (EDTA) to the formulation of propofol emulsion significantly reduced the extent to which bacterial growth was supported. Zeneca has received no reports of infection or fever related to administration of propofol in the United States since the release of a new propofol formulation with EDTA in July 1996. The influence of EDTA on the pharmacokinetics of propofol has not been reported, and the Food and Drug Administration required this investigation before release of the new formulation of propofol.

The purpose of this study was to (1) examine the influence of method of administration (bolus *vs.* infusion) and dose (infusion rate) on the pharmacokinetics of propofol; (2) examine the influence of age, height, weight, and gender on the pharmacokinetics of propofol using a population approach; and (3) study the influence of EDTA on the pharmacokinetics of propofol. The null hypotheses were that EDTA, method of administration, dose, age, height, weight, gender, and EDTA do not influence the pharmacokinetics of propofol.

## Methods

### Study Design

After the study was approved by the Institutional Review Board and after giving written informed consent, 25 American Society of Anesthesiologists status I and II volunteers were enrolled in this study. One volunteer dropped out of the study before completion because of depression and was not included in the analysis. The study design was a randomized, double-blind, age-stratified, two-period, crossover trial. The volunteers were stratified into three age groups—18–34 yr, 35–65 yr, and >65 yr—of eight volunteers each. Each volunteer was studied twice, receiving (in a randomized, double-blind, crossover fashion) either propofol without EDTA (the commercially available formulation of Diprivan before July 1996) or propofol with EDTA (the commercially available formulation of Diprivan in the United States after July 1996) in each study session. All volunteers received an initial bolus dose over  $\approx 20$  s of either 2.0 mg/kg for volunteers aged  $\leq 65$  yr or 1.0 mg/kg for volunteers aged >65 yr, followed 1 h later by an infusion administered over 60 min. The infusion rate was assigned according to a nonblinded, randomized design to 25, 50, 100, or 200  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , with two volunteers in each age group assigned to each infusion rate.

### Acquisition, Handling, and Processing of Samples

Propofol was administered *via* an 18-gauge catheter inserted into a forearm vein. A 20-gauge catheter was inserted into the radial artery for blood pressure monitoring and for sample collection. Samples of 4–7 ml of arterial blood were taken at 0, 1, 2, 4, 8, 16, 30, 60, 62, 64, 68, 76, 90, 120, 122, 124, 128, 136, 150, 180, 240, 300, and 600 min and placed in heparinized tubes. The samples were placed on ice and centrifuged within 2 h of collection. The plasma was transferred to polypropylene tubes and frozen immediately. The tubes were stored at  $-20^\circ$  until assayed.

### Propofol Assay

Propofol was assayed using liquid-liquid extraction followed by reverse-phase high-performance liquid chromatography with fluorescence detection. The lower limit of detection was 2.0 ng/ml.

### Pharmacokinetic Analysis

**Influence of Method of Administration.** The design of this study was chosen to provide safety and



efficacy data about two common types of propofol use, bolus administration and continuous infusion. (The safety and efficacy data are not addressed in this article.) This design also permitted an evaluation of the influence of method of administration on the pharmacokinetics of propofol. The infusion was started 1 h after the bolus dose to (1) permit an adequate period of observation after delivery of the bolus dose, and (2) allow the concentrations of propofol in plasma to decline to low levels before starting the continuous infusion.

For each volunteer, we estimated the individual pharmacokinetics based on the observed concentrations starting 62 min after the bolus dose (2 min after the start of the infusion) using NONMEM.<sup>‡‡</sup> Although the dose regimen included the bolus dose information, NONMEM did not attempt to fit the model to the observations in the 60 min after administration of the bolus dose. Therefore, the resulting pharmacokinetic parameters described the observations from each individual based on the infusion data only. We then used the infusion-based pharmacokinetics to predict the observations in the 60 min after the bolus injection in the same individual. For this analysis, the two study sessions for each individual were treated as separate studies because the pharmacokinetics during the infusion were compared with the observations immediately after the bolus dose in the same study (*i.e.*, each study served as its own control).

For each of the samples in the first 60 min after the bolus injection, we calculated a ratio of the measured concentration at each time  $t$  to that predicted by pharmacokinetics estimated from the infusion data:

$$\text{ratio}(t) = \frac{\text{Concentration}(t)_{\text{measured}}}{\text{Concentration}(t)_{\text{predicted}}}$$

If mode of drug delivery has no effect on pharmacokinetics, the ratio in this equation should be 1 (the infusion pharmacokinetics should predict the bolus response). If the ratio differs significantly from 1, then there are statistically (but perhaps not clinically) significant differences in the pharmacokinetics after bolus injection and during continuous infusions.

We used the infusion data to predict the response to the bolus dose and not the response to predict the

infusion data because the response to the bolus dose was observed for only 60 min before the infusion was started. It would not be reasonable to expect the pharmacokinetics estimated from just 60 min of postdose data to predict the observations during the 1-h infusion followed by 8 h of postinfusion data.

**Influence of Infusion Rate.** The four infusion rates selected for this study, 25, 50, 100, and 200  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , span the clinical range of infusions of propofol during the maintenance of anesthesia. Had the study started with an infusion, linearity regarding infusion rate could have been determined by dividing all observed concentrations by the infusion rate and demonstrating that the rate-normalized concentrations did not differ between groups. The study design was modestly complicated by the initial bolus dose, whose influence had to be accounted for before dose normalization of the concentrations. This was accomplished by individually fitting a three-compartment model in NONMEM to all the observations in each study session and then calculating the contribution of the bolus dose at each point in time to the observed concentration. The contribution of the bolus dose was subtracted from the observed concentrations during and after the infusion, providing an estimate of the concentration that would have been observed had no bolus dose been administered before the infusion.

The influence of infusion rate was determined by dividing the observed concentrations, less the adjustment for the bolus dose, by the infusion rate. The resulting time *versus* concentration profiles were then graphed and visually examined for evidence of nonlinearity. In contrast to the more traditional assessment of linearity by comparing area under time concentration curves, this method provides an assessment of linearity that is true to the polyexponential nature of anesthetic pharmacokinetics. We also examined the concentrations at 68, 76, 90, and 120 min using Kruskal-Wallis nonparametric analysis of variance. A probability value  $<0.05$  was considered significant.

**Influence of Subject Covariates.** We used the approach described by Mandema *et al.*,<sup>16</sup> implemented as reported by Minto *et al.* for remifentanyl,<sup>17</sup> to develop a population pharmacokinetic model for the new EDTA-containing propofol emulsion, because this is the only propofol formulation now available in the United States. All concentrations from the sessions where propofol with EDTA was given were used in the analysis. Two- and three-compartment population pharmacokinetic

‡‡ Beal SL, Sheiner LB: NONMEM User's Guide. San Francisco, University of California San Francisco, 1979.



models were estimated by NONMEM using the first-order conditional estimation and  $\eta$ - $\epsilon$  interaction to reduce the influence of model misspecification. Specifically, the  $\eta$ - $\epsilon$  interaction option accounts for the interaction between intra- and interindividual variability.<sup>§§</sup> The structural model was chosen according to the objective function (minus twice the log likelihood  $[-2LL]$ ), with a decrease of 6.6 for one additional parameter considered significant ( $P < 0.01$ ).

The interindividual error on each of the model parameters ( $V_1$ ,  $V_2$ ,  $V_3$ ,  $Cl_1$ ,  $Cl_2$ ,  $Cl_3$ ) was modeled using a log-normal variance model:

$$P_i = \theta_{TV} e^{\eta_i}$$

where  $P_i$  is the parameter of an individual and  $\eta_i$  is a random variable that describes the interindividual variability between the parameter from the value in the typical individual. The residual intraindividual error was modeled with a constant coefficient of variation model. Empirical Bayesian estimates<sup>18,19</sup> of the pharmacokinetic parameters of each individual were calculated. Bayesian statistics applied to pharmacokinetics balance the uncertainty in the measured concentrations against the uncertainty in a person's parameter estimates. The relation between the subject covariates (age, gender, weight, height, lean body mass [LBM], and body surface area [BSA]) and the pharmacokinetic parameters was explored using a generalized additive model (GAM) implemented in S plus.<sup>16,17</sup> The GAM function performed a stepwise search to find the significant covariates and best form (linear or nonlinear) of each important covariate.

Lean body mass was calculated from gender, weight (in kilograms), and height (in centimeters)<sup>|||</sup>: men,  $LBM = 1.1 \times \text{weight} - 128 \times (\text{weight}/\text{height})^2$ ; women,  $LBM = 1.07 \times \text{weight} - 148 \times (\text{weight}/\text{height})^2$ . Body surface area was calculated from weight (in kilograms) and height (in centimeters)<sup>20</sup>:  $BSA = \text{weight}^{0.425} \times \text{height}^{0.725} \times 0.007184$ .

The covariates identified by the GAM analysis were then incorporated into the structural model and tested with NONMEM for their statistical significance, using the NONMEM objective function and the standard errors of the estimated parameters. A parameter was de-

leted from the final model if  $\pm 2 \times \text{SE}$  of the parameter included 0.

As used previously,<sup>21</sup> we described the quality of the goodness of fit using the weighted residual (WR), defined as (Measured - Predicted)/Predicted.

The median weighted residual (MDWR), calculated as the median WR over all of the observations, is a measure of bias. The median absolute weighted residual (MDAWR), calculated as the median of the absolute value of the WR, is a measure of inaccuracy of the fit. We visually examined the goodness of fit by plotting the measured/predicted values on a logarithmic scale for each volunteer as a function of time. The WRs were only calculated for observations from the new EDTA formulation, as these were the data used to estimate the pharmacokinetic model.

We also calculated the ability of the model to describe the concentrations observed after administration of propofol emulsion without EDTA. Because these data were not used to estimate the model parameters, the ability of the model to describe these observations represents a measure of the performance of this model. It also helps measure the influence of EDTA on the pharmacokinetics of propofol. These measures were therefore based on the performance error (PE), also defined as (Measured - Predicted)/Predicted.

We calculated the MDPE and MDAPE as described for the WR, *mutatis mutandis*.

Because age did prove to be a significant covariate (see results), we performed an additional analysis to ensure that this finding was not due simply to the lower bolus dose given to the elderly volunteers. As in the section on the influence of infusion rate, the concentrations that were corrected to remove the contribution of the bolus dose and normalized to dose (normalized, corrected concentrations) were compared with age, and a linear least-squares fit was done for four representative time points (68, 76, 128, and 136 min). Then the full covariate model was used to predict the concentration after a 60-min infusion at  $200 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  into a typical volunteer (77 kg, 175 cm, female) at ages 25, 50, and 75 yr, and those predicted concentrations were normalized. The predictions of the model were compared with the normalized, corrected concentrations from the volunteers.

**Influence of Disodium Edetate on Pharmacokinetics of Propofol.** Each volunteer received virtually identical bolus doses of propofol and infusions in each of the two sessions, permitting direct comparison of

§§ Beal SL, Sheiner LB: NONMEM User's Guide. Part IV. San Francisco, University of California San Francisco, 1979, p 35.

||| James WPT: Research on Obesity: London. London, Her Majesty's Stationary Office, 1976.



Table 1. Study Population

inf	Age (yr)	Weight (kg)	Height (cm)	Gender
25	34	46.3	158	F
25	31	123	196	M
25	62	79.4	170	M
25	65	79.4	182	M
25	77	74.8	183	M
25	70	62.6	175	M
50	30	64.4	170	M
50	27	74.8	188	M
50	46	93.4	182	M
50	41	90.7	178	F
50	72	88.4	183	M
50	75	64.4	168	F
100	29	95.2	188	M
100	26	88.4	178	M
100	55	44.7	168	F
100	51	79.8	175	F
100	81	74.8	178	M
100	72	70.3	170	F
200	31	91.2	180	F
200	25	63.5	158	F
200	62	86.2	180	M
200	38	88.4	173	F
200	74	70.3	160	F
200	75	44.4	155	F

concentrations of propofol in plasma between the two sessions. For each individual we calculated the ratio at each time  $t$  of the concentrations measured when propofol without EDTA was administered with the concentrations measured when propofol with EDTA was administered:

$$\text{ratio}(t) = \frac{\text{Concentration}(t)_{\text{without EDTA}}}{\text{Concentration}(t)_{\text{with EDTA}}}$$

We plotted this ratio over time for all individuals to examine any systematic deviations from 1. We also calculated confidence bounds about each point for a probability of 0.95. A Bonferroni correction was not performed to maintain sensitivity to any deviation of the ratio from 1.

## Results

The demographic data of the study population are summarized in table 1 by order of infusion group and age group. The ages were divided evenly between the different doses by study design. The study was not for-

mally stratified by gender. By chance, only one woman was included in the  $25\text{-}\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  infusion group, and only one man was included in the  $200\text{-}\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  infusion group. Taking the two low-dose and the two high-dose groups together, only three women were included in the 25- and  $50\text{-}\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  infusion group, but eight women were assigned randomly to the 100- and  $200\text{-}\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  group. These differences were not statistically significant (Pearson's chi-square test with Yates's continuity correction). The groups were otherwise homogeneous regarding the observed covariates.

All measured concentrations were included in the pharmacokinetic analysis. In each of two volunteers, one measurement for concentration in plasma was not available because the tube broke during centrifugation. Therefore, for 46 study sessions, we had 22 measurements of concentration in plasma, and for 2 study sessions we had 21 measurements. No points were lower than the limit of quantification of the assay. The investigators could not clinically distinguish a difference between the volunteers who received EDTA and those who did not.

### Influence of Method of Administration

Figure 1 (top) shows the ratio of concentrations after bolus injection to the concentrations predicted from the infusion data. The bias is statistically significant (fig. 1, middle), as shown by the mean and 95% confidence interval for the ratio of measured to predicted value. The 2- and 4-min samples show a statistically significant negative bias. At all other times the bias is positive and statistically significant. Figure 1 (bottom) shows that, although the bias may be statistically significant, it pales in comparison to the overall interindividual variability in concentration after bolus injection. The predictions of the pharmacokinetic models based on the infusion data alone (fig. 1, dashed lines) follow the same trend as the actual observations after administration of the bolus dose. Therefore, the shape and magnitude of the concentrations after bolus administration are fairly well described by infusion pharmacokinetics, despite a small but statistically significant bias.

### Influence of Infusion Rate

Figure 2 shows the concentrations observed after four different infusion rates, each demarcated by a unique line type. The concentrations are all normalized to the infusion rate, using the correction for the prior bolus



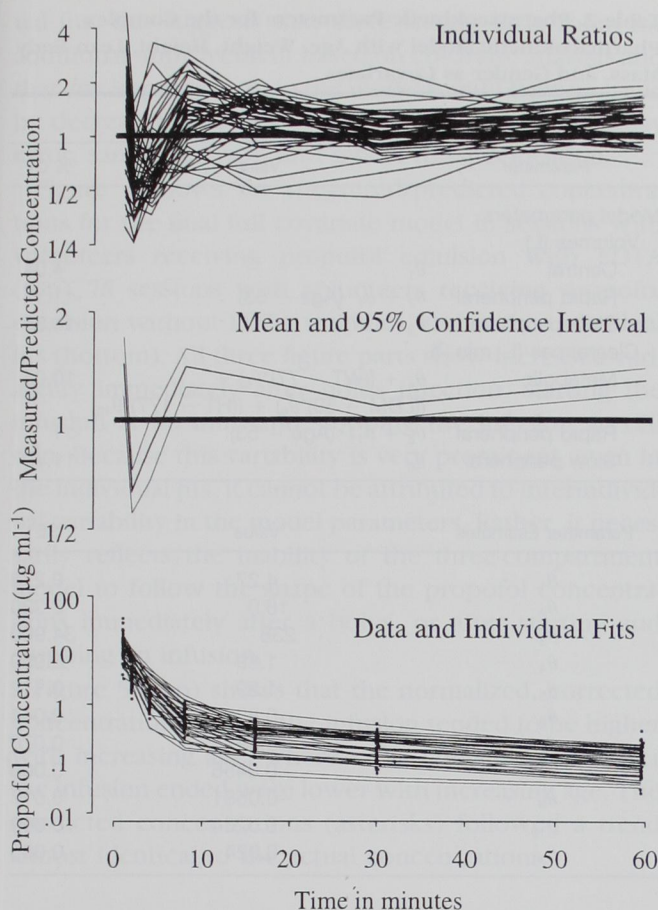


Fig. 1. (Top) The ratio of each volunteer's concentrations after bolus injection to the predicted concentrations based on the infusion data from the same study session. (Middle) The mean ratio at each point in time (solid line), surrounded by 95% confidence bands (dashed lines). The bias is statistically significant, as the confidence bands consistently exclude 1. The bias is unlikely to be clinically significant, however (bottom) because the individual fits (dashed lines) describe the data (solid circles) with little visible bias.

dose described in methods. Figure 3 suggests that the normalized, corrected concentrations are indistinguishable for the four different infusion rates.

Figure 3 shows the means (white bands) and distributions for the normalized, corrected concentrations in the four infusion rate groups at four representative time points. There is no suggestion that any single group has concentrations either higher or lower than would be expected based on simple linear pharmacokinetics. Therefore, the levels in the  $50\text{-}\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  group are nearly exactly twice the levels in the  $25\text{-}\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  group, and the levels in the  $100\text{-}\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$

groups are the respective expected proportions higher than the  $25\text{-}\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  groups. When the concentrations are divided by the infusion rates, the groups are indistinguishable. Therefore, the pharmacokinetics of propofol are linear from  $25$  to  $200\text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ . The lack of an effect of infusion rate on the concentrations was confirmed by the Kruskal-Wallis non-parametric analysis of variance, which identified no significant differences between the groups ( $P = 0.12$ ).

#### Influence of Subject Covariates

The GAM analysis was used to identify potentially significant covariates. The best models included age as a covariate of  $V_2$  and  $Cl_2$  and weight, height, LBM, and gender as covariates of  $Cl_1$ . All parameters entered the model linearly. This initial model was refined with NONMEM according to  $-2LL$  and the SEs of the parameter estimates. Only gender as a covariate on  $Cl_1$  did not remain in the model. Table 2 shows the final pharmacokinetic model of propofol emulsion containing EDTA. NONMEM estimated negligible interindividual variability for  $V_2$  and  $Cl_2$ .

Table 3 shows the measures of goodness of fit of the model. The observed concentrations in plasma were described reasonably accurately by the models with and without covariates. The addition of the covariates reduced the inaccuracy from 23.00% to 17.39%. The virtually identical performance of the model in describing the observed concentrations in those studies in which

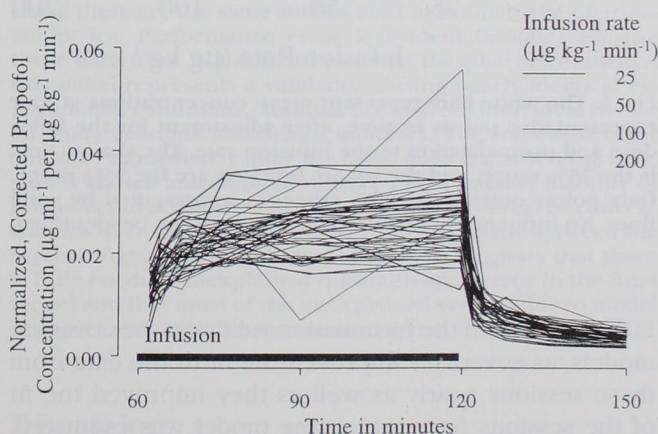


Fig. 2. The concentrations observed during the infusion, adjusted for the effect of the bolus dose and normalized to the infusion rate. Each different rate is represented by a separate line type, as indicated on the legend. No evidence of nonlinearity can be identified visually.



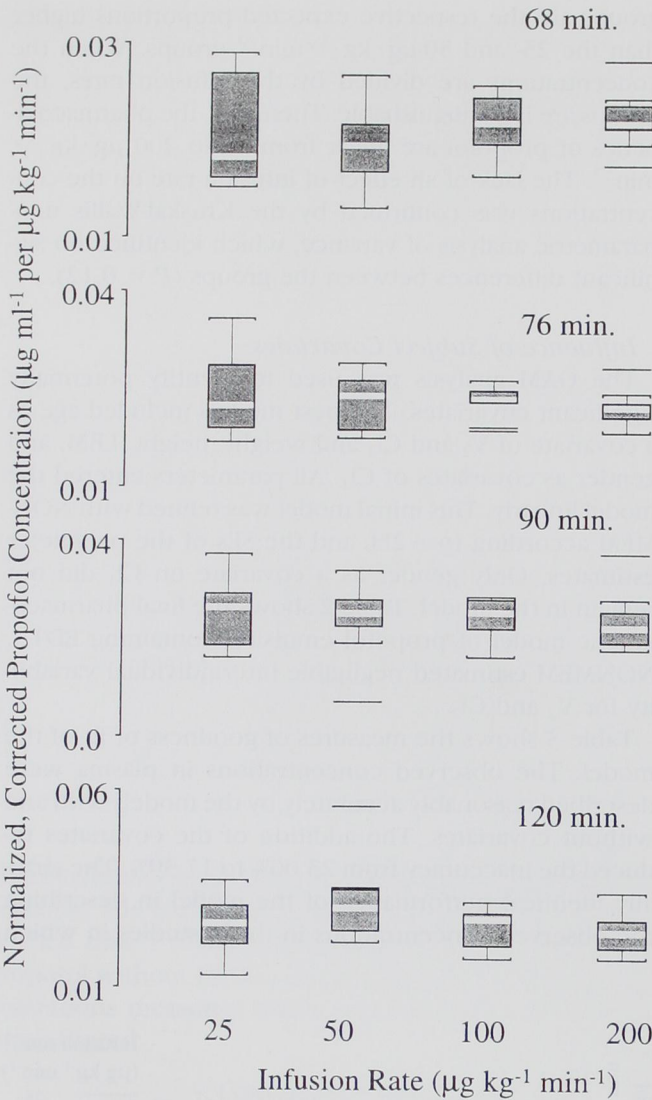


Fig. 3. The white bars represent mean concentrations at four representative points in time, after adjustment for the bolus dose and normalization to the infusion rate. The shaded area is the 75% range, and the square brackets are the 95% range. Data points outside the 95% range are represented by solid lines. No influence of rate on concentration can be identified.

EDTA was not in the formulation validated the covariate models, as covariates improved the fit to the data from these sessions nearly as well as they improved the fit of the sessions from which the model was estimated. The individual fits show a MDAWR of 14.18%, which was very nearly the residual error seen in the full covariate model. As the covariates could not possibly do any better than the model parameters estimated in individ-

Table 2. Pharmacokinetic Parameters for the Complex Pharmacokinetic Model with Age, Weight, Height, Lean Body Mass, and Gender as Covariates

Parameter	NONMEM	
	Value	% CV
Model parameters		
Volumes (L)		
Central	$\theta_1$	4.04
Rapid peripheral	$\theta_2 + \theta_7 \cdot (\text{Age} - 53)$	<1
Slow peripheral	$\theta_3$	14.35
Clearances (L · min <sup>-1</sup> )		
Metabolic	$\theta_4 + ((\text{WT} - 77) \cdot \theta_8) + ((\text{LBM} - 59) \cdot \theta_9) + ((\text{HT} - 177) \cdot \theta_{10})$	10.05
Rapid peripheral	$\theta_5 + \theta_{11} \cdot (\text{Age} - 53)$	<1
Slow peripheral	$\theta_6$	11.79

Parameter Estimates	Value	SE
$\theta_1$	4.27	0.278
$\theta_2$	18.9	2.330
$\theta_3$	238	34.900
$\theta_4$	1.89	0.059
$\theta_5$	1.29	0.112
$\theta_6$	0.836	0.044
$\theta_7$	-0.391	0.070
$\theta_8$	0.0456	0.009
$\theta_9$	-0.0681	0.017
$\theta_{10}$	0.0264	0.009
$\theta_{11}$	-0.024	0.005

Table 3. Measures of Goodness of Fit

Model	Weighted Residuals (%)	Performance Error (%)
No covariates		
Median	-1.56	-3.16
Median absolute	23.00	21.56
Covariate		
Median	-1.86	-2.98
Median absolute	17.39	18.63
Individual fits		
Median	0.31	
Median absolute	14.18	

The population model with and without covariates was estimated from the observed concentrations following administration of propofol emulsion with EDTA. The model was applied both retrospectively to the data from which it was estimated (weighted residuals) as well as to the observed concentrations following administration of propofol emulsion without EDTA (test of performance error). The latter represents a validation of the model under nearly identical experimental circumstances. The individual fits were performed for every study session, and thus there is no "performance error" calculation for those results.



ual fits, this suggests that there is very little room for additional improvement based on covariate analysis and that any improvement in the model would have to come by decreasing sources of intrasubject variability: assay error, sampling error, and model misspecification.

Figure 4 shows the measured/predicted concentrations for the final full covariate model in sessions with volunteers receiving propofol emulsion with EDTA (top), in sessions with volunteers receiving propofol emulsion without EDTA (middle), and in the individual fits (bottom). All three figure parts show increased variability immediately after bolus injection, starting the infusion at 60 min, and stopping the infusion at 120 min. Because this variability is very prominent, even in the individual fits, it cannot be attributed to interindividual variability in the model parameters. Rather, it necessarily reflects the inability of the three-compartment model to follow the shape of the propofol concentrations immediately after a bolus, or after starting and stopping an infusion.

Figure 5 (top) shows that the normalized, corrected concentrations during the infusion tended to be higher with increasing age, whereas the concentrations after the infusion ended were lower with increasing age. The predicted concentrations (asterisks) followed a trend almost identical to the actual concentrations.

#### *Influence of Disodium Edetate on Pharmacokinetics of Propofol*

Figure 6 shows the ratio of concentrations after administration of propofol emulsion without EDTA to administration of propofol emulsion with EDTA in each individual over time. There is no suggestion in figure 6 that the presence of EDTA resulted in any systematic difference in concentration between the two groups. Figure 6 (bottom) shows the mean and 95% confidence interval over time. The mean ratios ranged from 0.96 to 1.15. The bounds included 1 at each time, strongly suggesting that the concentrations in plasma after administration of propofol emulsion are not influenced by the presence of EDTA in the formulation. The results of this nonparametric method are consistent with the validation of the pharmacokinetic model mentioned previously: The model derived from the formulation containing EDTA performed just as well describing the data from the formulation without EDTA as it did describing the data from which it was derived.

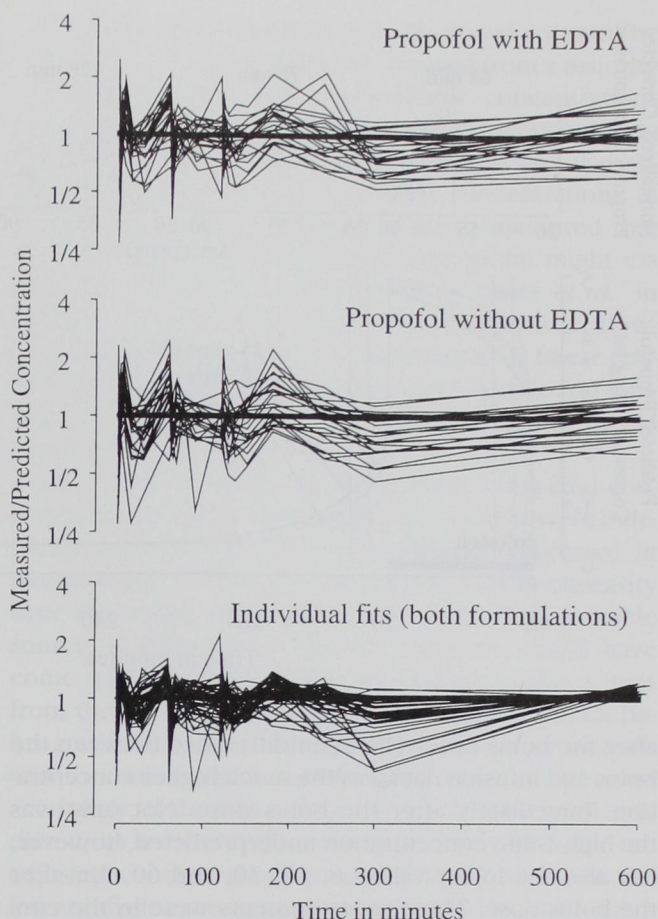


Fig. 4. The ability of the final pharmacokinetic model, including covariates, to describe the concentrations observed after administration of propofol emulsion with EDTA (top) and without EDTA (middle). Residual errors are evident (top) because these are the same studies used to estimate the pharmacokinetics. Performance error is evident (middle) because these data were not used to estimate the pharmacokinetics; this panel represents a validation during nearly identical experimental conditions. Residual errors from individual fits for all study sessions are shown (bottom). The increased error (bottom) immediately after the bolus dose and when the infusion is started and stopped reflects a fundamental inability of the model to accommodate the shape of the observed concentrations over time. The similarity in overall error between the top two figure parts and the bottom part suggests that there is little residual unexplained interindividual error in the final model and that most of the unexplained error is due to model misspecification and measurement error.

## Discussion

### *Influence of Method of Administration*

In this study, the pharmacokinetics based on the infusion data generally underpredicted the observations



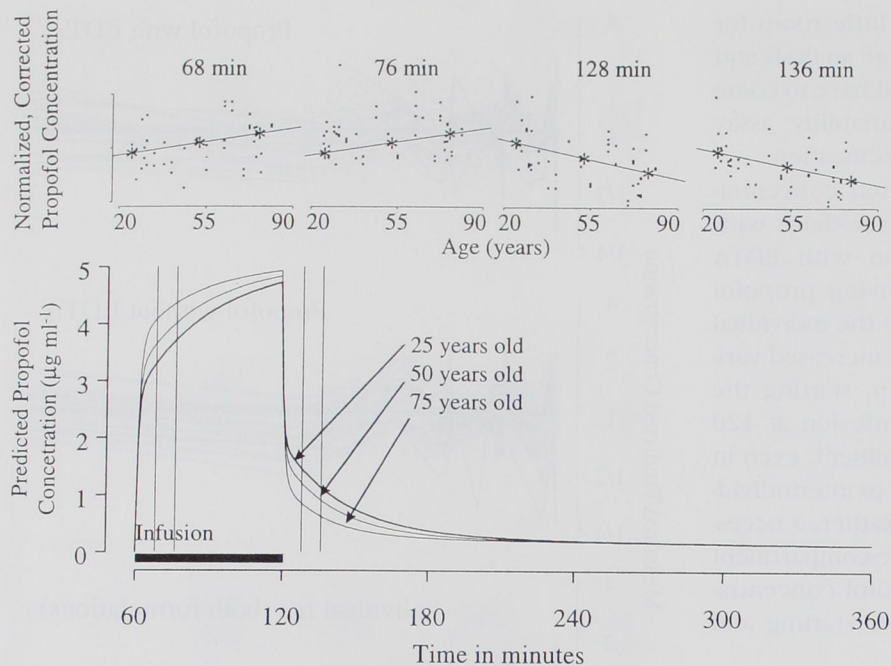


Fig. 5. Comparison of the measured with the predicted concentrations during the infusion. The four graphs show the relationship of the normalized, corrected concentrations at 68, 76, 128, and 136 min to age. The line through the data is a linear least-squares fit. The asterisks represent the predicted normalized concentration for a 77-kg, 175-cm woman at ages 25, 50, and 75 yr. During the infusion, the concentrations tended to be higher in the elderly, whereas after the end of the infusion the opposite was observed. The full time course of the predicted concentrations after an infusion at  $200 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  is shown (bottom). The vertical lines represent the four time points chosen for the comparison above.

after the bolus dose. The main difference between the bolus and infusion data was the much higher concentration immediately after the bolus dose. Not only was the high 1-min concentration underpredicted, however, but also the lower values 8, 15, 30, and 60 min after the bolus dose. These measurements were in the concentration range observed during and after the infusion.

Studies with computer-controlled infusion pumps have provided additional evidence that the mode of drug administration influences the pharmacokinetics of propofol. In these studies, pharmacokinetic models derived from studies with a bolus dose and a brief infusion<sup>6,9,22,23</sup> have predicted the concentrations during the computer-controlled infusion only poorly. It is noteworthy that parameters from a bolus dose-only study with propofol<sup>2</sup> resulted in the worst prediction of five evaluated parameter sets.<sup>6</sup>

One possible explanation for this persistent difference could be physiologic. Lange *et al.*<sup>24</sup> observed that after a 2.0-mg/kg bolus dose of propofol for induction of anesthesia for cardiac surgery, blood flow in the liver was reduced by 14%. This reduction continued until sternotomy. Therefore, it appears from these data and the results of the current study that bolus doses of propofol cause a small but persistent change in blood flow in the liver, resulting in decreased clearance and concentrations higher than those predicted from infusion

data. This mechanism could explain the underprediction of most of our postbolus concentrations, especially if the change in blood flow in the liver is long-lasting, but does not explain the overprediction of the 2- and 4-min values.

Another possible explanation is model misspecification. Pharmacokinetic models typically assume that the central compartment is well stirred. That is, an injected bolus dose of propofol is assumed to distribute immediately and homogeneously in the central compartment. Investigations by Henthorn *et al.*<sup>25</sup> and Krejcie *et al.*<sup>26</sup> however, have demonstrated multiple peaks after bolus injection because of rapid recirculation. Because traditional compartmental models are represented by monotonic functions, these recirculation oscillations cannot be described. Therefore, no conventional compartmental model can properly describe the actual concentrations after bolus injection. The inability of our three-compartment model to describe the initial high peak is certainly consistent with this type of model misspecification, but the influence of recirculation on some of the later postbolus values should be negligible. Further, it should be kept in mind that all models are, by definition, simplifications of complex physiologic processes that may change with time and drug concentration. In all likelihood, both decreased blood flow in the liver and model misspecification played a part in the suboptimal



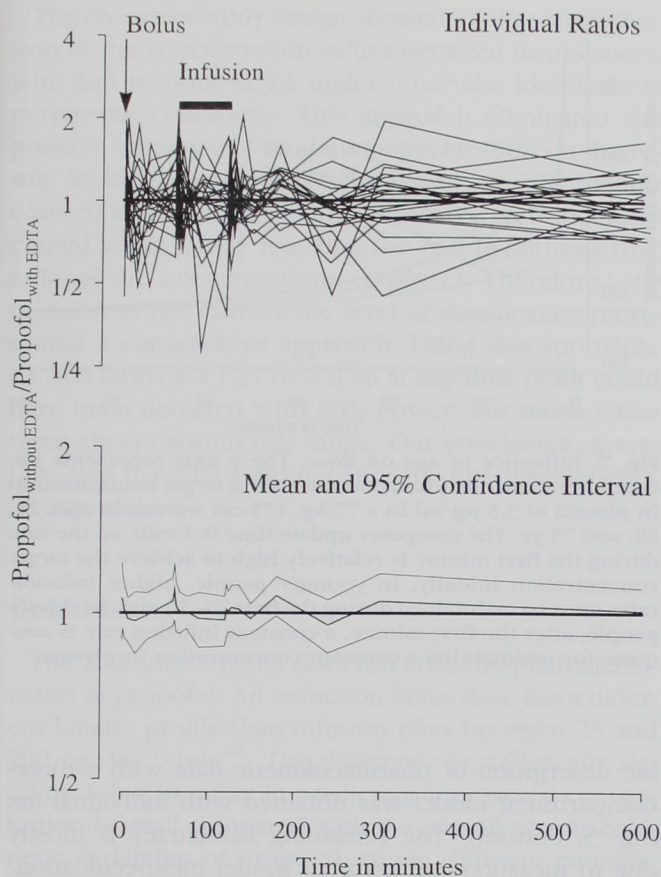


Fig. 6. The ratio of concentrations after administration of propofol emulsion without EDTA to administration of propofol emulsion with EDTA at each point in time for each volunteer is shown (top). The mean ratio at each point in time (solid line) and the 95% confidence bounds (dashed lines) also are illustrated (bottom). The confidence bounds include 1 at each point in time, confirming the visual impression from the top part that the pharmacokinetics of propofol are not influenced by EDTA.

prediction of the postbolus concentrations by the models derived from infusion data only.

#### *Influence of Infusion Rate*

Linearity can be understood in terms of the superposition principle, which says that the concentration obtained from multiple simultaneous infusions is the same as the sum of the concentrations when the infusions are given separately. This is only the case if no saturation effects are evident. That is, doubling the infusion rate doubles the concentrations. If a clearance saturates at a particular infusion rate, then increasing the rate results in a greater than proportional increase in concentration.

Evidence for nonlinearity was discussed recently by Coetzee *et al.*<sup>9</sup> A parameter set obtained from a majority of blood samples with subanesthetic concentrations consistently underpredicted the concentrations during the computer-controlled infusion. Vuyk *et al.*<sup>6</sup> also observed an underprediction of high concentrations in plasma with these parameters. They conjectured that the nonlinearity of the kinetics of propofol might explain the findings. An investigation of Bailey *et al.*<sup>7</sup> in patients undergoing coronary revascularization, however, found no evidence for nonlinearity. A linear relationship between concentration at steady state and infusion rate also was found in patients during regional anesthesia.<sup>1</sup>

In the current study, the normalized, corrected concentration measurements during the infusion were independent of the rate. This is graphically expressed in figures 2 and 3. There was no evidence for nonlinearity over the range of infusion rates studied. A possible source of bias in our analysis, however, could have come from the subtraction of predicted bolus values from the measured concentrations. Although both bolus and infusion data were used in this set of analyses and the bolus phase was probably represented more accurately, if the bolus concentrations were underpredicted, as in the analysis here, this would make the adjusted concentrations proportionately higher in the lower infusion rate groups, thereby masking the nonlinearity as reported by Coetzee *et al.*<sup>9</sup> and Vuyk *et al.*<sup>6</sup>

A recent study may shed light on the apparent discrepancy among studies that demonstrate linearity and those that do not. Pavlin *et al.*<sup>27</sup> observed a pharmacokinetic interaction of propofol and alfentanil in a well-controlled volunteer study. The concentrations of propofol were considerably higher when alfentanil was infused concurrently with alfentanil compared with an infusion of the propofol alone. Altered first-pass uptake of propofol in the lung<sup>28,29</sup> or changes in blood flow in the liver might have been causal for this pharmacokinetic interaction. It is possible that the nonlinearity in the pharmacokinetics of propofol discussed by Coetzee *et al.*<sup>9</sup> and Vuyk *et al.*<sup>6</sup> may have been due to a pharmacokinetic interaction between propofol and opioids.

#### *Influence of Subject Covariates*

Covariate models attempt to explain and thereby reduce the interindividual variability of the parameters. We derived a full pharmacokinetic model using the data from the administration of propofol with EDTA, using



a GAM analysis to identify potentially significant covariates. All the covariates detected by the GAM analysis were tested for significance using the objective criterion of NONMEM. After deleting gender, the remaining covariates were significant based on the  $-2LL$  and the SE. Age was significant for  $V_2$  and  $Cl_2$ . This indicates that intercompartmental drug distribution is influenced by age. The metabolic clearance is influenced by weight, LBM, and height. Although weight, LBM, and height all correlate with each other, inclusion of all three covariates improved the fit significantly ( $P < 0.01$ ) compared with inclusion of any combination of just two of these covariates. Most previously published pharmacokinetic models for propofol have been weight proportional.<sup>4,5,21</sup> Only Dyck *et al.*<sup>22</sup> and Kirkpatrick *et al.*<sup>2</sup> found an effect of age. The effect of age we found for propofol in our study looks similar to that found for thiopental in other studies.<sup>30,31</sup>

The age stratification of our study population made these data well suited to detection of an effect of age, although the lower bolus dose received by the volunteers older than 65 yr may have been a confounding factor. We addressed the latter issue by comparing the model prediction with the normalized, corrected concentrations. During the infusion, the normalized, corrected concentrations are higher in the elderly, whereas the concentrations are lower after the infusion is stopped. The model also predicts age-related changes of very similar magnitude. Although we cannot be sure that we are subtracting the correct bolus contribution to obtain the normalized, corrected concentrations, it is probable that age is an important independent covariate. To illustrate the influence of age on dose, we calculated the infusion rates required to reach and maintain a concentration of propofol in plasma of  $3.5 \mu\text{g/ml}$  with a computer-controlled infusion pump in the same hypothetical volunteer as before at ages 25, 50, and 75 yr. The time course of the infusion rates shows that younger people need higher infusion rates during the first 20–30 min to achieve the same concentration (fig. 7). A noteworthy corollary from the data and the simulations is that older people have a faster decrease in concentration after an infusion is stopped.

The covariate-adjusted pharmacokinetic model for propofol with EDTA accurately described the concentrations observed after administration of the propofol without EDTA. Figure 5 (top and middle) shows that the residual error and the prospectively applied performance error were of similar magnitude. The best possi-

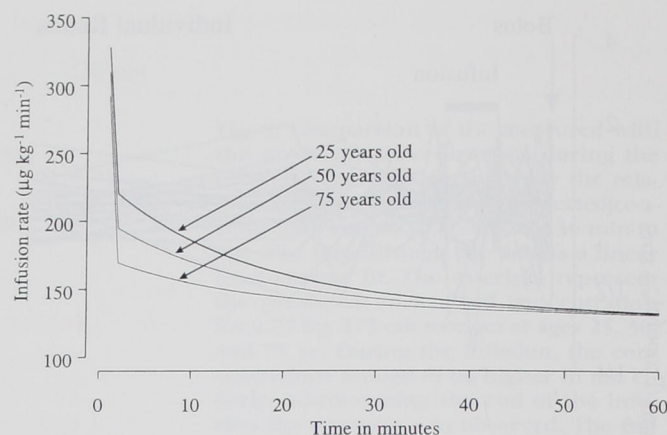


Fig. 7. Influence of age on dose. The y axis represents the computer-controlled infusion rates for a target concentration in plasma of  $3.5 \mu\text{g/ml}$  in a 77-kg, 175-cm woman at ages 25, 50, and 75 yr. The computer update time is 1 min, so the rate during the first minute is relatively high to achieve the target concentration initially. In younger people, higher infusion rates must be maintained during the first 20–30 min. In elderly people, after the first minute, a constant infusion rate is adequate for maintaining a constant concentration in plasma.

ble description of pharmacokinetic data with a three-compartment model was obtained with individual fits (fig. 5, bottom). The remaining inaccuracy is mostly due to measurement error or model misspecification. Because the accuracy of the covariate-adjusted model closely approaches that of the individual fits, further refinements in the pharmacokinetics of propofol cannot be expected from further inclusion of covariates.

#### *Influence of Disodium Edetate on Pharmacokinetics of Propofol*

The small quantity of EDTA added to propofol ( $<1\%$ ) was not expected to alter the pharmacokinetic profile remarkably. The toxicity of EDTA when infused at high rates has been investigated and reported by Dudley *et al.*<sup>32</sup> in 1955 and by Meltzer and colleagues in 1961.<sup>33</sup> In most patients, they observed moderate orthostatic hypotension. As hypotension can be associated with reduced blood flow in the liver, this suggests the possibility that EDTA might reduce clearance of propofol. Bolus injections of propofol without EDTA have been shown to reduce blood flow in the liver.<sup>24</sup> It was theoretically possible that the addition of EDTA to the formulation of propofol might exacerbate the hypotensive effects of a bolus dose, further reducing blood flow in the liver and altering clearance of propofol.



The crossover study design allowed for direct comparison of the concentration values between formulations with and without EDTA under otherwise identical experimental conditions. This approach eliminated the possible influence of model misspecification on the result. Multiple comparisons with *t* tests normally require correction of the significance level. We were not concerned about falsely rejecting the null hypothesis (the ratio of the concentrations equals 1). Therefore, our decision to not correct the level of significance represented a conservative approach. Using this approach, a mean ratio of  $>1.17$  or  $<0.83$  at any time point could have been detected with 80% power; our mean ratios were always within this range. Our conclusion, therefore, was that EDTA did not alter the pharmacokinetics of propofol.

## Conclusion

The addition of EDTA does not alter the pharmacokinetics of propofol. An induction bolus dose has a different kinetic profile than infusion rates between 25 and  $200 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . The difference is statistically significant, but its effect in predicting a measured concentration is small compared with the overall pharmacokinetic variability of propofol among different patients. The pharmacokinetics of propofol are linear for clinically relevant infusion rates. Age, weight, height, and LBM are significant covariates for propofol pharmacokinetics. "Prospective" evaluation of the derived parameters during nearly identical experimental conditions with the same volunteers showed performance errors that were of the same order of magnitude as the WRs in the model from which the parameters were derived.

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